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(54) Title: METHODS AND COMPOSITIONS FOR DIAGNOSIS AND PROGNOSIS OF RENAL INJURY AND RENAL FAILURE

(57) Abstract: The present invention relates to methods and compositions for monitoring, diagnosis, prognosis, and determination of treatment regimens in subjects suffering from or suspected of having a renal injury. In particular, the invention relates to using assays that detect one or more of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin as diagnostic and prognostic biomarker assays in renal injuries.

METHODS AND COMPOSITIONS FOR DIAGNOSIS AND PROGNOSIS OF RENAL INJURY AND RENAL FAILURE

[0001] The present invention claims priority from U.S. Provisional Application Nos. 62/174,456 filed June 11, 2015; 62/174,458 filed June 11, 2015; 62/174,460 filed June 11, 2015; and 62/174,461 filed June 11, 2015, each of which is hereby incorporated in its entirety including all tables, figures, and claims.

BACKGROUND OF THE INVENTION

[0002] The following discussion of the background of the invention is merely provided to aid the reader in understanding the invention and is not admitted to describe or constitute prior art to the present invention.

[0003] The kidney is responsible for water and solute excretion from the body. Its functions include maintenance of acid-base balance, regulation of electrolyte concentrations, control of blood volume, and regulation of blood pressure. As such, loss of kidney function through injury and/or disease results in substantial morbidity and mortality. A detailed discussion of renal injuries is provided in Harrison's Principles of Internal Medicine, 17th Ed., McGraw Hill, New York, pages 1741-1830, which are hereby incorporated by reference in their entirety. Renal disease and/or injury may be acute or chronic. Acute and chronic kidney disease are described as follows (from Current Medical Diagnosis & Treatment 2008, 47th Ed, McGraw Hill, New York, pages 785-815, which are hereby incorporated by reference in their entirety): "Acute renal failure is worsening of renal function over hours to days, resulting in the retention of nitrogenous wastes (such as urea nitrogen) and creatinine in the blood. Retention of these substances is called azotemia. Chronic renal failure (chronic kidney disease) results from an abnormal loss of renal function over months to years".

[0004] Acute renal failure (ARF, also known as acute kidney injury, or AKI) is an abrupt (typically detected within about 48 hours to 1 week)reduction in glomerular filtration. This loss of filtration capacity results in retention of nitrogenous (urea and creatinine) and non-nitrogenous waste products that are normally excreted by the kidney, a reduction in urine output, or both. It is reported that ARF complicates about 5% of hospital admissions, 4-15% of cardiopulmonary bypass surgeries, and up to 30% of intensive care admissions. ARF may be categorized as prerenal, intrinsic renal, or

postrenal in causation. Intrinsic renal disease can be further divided into glomerular, tubular, interstitial, and vascular abnormalities. Major causes of ARF are described in the following table, which is adapted from the Merck Manual, 17th ed., Chapter 222, and which is hereby incorporated by reference in their entirety:

Type	**Risk Factors**
Prerenal	
ECF volume depletion	Excessive diuresis, hemorrhage, GI losses, loss of intravascular fluid into the extravascular space (due to ascites, peritonitis, pancreatitis, or burns), loss of skin and mucus membranes, renal salt- and water-wasting states
Low cardiac output	Cardiomyopathy, MI, cardiac tamponade, pulmonary embolism, pulmonary hypertension, positive-pressure mechanical ventilation
Low systemic vascular resistance	Septic shock, liver failure, antihypertensive drugs
Increased renal vascular resistance	NSAIDs, cyclosporines, tacrolimus, hypercalcemia, anaphylaxis, anesthetics, renal artery obstruction, renal vein thrombosis, sepsis, hepatorenal syndrome
Decreased efferent arteriolar tone (leading to decreased GFR from reduced glomerular transcapillary pressure, especially in patients with bilateral renal artery stenosis)	ACE inhibitors or angiotensin II receptor blockers
Intrinsic Renal	
Acute tubular injury	Ischemia (prolonged or severe prerenal state): surgery, hemorrhage, arterial or venous obstruction; Toxins: NSAIDs, cyclosporines, tacrolimus, aminoglycosides, foscarnet, ethylene glycol, hemoglobin, myoglobin, ifosfamide, heavy metals, methotrexate, radiopaque contrast agents, streptozotocin
Acute glomerulonephritis	ANCA-associated: Crescentic glomerulonephritis, polyarteritis nodosa, Wegener's granulomatosis; Anti-GBM glomerulonephritis: Goodpasture's syndrome; Immune-complex: Lupus glomerulonephritis, postinfectious glomerulonephritis, cryoglobulinemic glomerulonephritis
Acute tubulointerstitial nephritis	Drug reaction (eg, β-lactams, NSAIDs, sulfonamides, ciprofloxacin, thiazide diuretics, furosemide, phenytoin, allopurinol, pyelonephritis, papillary necrosis
Acute vascular nephropathy	Vasculitis, malignant hypertension, thrombotic microangiopathies, scleroderma, atheroembolism
Infiltrative diseases	Lymphoma, sarcoidosis, leukemia
Postrenal	

Type	Risk Factors
Tubular precipitation	Uric acid (tumor lysis), sulfonamides, triamterene, acyclovir, indinavir, methotrexate, ethylene glycol ingestion, myeloma protein, myoglobin
Ureteral obstruction	Intrinsic: Calculi, clots, sloughed renal tissue, fungus ball, edema, malignancy, congenital defects; Extrinsic: Malignancy, retroperitoneal fibrosis, ureteral trauma during surgery or high impact injury
Bladder obstruction	Mechanical: Benign prostatic hyperplasia, prostate cancer, bladder cancer, urethral strictures, phimosis, paraphimosis, urethral valves, obstructed indwelling urinary catheter; Neurogenic: Anticholinergic drugs, upper or lower motor neuron lesion

[0005] In the case of ischemic ARF, the course of the disease may be divided into four phases. During an initiation phase, which lasts hours to days, reduced perfusion of the kidney is evolving into injury. Glomerular ultrafiltration reduces, the flow of filtrate is reduced due to debris within the tubules, and back leakage of filtrate through injured epithelium occurs. Renal injury can be mediated during this phase by reperfusion of the kidney. Initiation is followed by an extension phase which is characterized by continued ischemic injury and inflammation and may involve endothelial damage and vascular congestion. During the maintenance phase, lasting from 1 to 2 weeks, renal cell injury occurs, and glomerular filtration and urine output reaches a minimum. A recovery phase can follow in which the renal epithelium is repaired and GFR gradually recovers. Despite this, the survival rate of subjects with ARF may be as low as about 60%.

[0006] Acute kidney injury caused by radiocontrast agents (also called contrast media) and other nephrotoxins such as cyclosporine, antibiotics including aminoglycosides and anticancer drugs such as cisplatin manifests over a period of days to about a week. Contrast induced nephropathy (CIN, which is AKI caused by radiocontrast agents) is thought to be caused by intrarenal vasoconstriction (leading to ischemic injury) and from the generation of reactive oxygen species that are directly toxic to renal tubular epithelial cells. CIN classically presents as an acute (onset within 24-48h) but reversible (peak 3-5 days, resolution within 1 week) rise in blood urea nitrogen and serum creatinine.

[0007] A commonly reported criteria for defining and detecting AKI is an abrupt (typically within about 2-7 days or within a period of hospitalization) elevation of serum creatinine. Although the use of serum creatinine elevation to define and detect AKI is

well established, the magnitude of the serum creatinine elevation and the time over which it is measured to define AKI varies considerably among publications. Traditionally, relatively large increases in serum creatinine such as 100%, 200%, an increase of at least 100% to a value over 2 mg/dL and other definitions were used to define AKI. However, the recent trend has been towards using smaller serum creatinine rises to define AKI. The relationship between serum creatinine rise, AKI and the associated health risks are reviewed in Praught and Shlipak, *Curr Opin Nephrol Hypertens* 14:265-270, 2005 and Chertow et al, *J Am Soc Nephrol* 16: 3365-3370, 2005, which, with the references listed therein, are hereby incorporated by reference in their entirety. As described in these publications, acute worsening renal function (AKI) and increased risk of death and other detrimental outcomes are now known to be associated with very small increases in serum creatinine. These increases may be determined as a relative (percent) value or a nominal value. Relative increases in serum creatinine as small as 20% from the pre-injury value have been reported to indicate acutely worsening renal function (AKI) and increased health risk, but the more commonly reported value to define AKI and increased health risk is a relative increase of at least 25%. Nominal increases as small as 0.3 mg/dL, 0.2 mg/dL or even 0.1 mg/dL have been reported to indicate worsening renal function and increased risk of death. Various time periods for the serum creatinine to rise to these threshold values have been used to define AKI, for example, ranging from 2 days, 3 days, 7 days, or a variable period defined as the time the patient is in the hospital or intensive care unit. These studies indicate there is not a particular threshold serum creatinine rise (or time period for the rise) for worsening renal function or AKI, but rather a continuous increase in risk with increasing magnitude of serum creatinine rise.

[0008] One study (Lassnigg et all, J Am Soc Nephrol 15:1597-1605, 2004, hereby incorporated by reference in its entirety) investigated both increases and decreases in serum creatinine. Patients with a mild fall in serum creatinine of -0.1 to -0.3 mg/dL following heart surgery had the lowest mortality rate. Patients with a larger fall in serum creatinine (more than or equal to -0.4 mg/dL) or any increase in serum creatinine had a larger mortality rate. These findings caused the authors to conclude that even very subtle changes in renal function (as detected by small creatinine changes within 48 hours of surgery) seriously effect patient's outcomes. In an effort to reach consensus on a unified classification system for using serum creatinine to define AKI in clinical trials and in clinical practice, Bellomo *et al., Crit Care*. 8(4):R204-12, 2004, which is hereby

incorporated by reference in its entirety, proposes the following classifications for stratifying AKI patients:

"Risk": serum creatinine increased 1.5 fold from baseline OR urine production of <0.5 ml/kg body weight/hr for 6 hours;

"Injury": serum creatinine increased 2.0 fold from baseline OR urine production <0.5 ml/kg/hr for 12 h;

"Failure": serum creatinine increased 3.0 fold from baseline OR creatinine >355 μmol/l (with a rise of >44) or urine output below 0.3 ml/kg/hr for 24 h or anuria for at least 12 hours;

And included two clinical outcomes:

"Loss": persistent need for renal replacement therapy for more than four weeks.

"ESRD": end stage renal disease—the need for dialysis for more than 3 months.

These criteria are called the RIFLE criteria, which provide a useful clinical tool to classify renal status. As discussed in Kellum, *Crit. Care Med.* 36: S141-45, 2008 and Ricci *et al., Kidney Int.* 73, 538-546, 2008, each hereby incorporated by reference in its entirety, the RIFLE criteria provide a uniform definition of AKI which has been validated in numerous studies.

[0009] More recently, Mehta *et al., Crit. Care* 11:R31 (doi:10.1186.cc5713), 2007, hereby incorporated by reference in its entirety, proposes the following similar classifications for stratifying AKI patients, which have been modified from RIFLE:

"Stage I": increase in serum creatinine of more than or equal to 0.3 mg/dL (≥ 26.4 μmol/L) or increase to more than or equal to 150% (1.5-fold) from baseline OR urine output less than 0.5 mL/kg per hour for more than 6 hours;

"Stage II": increase in serum creatinine to more than 200% (> 2-fold) from baseline OR urine output less than 0.5 mL/kg per hour for more than 12 hours;

"Stage III": increase in serum creatinine to more than 300% (> 3-fold) from baseline OR serum creatinine ≥ 354 μmol/L accompanied by an acute increase of at least 44 μmol/L OR urine output less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours.

[0010] The CIN Consensus Working Panel (McCollough et al, Rev Cardiovasc Med. *2006;7(4):177-197,* hereby incorporated by reference in its entirety*)* uses a serum

creatinine rise of 25% to define Contrast induced nephropathy (which is a type of AKI).Although various groups propose slightly different criteria for using serum creatinine to detect AKI, the consensus is that small changes in serum creatinine, such as 0.3 mg/dL or 25%, are sufficient to detect AKI (worsening renal function) and that the magnitude of the serum creatinine change is an indicator of the severity of the AKI and mortality risk.

[0011] Although serial measurement of serum creatinine over a period of days is an accepted method of detecting and diagnosing AKI and is considered one of the most important tools to evaluate AKI patients, serum creatinine is generally regarded to have several limitations in the diagnosis, assessment and monitoring of AKI patients. The time period for serum creatinine to rise to values (e.g., a 0.3 mg/dL or 25% rise) considered diagnostic for AKI can be 48 hours or longer depending on the definition used. Since cellular injury in AKI can occur over a period of hours, serum creatinine elevations detected at 48 hours or longer can be a late indicator of injury, and relying on serum creatinine can thus delay diagnosis of AKI. Furthermore, serum creatinine is not a good indicator of the exact kidney status and treatment needs during the most acute phases of AKI when kidney function is changing rapidly. Some patients with AKI will recover fully, some will need dialysis (either short term or long term) and some will have other detrimental outcomes including death, major adverse cardiac events and chronic kidney disease. Because serum creatinine is a marker of filtration rate, it does not differentiate between the causes of AKI (pre-renal, intrinsic renal, post-renal obstruction, atheroembolic, etc) or the category or location of injury in intrinsic renal disease (for example, tubular, glomerular or interstitial in origin). Urine output is similarly limited, Knowing these things can be of vital importance in managing and treating patients with AKI.

[0012] These limitations underscore the need for better methods to detect and assess AKI, particularly in the early and subclinical stages, but also in later stages when recovery and repair of the kidney can occur. Furthermore, there is a need to better identify patients who are at risk of having an AKI.

BRIEF SUMMARY OF THE INVENTION

[0013] It is an object of the invention to provide methods and compositions for evaluating renal function in a subject. As described herein, measurement of one or more

markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin (collectively referred to herein as "kidney injury markers, and individually as a "kidney injury marker") can be used for diagnosis, prognosis, risk stratification, staging, monitoring, categorizing and determination of further diagnosis and treatment regimens in subjects suffering or at risk of suffering from an injury to renal function, reduced renal function, and/or acute renal failure (also called acute kidney injury).

[0014] These kidney injury markers may be used, individually or in panels comprising a plurality of kidney injury markers, for risk stratification (that is, to identify subjects at risk for a future injury to renal function, for future progression to reduced renal function, for future progression to ARF, for future improvement in renal function, *etc.*); for diagnosis of existing disease (that is, to identify subjects who have suffered an injury to renal function, who have progressed to reduced renal function, who have progressed to ARF, *etc.*); for monitoring for deterioration or improvement of renal function; and for predicting a future medical outcome, such as improved or worsening renal function, a decreased or increased mortality risk, a decreased or increased risk that a subject will require renal replacement therapy (*i.e.*, hemodialysis, peritoneal dialysis, hemofiltration, and/or renal transplantation, a decreased or increased risk that a subject will recover from an injury to renal function, a decreased or increased risk that a subject will recover from ARF, a decreased or increased risk that a subject will progress to end stage renal disease, a decreased or increased risk that a subject will progress to chronic renal failure, a decreased or increased risk that a subject will suffer rejection of a transplanted kidney, *etc.*

[0015] In a first aspect, the present invention relates to methods for evaluating renal status in a subject. These methods comprise performing an assay method that is configured to detect one or more kidney injury markers of the present invention in a body fluid sample obtained from the subject. The assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are then correlated to the renal status of the subject. This correlation to renal status may include correlating the assay result(s) to one or more of risk stratification, diagnosis, prognosis, staging, classifying and monitoring of the subject as described herein. Thus, the present invention utilizes one or more kidney injury markers of the present invention for the evaluation of renal injury.

[0016] In certain embodiments, the methods for evaluating renal status described herein are methods for risk stratification of the subject; that is, assigning a likelihood of one or more future changes in renal status to the subject. In these embodiments, the assay result(s) is/are correlated to one or more such future changes. The following are preferred risk stratification embodiments.

[0017] In preferred risk stratification embodiments, these methods comprise determining a subject's risk for a future injury to renal function, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to a likelihood of such a future injury to renal function. For example, the measured concentration(s) may each be compared to a threshold value. For a "positive going" kidney injury marker, an increased likelihood of suffering a future injury to renal function is assigned to the subject when the measured concentration is above the threshold, relative to a likelihood assigned when the measured concentration is below the threshold. For a "negative going" kidney injury marker, an increased likelihood of suffering a future injury to renal function is assigned to the subject when the measured concentration is below the threshold, relative to a likelihood assigned when the measured concentration is above the threshold.

[0018] In other preferred risk stratification embodiments, these methods comprise determining a subject's risk for future reduced renal function, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to a likelihood of such reduced renal function. For example, the measured concentrations may each be compared to a threshold value. For a "positive going" kidney injury marker, an increased likelihood of suffering a future reduced renal function is assigned to the subject when the measured concentration is above the threshold, relative to a likelihood assigned when the measured concentration is below the threshold. For a "negative going" kidney injury marker, an increased likelihood of future reduced renal function is assigned to the subject when the measured concentration is below the threshold, relative to a likelihood assigned when the measured concentration is above the threshold.

[0019] In still other preferred risk stratification embodiments, these methods comprise determining a subject's likelihood for a future improvement in renal function, and the

assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to a likelihood of such a future improvement in renal function. For example, the measured concentration(s) may each be compared to a threshold value. For a "positive going" kidney injury marker, an increased likelihood of a future improvement in renal function is assigned to the subject when the measured concentration is below the threshold, relative to a likelihood assigned when the measured concentration is above the threshold. For a "negative going" kidney injury marker, an increased likelihood of a future improvement in renal function is assigned to the subject when the measured concentration is above the threshold, relative to a likelihood assigned when the measured concentration is below the threshold.

[0020] In yet other preferred risk stratification embodiments, these methods comprise determining a subject's risk for progression to ARF, and the result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to a likelihood of such progression to ARF. For example, the measured concentration(s) may each be compared to a threshold value. For a "positive going" kidney injury marker, an increased likelihood of progression to ARF is assigned to the subject when the measured concentration is above the threshold, relative to a likelihood assigned when the measured concentration is below the threshold. For a "negative going" kidney injury marker, an increased likelihood of progression to ARF is assigned to the subject when the measured concentration is below the threshold, relative to a likelihood assigned when the measured concentration is above the threshold.

[0021] And in other preferred risk stratification embodiments, these methods comprise determining a subject's outcome risk, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to a likelihood of the occurrence of a clinical outcome related to a renal injury suffered by the subject. For example, the measured concentration(s) may each be compared to a threshold value. For a "positive going" kidney injury marker, an increased likelihood of one or more of: acute kidney injury, progression to a worsening stage of AKI, mortality, a requirement for renal replacement therapy, a requirement for withdrawal of renal toxins, end stage renal disease, heart failure, stroke, myocardial infarction, progression to chronic

kidney disease, *etc.*, is assigned to the subject when the measured concentration is above the threshold, relative to a likelihood assigned when the measured concentration is below the threshold. For a "negative going" kidney injury marker, an increased likelihood of one or more of: acute kidney injury, progression to a worsening stage of AKI, mortality, a requirement for renal replacement therapy, a requirement for withdrawal of renal toxins, end stage renal disease, heart failure, stroke, myocardial infarction, progression to chronic kidney disease, *etc.*, is assigned to the subject when the measured concentration is below the threshold, relative to a likelihood assigned when the measured concentration is above the threshold.

[0022] In such risk stratification embodiments, preferably the likelihood or risk assigned is that an event of interest is more or less likely to occur within 180 days of the time at which the body fluid sample is obtained from the subject. In particularly preferred embodiments, the likelihood or risk assigned relates to an event of interest occurring within a shorter time period such as 18 months, 120 days, 90 days, 60 days, 45 days, 30 days, 21 days, 14 days, 7 days, 5 days, 96 hours, 72 hours, 48 hours, 36 hours, 24 hours, 12 hours, or less. A risk at 0 hours of the time at which the body fluid sample is obtained from the subject is equivalent to diagnosis of a current condition.

[0023] In preferred risk stratification embodiments, the subject is selected for risk stratification based on the pre-existence in the subject of one or more known risk factors for prerenal, intrinsic renal, or postrenal ARF. For example, a subject undergoing or having undergone major vascular surgery, coronary artery bypass, or other cardiac surgery; a subject having pre-existing congestive heart failure, preeclampsia, eclampsia, diabetes mellitus, hypertension, coronary artery disease, proteinuria, renal insufficiency, glomerular filtration below the normal range, cirrhosis, serum creatinine above the normal range, or sepsis; or a subject exposed to NSAIDs, cyclosporines, tacrolimus, aminoglycosides, foscarnet, ethylene glycol, hemoglobin, myoglobin, ifosfamide, heavy metals, methotrexate, radiopaque contrast agents, or streptozotocin are all preferred subjects for monitoring risks according to the methods described herein. This list is not meant to be limiting. By "pre-existence" in this context is meant that the risk factor exists at the time the body fluid sample is obtained from the subject. In particularly preferred embodiments, a subject is chosen for risk stratification based on an existing diagnosis of injury to renal function, reduced renal function, or ARF.

[0024] In other embodiments, the methods for evaluating renal status described herein are methods for diagnosing a renal injury in the subject; that is, assessing whether or not a subject has suffered from an injury to renal function, reduced renal function, or ARF. In these embodiments, the assay result(s) is/are correlated to the occurrence or nonoccurrence of a change in renal status. The following are preferred diagnostic embodiments.

[0025] In preferred diagnostic embodiments, these methods comprise diagnosing the occurrence or nonoccurrence of an injury to renal function, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the occurrence or nonoccurrence of such an injury. For example, each of the measured concentration(s) may be compared to a threshold value. For a positive going marker, an increased likelihood of the occurrence of an injury to renal function is assigned to the subject when the measured concentration is above the threshold (relative to the likelihood assigned when the measured concentration is below the threshold); alternatively, when the measured concentration is below the threshold, an increased likelihood of the nonoccurrence of an injury to renal function may be assigned to the subject (relative to the likelihood assigned when the measured concentration is above the threshold). For a negative going marker, an increased likelihood of the occurrence of an injury to renal function is assigned to the subject when the measured concentration is below the threshold (relative to the likelihood assigned when the measured concentration is above the threshold); alternatively, when the measured concentration is above the threshold, an increased likelihood of the nonoccurrence of an injury to renal function may be assigned to the subject (relative to the likelihood assigned when the measured concentration is below the threshold).

[0026] In other preferred diagnostic embodiments, these methods comprise diagnosing the occurrence or nonoccurrence of reduced renal function, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the occurrence or nonoccurrence of an injury causing reduced renal function. For example, each of the measured concentration(s) may be compared to a threshold value. For a positive going marker, an increased likelihood of the occurrence of an injury causing reduced renal function is assigned to the subject when the measured

concentration is above the threshold (relative to the likelihood assigned when the measured concentration is below the threshold); alternatively, when the measured concentration is below the threshold, an increased likelihood of the nonoccurrence of an injury causing reduced renal function may be assigned to the subject (relative to the likelihood assigned when the measured concentration is above the threshold). For a negative going marker, an increased likelihood of the occurrence of an injury causing reduced renal function is assigned to the subject when the measured concentration is below the threshold (relative to the likelihood assigned when the measured concentration is above the threshold); alternatively, when the measured concentration is above the threshold, an increased likelihood of the nonoccurrence of an injury causing reduced renal function may be assigned to the subject (relative to the likelihood assigned when the measured concentration is below the threshold).

[0027] In yet other preferred diagnostic embodiments, these methods comprise diagnosing the occurrence or nonoccurrence of ARF, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the occurrence or nonoccurrence of an injury causing ARF. For example, each of the measured concentration(s) may be compared to a threshold value. For a positive going marker, an increased likelihood of the occurrence of ARF is assigned to the subject when the measured concentration is above the threshold (relative to the likelihood assigned when the measured concentration is below the threshold); alternatively, when the measured concentration is below the threshold, an increased likelihood of the nonoccurrence of ARF may be assigned to the subject (relative to the likelihood assigned when the measured concentration is above the threshold). For a negative going marker, an increased likelihood of the occurrence of ARF is assigned to the subject when the measured concentration is below the threshold (relative to the likelihood assigned when the measured concentration is above the threshold); alternatively, when the measured concentration is above the threshold, an increased likelihood of the nonoccurrence of ARF may be assigned to the subject (relative to the likelihood assigned when the measured concentration is below the threshold).

[0028] In still other preferred diagnostic embodiments, these methods comprise diagnosing a subject as being in need of renal replacement therapy, and the assay result(s), for example a measured concentration of one or more markers selected from the

group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to a need for renal replacement therapy. For example, each of the measured concentration(s) may be compared to a threshold value. For a positive going marker, an increased likelihood of the occurrence of an injury creating a need for renal replacement therapy is assigned to the subject when the measured concentration is above the threshold (relative to the likelihood assigned when the measured concentration is below the threshold); alternatively, when the measured concentration is below the threshold, an increased likelihood of the nonoccurrence of an injury creating a need for renal replacement therapy may be assigned to the subject (relative to the likelihood assigned when the measured concentration is above the threshold). For a negative going marker, an increased likelihood of the occurrence of an injury creating a need for renal replacement therapy is assigned to the subject when the measured concentration is below the threshold (relative to the likelihood assigned when the measured concentration is above the threshold); alternatively, when the measured concentration is above the threshold, an increased likelihood of the nonoccurrence of an injury creating a need for renal replacement therapy may be assigned to the subject (relative to the likelihood assigned when the measured concentration is below the threshold).

[0029] In still other preferred diagnostic embodiments, these methods comprise diagnosing a subject as being in need of renal transplantation, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to a need for renal transplantation. For example, each of the measured concentration(s) may be compared to a threshold value. For a positive going marker, an increased likelihood of the occurrence of an injury creating a need for renal transplantation is assigned to the subject when the measured concentration is above the threshold (relative to the likelihood assigned when the measured concentration is below the threshold); alternatively, when the measured concentration is below the threshold, an increased likelihood of the nonoccurrence of an injury creating a need for renal transplantation may be assigned to the subject (relative to the likelihood assigned when the measured concentration is above the threshold). For a negative going marker, an increased likelihood of the occurrence of an injury creating a need for renal transplantation is assigned to the subject when the measured concentration is below the threshold (relative to the likelihood assigned when the measured concentration is above

the threshold); alternatively, when the measured concentration is above the threshold, an increased likelihood of the nonoccurrence of an injury creating a need for renal transplantation may be assigned to the subject (relative to the likelihood assigned when the measured concentration is below the threshold).

[0030] In still other embodiments, the methods for evaluating renal status described herein are methods for monitoring a renal injury in the subject; that is, assessing whether or not renal function is improving or worsening in a subject who has suffered from an injury to renal function, reduced renal function, or ARF. In these embodiments, the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the occurrence or nonoccurrence of a change in renal status. The following are preferred monitoring embodiments.

[0031] In preferred monitoring embodiments, these methods comprise monitoring renal status in a subject suffering from an injury to renal function, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the occurrence or nonoccurrence of a change in renal status in the subject. For example, the measured concentration(s) may be compared to a threshold value. For a positive going marker, when the measured concentration is above the threshold, a worsening of renal function may be assigned to the subject; alternatively, when the measured concentration is below the threshold, an improvement of renal function may be assigned to the subject. For a negative going marker, when the measured concentration is below the threshold, a worsening of renal function may be assigned to the subject; alternatively, when the measured concentration is above the threshold, an improvement of renal function may be assigned to the subject.

[0032] In other preferred monitoring embodiments, these methods comprise monitoring renal status in a subject suffering from reduced renal function, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the occurrence or nonoccurrence of a change in renal status in the subject. For example, the measured concentration(s) may be compared to a threshold value. For a positive going marker, when the measured concentration is above the threshold, a worsening of renal function may be assigned to the subject; alternatively,

when the measured concentration is below the threshold, an improvement of renal function may be assigned to the subject. For a negative going marker, when the measured concentration is below the threshold, a worsening of renal function may be assigned to the subject; alternatively, when the measured concentration is above the threshold, an improvement of renal function may be assigned to the subject.

[0033] In yet other preferred monitoring embodiments, these methods comprise monitoring renal status in a subject suffering from acute renal failure, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the occurrence or nonoccurrence of a change in renal status in the subject. For example, the measured concentration(s) may be compared to a threshold value. For a positive going marker, when the measured concentration is above the threshold, a worsening of renal function may be assigned to the subject; alternatively, when the measured concentration is below the threshold, an improvement of renal function may be assigned to the subject. For a negative going marker, when the measured concentration is below the threshold, a worsening of renal function may be assigned to the subject; alternatively, when the measured concentration is above the threshold, an improvement of renal function may be assigned to the subject.

[0034] In other additional preferred monitoring embodiments, these methods comprise monitoring renal status in a subject at risk of an injury to renal function due to the pre-existence of one or more known risk factors for prerenal, intrinsic renal, or postrenal ARF, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the occurrence or nonoccurrence of a change in renal status in the subject. For example, the measured concentration(s) may be compared to a threshold value. For a positive going marker, when the measured concentration is above the threshold, a worsening of renal function may be assigned to the subject; alternatively, when the measured concentration is below the threshold, an improvement of renal function may be assigned to the subject. For a negative going marker, when the measured concentration is below the threshold, a worsening of renal function may be assigned to the subject; alternatively, when the measured concentration is above the threshold, an improvement of renal function may be assigned to the subject.

[0035] In yet other preferred monitoring embodiments, these methods comprise monitoring renal status in a subject having, or at risk of, an injury to renal function for future persistence of acute kidney injury. "Future persistence" as used herein refers to an existing acute renal injury that will continue for a period selected from the group consisting of 21 days, 14 days, 7 days, 5 days, 96 hours, 72 hours, 48 hours, 36 hours, 24 hours, and 12 hours. In certain embodiments the subject has an acute kidney injury at the time the sample is obtained. This is not meant to imply that the subject must have an acute kidney injury at the time the sample is obtained, but rather that the subject, upon onset of an acute kidney injury, suffers from an acute kidney injury that will persist. In various embodiments, the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the future persistence of the acute kidney injury in the subject. For example, the measured concentration(s) may be compared to a threshold value. For a positive going marker, when the measured concentration is above the threshold, a future persistence of acute kidney injury may be assigned to the subject; alternatively, when the measured concentration is below the threshold, afuture improvement of renal function may be assigned to the subject. For a negative going marker, when the measured concentration is below the threshold, a future persistence of acute kidney injury may be assigned to the subject; alternatively, when the measured concentration is above the threshold, a future improvement of renal function may be assigned to the subject.

[0036] In still other embodiments, the methods for evaluating renal status described herein are methods for classifying a renal injury in the subject; that is, determining whether a renal injury in a subject is prerenal, intrinsic renal, or postrenal; and/or further subdividing these classes into subclasses such as acute tubular injury, acute glomerulonephritis acute tubulointerstitial nephritis, acute vascular nephropathy, or infiltrative disease; and/or assigning a likelihood that a subject will progress to a particular RIFLE stage. In these embodiments, the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to a particular class and/or subclass. The following are preferred classification embodiments.

[0037] In preferred classification embodiments, these methods comprise determining whether a renal injury in a subject is prerenal, intrinsic renal, or postrenal; and/or further

subdividing these classes into subclasses such as acute tubular injury, acute glomerulonephritis acute tubulointerstitial nephritis, acute vascular nephropathy, or infiltrative disease; and/or assigning a likelihood that a subject will progress to a particular RIFLE stage, and the assay result(s), for example a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and/or Tenascin, is/are correlated to the injury classification for the subject. For example, the measured concentration may be compared to a threshold value, and when the measured concentration is above the threshold, a particular classification is assigned; alternatively, when the measured concentration is below the threshold, a different classification may be assigned to the subject.

[0038] A variety of methods may be used by the skilled artisan to arrive at a desired threshold value for use in these methods. For example, the threshold value may be determined from a population of normal subjects by selecting a concentration representing the 75th, 85th, 90th, 95th, or 99th percentile of a kidney injury marker measured in such normal subjects. Alternatively, the threshold value may be determined from a "diseased" population of subjects, e.g., those suffering from an injury or having a predisposition for an injury (e.g., progression to ARF or some other clinical outcome such as death, dialysis, renal transplantation, *etc.*), by selecting a concentration representing the 75th, 85th, 90th, 95th, or 99th percentile of a kidney injury marker measured in such subjects. In another alternative, the threshold value may be determined from a prior measurement of a kidney injury marker in the same subject; that is, a temporal change in the level of a kidney injury marker in the subject may be used to assign risk to the subject.

[0039] The foregoing discussion is not meant to imply, however, that the kidney injury markers of the present invention must be compared to corresponding individual thresholds. Methods for combining assay results can comprise the use of multivariate logistical regression, loglinear modeling, neural network analysis, n-of-m analysis, decision tree analysis, calculating ratios of markers, *etc*. This list is not meant to be limiting. In these methods, a composite result which is determined by combining individual markers may be treated as if it is itself a marker; that is, a threshold may be determined for the composite result as described herein for individual markers, and the composite result for an individual patient compared to this threshold.

[0040] The ability of a particular test to distinguish two populations can be established using ROC analysis. For example, ROC curves established from a "first"

subpopulation which is predisposed to one or more future changes in renal status, and a "second" subpopulation which is not so predisposed can be used to calculate a ROC curve, and the area under the curve provides a measure of the quality of the test. Preferably, the tests described herein provide a ROC curve area greater than 0.5, preferably at least 0.6, more preferably 0.7, still more preferably at least 0.8, even more preferably at least 0.9, and most preferably at least 0.95.

[0041] In certain aspects, the measured concentration of one or more kidney injury markers, or a composite of such markers, may be treated as continuous variables. For example, any particular concentration can be converted into a corresponding probability of a future reduction in renal function for the subject, the occurrence of an injury, a classification, etc. In yet another alternative, a threshold that can provide an acceptable level of specificity and sensitivity in separating a population of subjects into "bins" such as a "first" subpopulation (e.g., which is predisposed to one or more future changes in renal status, the occurrence of an injury, a classification, etc.) and a "second" subpopulation which is not so predisposed. A threshold value is selected to separate this first and second population by one or more of the following measures of test accuracy:

an odds ratio greater than 1, preferably at least about 2 or more or about 0.5 or less, more preferably at least about 3 or more or about 0.33 or less, still more preferably at least about 4 or more or about 0.25 or less, even more preferably at least about 5 or more or about 0.2 or less, and most preferably at least about 10 or more or about 0.1 or less;

a specificity of greater than 0.5, preferably at least about 0.6, more preferably at least about 0.7, still more preferably at least about 0.8, even more preferably at least about 0.9 and most preferably at least about 0.95, with a corresponding sensitivity greater than 0.2, preferably greater than about 0.3, more preferably greater than about 0.4, still more preferably at least about 0.5, even more preferably about 0.6, yet more preferably greater than about 0.7, still more preferably greater than about 0.8, more preferably greater than about 0.9, and most preferably greater than about 0.95;

a sensitivity of greater than 0.5, preferably at least about 0.6, more preferably at least about 0.7, still more preferably at least about 0.8, even more preferably at least about 0.9 and most preferably at least about 0.95, with a corresponding specificity greater than 0.2, preferably greater than about 0.3, more preferably greater than about 0.4, still more preferably at least about 0.5, even more preferably about 0.6, yet more preferably greater

than about 0.7, still more preferably greater than about 0.8, more preferably greater than about 0.9, and most preferably greater than about 0.95;

at least about 75% sensitivity, combined with at least about 75% specificity;

a positive likelihood ratio (calculated as sensitivity/(1-specificity)) of greater than 1, at least about 2, more preferably at least about 3, still more preferably at least about 5, and most preferably at least about 10; or

a negative likelihood ratio (calculated as (1-sensitivity)/specificity) of less than 1, less than or equal to about 0.5, more preferably less than or equal to about 0.3, and most preferably less than or equal to about 0.1.

The term "about" in the context of any of the above measurements refers to +/- 5% of a given measurement.

[0042] Multiple thresholds may also be used to assess renal status in a subject. For example, a "first" subpopulation which is predisposed to one or more future changes in renal status, the occurrence of an injury, a classification, etc., and a "second" subpopulation which is not so predisposed can be combined into a single group. This group is then subdivided into three or more equal parts (known as tertiles, quartiles, quintiles, etc., depending on the number of subdivisions). An odds ratio is assigned to subjects based on which subdivision they fall into. If one considers a tertile, the lowest or highest tertile can be used as a reference for comparison of the other subdivisions. This reference subdivision is assigned an odds ratio of 1. The second tertile is assigned an odds ratio that is relative to that first tertile. That is, someone in the second tertile might be 3 times more likely to suffer one or more future changes in renal status in comparison to someone in the first tertile. The third tertile is also assigned an odds ratio that is relative to that first tertile.

[0043] In certain embodiments, the assay method is an immunoassay. Antibodies for use in such assays will specifically bind a full length kidney injury marker of interest, and may also bind one or more polypeptides that are "related" thereto, as that term is defined hereinafter. Numerous immunoassay formats are known to those of skill in the art. Preferred body fluid samples are selected from the group consisting of urine, blood, serum, saliva, tears, and plasma.

[0044] The foregoing method steps should not be interpreted to mean that the kidney injury marker assay result(s) is/are used in isolation in the methods described herein.

Rather, additional variables or other clinical indicia may be included in the methods described herein. For example, a risk stratification, diagnostic, classification, monitoring, etc. method may combine the assay result(s) with one or more variables measured for the subject selected from the group consisting of demographic information (e.g., weight, sex, age, race), medical history (e.g., family history, type of surgery, pre-existing disease such as aneurism, congestive heart failure, preeclampsia, eclampsia, diabetes mellitus, hypertension, coronary artery disease, proteinuria, renal insufficiency, or sepsis, type of toxin exposure such as NSAIDs, cyclosporines, tacrolimus, aminoglycosides, foscarnet, ethylene glycol, hemoglobin, myoglobin, ifosfamide, heavy metals, methotrexate, radiopaque contrast agents, or streptozotocin), clinical variables (e.g., blood pressure, temperature, respiration rate), risk scores (APACHE score, PREDICT score, TIMI Risk Score for UA/NSTEMI, Framingham Risk Score), a glomerular filtration rate, an estimated glomerular filtration rate, a urine production rate, a serum or plasma creatinine concentration, a urine creatinine concentration, a fractional excretion of sodium, a urine sodium concentration, a urine creatinine to serum or plasma creatinine ratio, a urine specific gravity, a urine osmolality, a urine urea nitrogen to plasma urea nitrogen ratio, a plasma BUN to creatnine ratio, a renal failure index calculated as urine sodium / (urine creatinine / plasma creatinine), a serum or plasma neutrophil gelatinase (NGAL) concentration, a urine NGAL concentration, a serum or plasma cystatin C concentration, a serum or plasma cardiac troponin concentration, a serum or plasma BNP concentration, a serum or plasma NTproBNP concentration, and a serum or plasma proBNP concentration. Other measures of renal function which may be combined with one or more kidney injury marker assay result(s) are described hereinafter and in Harrison's Principles of Internal Medicine, 17th Ed., McGraw Hill, New York, pages 1741-1830, and Current Medical Diagnosis & Treatment 2008, 47th Ed, McGraw Hill, New York, pages 785-815, each of which are hereby incorporated by reference in their entirety.

[0045] When more than one marker is measured, the individual markers may be measured in samples obtained at the same time, or may be determined from samples obtained at different (e.g., an earlier or later) times. The individual markers may also be measured on the same or different body fluid samples. For example, one kidney injury marker may be measured in a serum or plasma sample and another kidney injury marker may be measured in a urine sample. In addition, assignment of a likelihood may combine

an individual kidney injury marker assay result with temporal changes in one or more additional variables.

[0046] In various related aspects, the present invention also relates to devices and kits for performing the methods described herein. Suitable kits comprise reagents sufficient for performing an assay for at least one of the described kidney injury markers, together with instructions for performing the described threshold comparisons.

[0047] In certain embodiments, reagents for performing such assays are provided in an assay device, and such assay devices may be included in such a kit. Preferred reagents can comprise one or more solid phase antibodies, the solid phase antibody comprising antibody that detects the intended biomarker target(s) bound to a solid support. In the case of sandwich immunoassays, such reagents can also include one or more detectably labeled antibodies, the detectably labeled antibody comprising antibody that detects the intended biomarker target(s) bound to a detectable label. Additional optional elements that may be provided as part of an assay device are described hereinafter.

[0048] Detectable labels may include molecules that are themselves detectable (e.g., fluorescent moieties, electrochemical labels, ecl (electrochemical luminescence) labels, metal chelates, colloidal metal particles, *etc.*) as well as molecules that may be indirectly detected by production of a detectable reaction product (*e.g.*, enzymes such as horseradish peroxidase, alkaline phosphatase, *etc.*) or through the use of a specific binding molecule which itself may be detectable (*e.g.*, a labeled antibody that binds to the second antibody, biotin, digoxigenin, maltose, oligohistidine, 2,4-dintrobenzene, phenylarsenate, ssDNA, dsDNA, *etc.*).

[0049] Generation of a signal from the signal development element can be performed using various optical, acoustical, and electrochemical methods well known in the art. Examples of detection modes include fluorescence, radiochemical detection, reflectance, absorbance, amperometry, conductance, impedance, interferometry, ellipsometry, *etc.* In certain of these methods, the solid phase antibody is coupled to a transducer (*e.g.*, a diffraction grating, electrochemical sensor, etc) for generation of a signal, while in others, a signal is generated by a transducer that is spatially separate from the solid phase antibody (*e.g.*, a fluorometer that employs an excitation light source and an optical detector). This list is not meant to be limiting. Antibody-based biosensors may

also be employed to determine the presence or amount of analytes that optionally eliminate the need for a labeled molecule.

DETAILED DESCRIPTION OF THE INVENTION

[0050] The present invention relates to methods and compositions for diagnosis, differential diagnosis, risk stratification, monitoring, classifying and determination of treatment regimens in subjects suffering or at risk of suffering from injury to renal function, reduced renal function and/or acute renal failure through measurement of one or more kidney injury markers. In various embodiments, a measured concentration of one or more markers selected from the group consisting of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin or one or more markers related thereto, and optionally one or more additional kidney injury markers known in the art, are correlated to the renal status of the subject.

[0051] For purposes of this document, the following definitions apply:

As used herein, an "injury to renal function" is an abrupt (within 14 days, preferably within 7 days, more preferably within 72 hours, and still more preferably within 48 hours) measurable reduction in a measure of renal function. Such an injury may be identified, for example, by a decrease in glomerular filtration rate or estimated GFR, a reduction in urine output, an increase in serum creatinine, an increase in serum cystatin C, a requirement for renal replacement therapy, *etc.* "Improvement in Renal Function" is an abrupt (within 14 days, preferably within 7 days, more preferably within 72 hours, and still more preferably within 48 hours) measurable increase in a measure of renal function. Preferred methods for measuring and/or estimating GFR are described hereinafter.

As used herein, "reduced renal function" is an abrupt (within 14 days, preferably within 7 days, more preferably within 72 hours, and still more preferably within 48 hours) reduction in kidney function identified by an absolute increase in serum creatinine of greater than or equal to 0.1 mg/dL ($\geq$ 8.8 μmol/L), a percentage increase in serum creatinine of greater than or equal to 20% (1.2-fold from baseline), or a reduction in urine output (documented oliguria of less than 0. 5 ml/kg per hour).

As used herein, "acute renal failure" or "ARF" is an abrupt (within 14 days, preferably within 7 days, more preferably within 72 hours, and still more preferably within 48 hours) reduction in kidney function identified by an absolute increase in serum creatinine of

greater than or equal to 0.3 mg/dl (≥ 26.4 μmol/l), a percentage increase in serum creatinine of greater than or equal to 50% (1. 5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for at least 6 hours). This term is synonymous with "acute kidney injury" or "AKI."

[0052] In this regard, the skilled artisan will understand that the signals obtained from an immunoassay are a direct result of complexes formed between one or more antibodies and the target biomolecule (*i.e.*, the analyte) and polypeptides containing the necessary epitope(s) to which the antibodies bind. While such assays may detect the full length biomarker and the assay result be expressed as a concentration of a biomarker of interest, the signal from the assay is actually a result of all such "immunoreactive" polypeptides present in the sample. Expression of biomarkers may also be determined by means other than immunoassays, including protein measurements (such as dot blots, western blots, chromatographic methods, mass spectrometry, *etc.*) and nucleic acid measurements (mRNA quatitation). This list is not meant to be limiting.

[0053] As used herein, the term "Follistatin-related protein 3" refers to one or more polypeptides present in a biological sample that are derived from a Follistatin-related protein 3 precursor (human precursor Swiss-Prot entry O95633 (SEQ ID NO: 1)):

```
         10          20          30          40          50
MRPGAPGPLW PLPWGALAWA VGFVSSMGSG NPAPGGVCWL QQGQEATCSL
         60          70          80          90         100
VLQTDVTRAE CCASGNIDTA WSNLTHPGNK INLLGFLGLV HCLPCKDSCD
        110         120         130         140         150
GVECGPGKAC RMLGGRPRCE CAPDCSGLPA RLQVCGSDGA TYRDECELRA
        160         170         180         190         200
ARCRGHPDLS VMYRGRCRKS CEHVVCPRPQ SCVVDQTGSA HCVVCRAAPC
        210         220         230         240         250
PVPSSPGQEL CGNNNVTYIS SCHMRQATCF LGRSIGVRHA GSCAGTPEEP
        260
PGGESAEEEE NFV
```

[0054] The following domains have been identified in Follistatin-related protein 3:

Residues	Length	Domain ID
1-26	26	signal sequence
27-263	237	Follistatin-related protein 3
1-26		missing in Follistatin-related protein 3 Isoform 2

[0055] As used herein, the term "Cathepsin B" refers to one or more polypeptides present in a biological sample that are derived from a Cathepsin B precursor (human precursor Swiss-Prot entry P07858 (SEQ ID NO: 2)):

```
         10         20         30         40         50
MWQLWASLCC LLVLANARSR PSFHPLSDEL VNYVNKRNTT WQAGHNFYNV
         60         70         80         90        100
DMSYLKRLCG TFLGGPKPPQ RVMFTEDLKL PASFDAREQW PQCPTIKEIR
        110        120        130        140        150
DQGSCGSCWA FGAVEAISDR ICIHTNAHVS VEVSAEDLLT CCGSMCGDGC
        160        170        180        190        200
NGGYPAEAWN FWTRKGLVSG GLYESHVGCR PYSIPPCEHH VNGSRPPCTG
        210        220        230        240        250
EGDTPKCSKI CEPGYSPTYK QDKHYGYNSY SVSNSEKDIM AEIYKNGPVE
        260        270        280        290        300
GAFSVYSDFL LYKSGVYQHV TGEMMGGHAI RILGWGVENG TPYWLVANSW
        310        320        330
NTDWGDNGFF KILRGQDHCG IESEVVAGIP RTDQYWEKI
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[0056] The following domains have been identified in Cathepsin B:

Residues	Length	Domain ID
1-17	17	signal sequence
18-79	62	activation peptide
80-333	254	Cathepsin B
80-126-	47	Cathepsin B light chain
129-333	205	Cathepsin B heavy chain
334-339	6	propeptide

[0057] As used herein, the term "Tenascin" refers to one or more polypeptides present in a biological sample that are derived from a Tenascin precursor (human precursor Swiss-Prot entry P24821 (SEQ ID NO: 3)):

```
         10         20         30         40         50
MGAMTQLLAG VFLAFLALAT EGGVLKKVIR HKRQSGVNAT LPEENQPVVF
         60         70         80         90        100
NHVYNIKLPV GSQCSVDLES ASGEKDLAPP SEPSESFQEH TVDGENQIVF
        110        120        130        140        150
THRINIPRRA CGCAAAPDVK ELLSRLEELE NLVSSLREQC TAGAGCCLQP
        160        170        180        190        200
ATGRLDTRPF CSGRGNFSTE GCGCVCEPGW KGPNCSEPEC PGNCHLRGRC
        210        220        230        240        250
IDGQCICDDG FTGEDCSQLA CPSDCNDQGK CVNGVCICFE GYAGADCSRE
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       260         270         280         290         300
ICPVPCSEEH GTCVDGLCVC HDGFAGDDCN KPLCLNNCYN RGRCVENECV
       310         320         330         340         350
CDEGFTGEDC SELICPNDCF DRGRCINGTC YCEEGFTGED CGKPTCPHAC
       360         370         380         390         400
HTQGRCEEGQ CVCDEGFAGV DCSEKRCPAD CHNRGRCVDG RCECDDGFTG
       410         420         430         440         450
ADCGELKCPN GCSGHGRCVN GQCVCDEGYT GEDCSQLRCP NDCHSRGRCV
       460         470         480         490         500
EGKCVCEQGF KGYDCSDMSC PNDCHQHGRC VNGMCVCDDG YTGEDCRDRQ
       510         520         530         540         550
CPRDCSNRGL CVDGQCVCED GFTGPDCAEL SCPNDCHGQG RCVNGQCVCH
       560         570         580         590         600
EGFMGKDCKE QRCPSDCHGQ GRCVDGQCIC HEGFTGLDCG QHSCPSDCNN
       610         620         630         640         650
LGQCVSGRCI CNEGYSGEDC SEVSPPKDLV VTEVTEETVN LAWDNEMRVT
       660         670         680         690         700
EYLVVYTPTH EGGLEMQFRV PGDQTSTIIQ ELEPGVEYFI RVFAILENKK
       710         720         730         740         750
SIPVSARVAT YLPAPEGLKF KSIKETSVEV EWDPLDIAFE TWEIIFRNMN
       760         770         780         790         800
KEDEGEITKS LRRPETSYRQ TGLAPGQEYE ISLHIVKNNT RGPGLKRVTT
       810         820         830         840         850
TRLDAPSQIE VKDVTDTTAL ITWFKPLAEI DGIELTYGIK DVPGDRTTID
       860         870         880         890         900
LTEDENQYSI GNLKPDTEYE VSLISRRGDM SSNPAKETFT TGLDAPRNLR
       910         920         930         940         950
RVSQTDNSIT LEWRNGKAAI DSYRIKYAPI SGGDHAEVDV PKSQQATTKT
       960         970         980         990        1000
TLTGLRPGTE YGIGVSAVKE DKESNPATIN AATELDTPKD LQVSETAETS
      1010        1020        1030        1040        1050
LTLLWKTPLA KFDRYRLNYS LPTGQWVGVQ LPRNTTSYVL RGLEPGQEYN
      1060        1070        1080        1090        1100
VLLTAEKGRH KSKPARVKAS TEQAPELENL TVTEVGWDGL RLNWTAADQA
      1110        1120        1130        1140        1150
YEHFIIQVQE ANKVEAARNL TVPGSLRAVD IPGLKAATPY TVSIYGVIQG
      1160        1170        1180        1190        1200
YRTPVLSAEA STGETPNLGE VVVAEVGWDA LKLNWTAPEG AYEYFFIQVQ
      1210        1220        1230        1240        1250
EADTVEAAQN LTVPGGLRST DLPGLKAATH YTITIRGVTQ DFSTTPLSVE
      1260        1270        1280        1290        1300
VLTEEVPDMG NLTVTEVSWD ALRLNWTTPD GTYDQFTIQV QEADQVEEAH
      1310        1320        1330        1340        1350
NLTVPGSLRS MEIPGLRAGT PYTVTLHGEV RGHSTRPLAV EVVTEDLPQL
      1360        1370        1380        1390        1400
GDLAVSEVGW DGLRLNWTAA DNAYEHFVIQ VQEVNKVEAA QNLTLPGSLR
      1410        1420        1430        1440        1450
AVDIPGLEAA TPYRVSIYGV IRGYRTPVLS AEASTAKEPE IGNLNVSDIT
      1460        1470        1480        1490        1500
PESFNLSWMA TDGIFETFTI EIIDSNRLLE TVEYNISGAE RTAHISGLPP
      1510        1520        1530        1540        1550
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STDFIVYLSG LAPSIRTKTI SATATTEALP LLENLTISDI NPYGFTVSWM
      1560       1570       1580       1590       1600
ASENAFDSFL VTVVDSGKLL DPQEFTLSGT QRKLELRGLI TGIGYEVMVS
      1610       1620       1630       1640       1650
GFTQGHQTKP LRAEIVTEAE PEVDNLLVSD ATPDGFRLSW TADEGVFDNF
      1660       1670       1680       1690       1700
VLKIRDTKKQ SEPLEITLLA PERTRDITGL REATEYEIEL YGISKGRRSQ
      1710       1720       1730       1740       1750
TVSAIATTAM GSPKEVIFSD ITENSATVSW RAPTAQVESF RITYVPITGG
      1760       1770       1780       1790       1800
TPSMVTVDGT KTQTRLVKLI PGVEYLVSII AMKGFEESEP VSGSFTTALD
      1810       1820       1830       1840       1850
GPSGLVTANI TDSEALARWQ PAIATVDSYV ISYTGEKVPE ITRTVSGNTV
      1860       1870       1880       1890       1900
EYALTDLEPA TEYTLRIFAE KGPQKSSTIT AKFTTDLDSP RDLTATEVQS
      1910       1920       1930       1940       1950
ETALLTWRPP RASVTGYLLV YESVDGTVKE VIVGPDTTSY SLADLSPSTH
      1960       1970       1980       1990       2000
YTAKIQALNG PLRSNMIQTI FTTIGLLYPF PKDCSQAMLN GDTTSGLYTI
      2010       2020       2030       2040       2050
YLNGDKAEAL EVFCDMTSDG GGWIVFLRRK NGRENFYQNW KAYAAGFGDR
      2060       2070       2080       2090       2100
REEFWLGLDN LNKITAQGQY ELRVDLRDHG ETAFAVYDKF SVGDAKTRYK
      2110       2120       2130       2140       2150
LKVEGYSGTA GDSMAYHNGR SFSTFDKDTD SAITNCALSY KGAFWYRNCH
      2160       2170       2180       2190       2200
RVNLMGRYGD NNHSQGVNWF HWKGHEHSIQ FAEMKLRPSN FRNLEGRRKR

A
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[0058] The following domains have been identified in Tenascin:

Residues	Length	Domain ID
1-22	22	signal sequence
23-2201	2179	Tenascin
1072-1435		missing in Tenascin Isoform 2
1527-1617		missing in Tenascin Isoform 2
1072-1435		missing in Tenascin isoform 3
1527-1617		missing in Tenascin isoform 4
1072-1617		missing in Tenascin isoform 5
1072-1708		missing in Tenascin isoform 6

[0059] As used herein, the term "Basigin" refers to one or more polypeptides present in a biological sample that are derived from a Basigin precursor (human precursor Swiss-Prot entry P35613 (SEQ ID NO: 4)):

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         10          20          30          40          50
MAAALFVLLG FALLGTHGAS GAAGFVQAPL SQQRWVGGSV ELHCEAVGSP
         60          70          80          90         100
VPEIQWWFEG QGPNDTCSQL WDGARLDRVH IHATYHQHAA STISIDTLVE
        110         120         130         140         150
EDTGTYECRA SNDPDRNHLT RAPRVKWVRA QAVVLVLEPG TVFTTVEDLG
        160         170         180         190         200
SKILLTCSLN DSATEVTGHR WLKGGVVLKE DALPGQKTEF KVDSDDQWGE
        210         220         230         240         250
YSCVFLPEPM GTANIQLHGP PRVKAVKSSE HINEGETAML VCKSESVPPV
        260         270         280         290         300
TDWAWYKITD SEDKALMNGS ESRFFVSSSQ GRSELHIENL NMEADPGQYR
        310         320         330         340         350
CNGTSSKGSD QAIITLRVRS HLAALWPFLG IVAEVLVLVT IIFIYEKRRK
        360         370         380
PEDVLDDDDA GSAPLKSSGQ HQNDKGKNVR QRNSS
```

[0060] The following domains have been identified in Basigin:

Residues	Length	Domain ID
1-21	21	signal sequence
22-385	364	Basigin
24-139		missing in Basigin Isoform 2
1-209		missing in Basigin Isoform 3
12-191		missing in Basigin Isoform 4
1-11		→ MKQSDASPQER (SEQ ID NO: 5) in Basigin Isoform 4

[0061] As used herein, the term "relating a signal to the presence or amount" of an analyte reflects this understanding. Assay signals are typically related to the presence or amount of an analyte through the use of a standard curve calculated using known concentrations of the analyte of interest. As the term is used herein, an assay is "configured to detect" an analyte if an assay can generate a detectable signal indicative of the presence or amount of a physiologically relevant concentration of the analyte. Because an antibody epitope is on the order of 8 amino acids, an immunoassay configured to detect a marker of interest will also detect polypeptides related to the

marker sequence, so long as those polypeptides contain the epitope(s) necessary to bind to the antibody or antibodies used in the assay.

[0062] The term "related marker" as used herein with regard to a biomarker such as one of the kidney injury markers described herein refers to one or more fragments, variants, etc., of a particular marker or its biosynthetic parent that may be detected as a surrogate for the marker itself or as independent biomarkers. The term also refers to one or more polypeptides present in a biological sample that are derived from the biomarker precursor complexed to additional species, such as binding proteins, receptors, heparin, lipids, sugars, *etc*.

[0063] The term "positive going" marker as that term is used herein refer to a marker that is determined to be elevated in subjects suffering from a disease or condition, relative to subjects not suffering from that disease or condition. The term "negative going" marker as that term is used herein refer to a marker that is determined to be reduced in subjects suffering from a disease or condition, relative to subjects not suffering from that disease or condition.

[0064] The term "subject" as used herein refers to a human or non-human organism. Thus, the methods and compositions described herein are applicable to both human and veterinary disease. Further, while a subject is preferably a living organism, the invention described herein may be used in post-mortem analysis as well. Preferred subjects are humans, and most preferably "patients," which as used herein refers to living humans that are receiving medical care for a disease or condition. This includes persons with no defined illness who are being investigated for signs of pathology.

[0065] Preferably, an analyte is measured in a sample. Such a sample may be obtained from a subject, or may be obtained from biological materials intended to be provided to the subject. For example, a sample may be obtained from a kidney being evaluated for possible transplantation into a subject, and an analyte measurement used to evaluate the kidney for preexisting damage. Preferred samples are body fluid samples.

[0066] The term "body fluid sample" as used herein refers to a sample of bodily fluid obtained for the purpose of diagnosis, prognosis, classification or evaluation of a subject of interest, such as a patient or transplant donor. In certain embodiments, such a sample may be obtained for the purpose of determining the outcome of an ongoing condition or the effect of a treatment regimen on a condition. Preferred body fluid samples include

blood, serum, plasma, cerebrospinal fluid, urine, saliva, sputum, and pleural effusions. In addition, one of skill in the art would realize that certain body fluid samples would be more readily analyzed following a fractionation or purification procedure, for example, separation of whole blood into serum or plasma components.

[0067] The term "diagnosis" as used herein refers to methods by which the skilled artisan can estimate and/or determine the probability ("a likelihood") of whether or not a patient is suffering from a given disease or condition. In the case of the present invention, "diagnosis" includes using the results of an assay, most preferably an immunoassay, for a kidney injury marker of the present invention, optionally together with other clinical characteristics, to arrive at a diagnosis (that is, the occurrence or nonoccurrence) of an acute renal injury or ARF for the subject from which a sample was obtained and assayed. That such a diagnosis is "determined" is not meant to imply that the diagnosis is 100% accurate. Many biomarkers are indicative of multiple conditions. The skilled clinician does not use biomarker results in an informational vacuum, but rather test results are used together with other clinical indicia to arrive at a diagnosis. Thus, a measured biomarker level on one side of a predetermined diagnostic threshold indicates a greater likelihood of the occurrence of disease in the subject relative to a measured level on the other side of the predetermined diagnostic threshold.

[0068] Similarly, a prognostic risk signals a probability ("a likelihood") that a given course or outcome will occur. A level or a change in level of a prognostic indicator, which in turn is associated with an increased probability of morbidity (e.g., worsening renal function, future ARF, or death) is referred to as being "indicative of an increased likelihood" of an adverse outcome in a patient.

[0069] Marker Assays

[0070] In general, immunoassays involve contacting a sample containing or suspected of containing a biomarker of interest with at least one antibody that specifically binds to the biomarker. A signal is then generated indicative of the presence or amount of complexes formed by the binding of polypeptides in the sample to the antibody. The signal is then related to the presence or amount of the biomarker in the sample. Numerous methods and devices are well known to the skilled artisan for the detection and analysis of biomarkers. *See, e.g.*, U.S. Patents 6,143,576; 6,113,855; 6,019,944; 5,985,579; 5,947,124; 5,939,272; 5,922,615; 5,885,527; 5,851,776; 5,824,799; 5,679,526; 5,525,524;

and 5,480,792, and *The Immunoassay Handbook*, David Wild, ed. Stockton Press, New York, 1994, each of which is hereby incorporated by reference in its entirety, including all tables, figures and claims.

[0071] The assay devices and methods known in the art can utilize labeled molecules in various sandwich, competitive, or non-competitive assay formats, to generate a signal that is related to the presence or amount of the biomarker of interest. Suitable assay formats also include chromatographic, mass spectrographic, and protein "blotting" methods. Additionally, certain methods and devices, such as biosensors and optical immunoassays, may be employed to determine the presence or amount of analytes without the need for a labeled molecule. *See, e.g.*, U.S. Patents 5,631,171; and 5,955,377, each of which is hereby incorporated by reference in its entirety, including all tables, figures and claims. One skilled in the art also recognizes that robotic instrumentation including but not limited to Beckman ACCESS®, Abbott AXSYM®, Roche ELECSYS®, Dade Behring STRATUS® systems are among the immunoassay analyzers that are capable of performing immunoassays. But any suitable immunoassay may be utilized, for example, enzyme-linked immunoassays (ELISA), radioimmunoassays (RIAs), competitive binding assays, and the like.

[0072] Antibodies or other polypeptides may be immobilized onto a variety of solid supports for use in assays. Solid phases that may be used to immobilize specific binding members include include those developed and/or used as solid phases in solid phase binding assays. Examples of suitable solid phases include membrane filters, cellulose-based papers, beads (including polymeric, latex and paramagnetic particles), glass, silicon wafers, microparticles, nanoparticles, TentaGels, AgroGels, PEGA gels, SPOCC gels, and multiple-well plates. An assay strip could be prepared by coating the antibody or a plurality of antibodies in an array on solid support. This strip could then be dipped into the test sample and then processed quickly through washes and detection steps to generate a measurable signal, such as a colored spot. Antibodies or other polypeptides may be bound to specific zones of assay devices either by conjugating directly to an assay device surface, or by indirect binding. In an example of the later case, antibodies or other polypeptides may be immobilized on particles or other solid supports, and that solid support immobilized to the device surface.

[0073] Biological assays require methods for detection, and one of the most common methods for quantitation of results is to conjugate a detectable label to a protein or nucleic

acid that has affinity for one of the components in the biological system being studied. Detectable labels may include molecules that are themselves detectable (*e.g.*, fluorescent moieties, electrochemical labels, metal chelates, *etc.*) as well as molecules that may be indirectly detected by production of a detectable reaction product (*e.g.*, enzymes such as horseradish peroxidase, alkaline phosphatase, *etc.*) or by a specific binding molecule which itself may be detectable (e.g., biotin, digoxigenin, maltose, oligohistidine, 2,4-dintrobenzene, phenylarsenate, ssDNA, dsDNA, etc.).

[0074] Preparation of solid phases and detectable label conjugates often comprise the use of chemical cross-linkers. Cross-linking reagents contain at least two reactive groups, and are divided generally into homofunctional cross-linkers (containing identical reactive groups) and heterofunctional cross-linkers (containing non-identical reactive groups). Homobifunctional cross-linkers that couple through amines, sulfhydryls or react non-specifically are available from many commercial sources. Maleimides, alkyl and aryl halides, alpha-haloacyls and pyridyl disulfides are thiol reactive groups. Maleimides, alkyl and aryl halides, and alpha-haloacyls react with sulfhydryls to form thiol ether bonds, while pyridyl disulfides react with sulfhydryls to produce mixed disulfides. The pyridyl disulfide product is cleavable. Imidoesters are also very useful for protein-protein cross-links. A variety of heterobifunctional cross-linkers, each combining different attributes for successful conjugation, are commercially available.

[0075] In certain aspects, the present invention provides kits for the analysis of the described kidney injury markers. The kit comprises reagents for the analysis of at least one test sample which comprise at least one antibody that a kidney injury marker. The kit can also include devices and instructions for performing one or more of the diagnostic and/or prognostic correlations described herein. Preferred kits will comprise an antibody pair for performing a sandwich assay, or a labeled species for performing a competitive assay, for the analyte. Preferably, an antibody pair comprises a first antibody conjugated to a solid phase and a second antibody conjugated to a detectable label, wherein each of the first and second antibodies that bind a kidney injury marker. Most preferably each of the antibodies are monoclonal antibodies. The instructions for use of the kit and performing the correlations can be in the form of labeling, which refers to any written or recorded material that is attached to, or otherwise accompanies a kit at any time during its manufacture, transport, sale or use. For example, the term labeling encompasses

advertising leaflets and brochures, packaging materials, instructions, audio or video cassettes, computer discs, as well as writing imprinted directly on kits.

[0076] Antibodies

[0077] The term "antibody" as used herein refers to a peptide or polypeptide derived from, modeled after or substantially encoded by an immunoglobulin gene or immunoglobulin genes, or fragments thereof, capable of specifically binding an antigen or epitope. *See, e.g.* Fundamental Immunology, 3rd Edition, W.E. Paul, ed., Raven Press, N.Y. (1993); Wilson (1994; J. Immunol. Methods 175:267-273; Yarmush (1992) J. Biochem. Biophys. Methods 25:85-97. The term antibody includes antigen-binding portions, i.e., "antigen binding sites," (e.g., fragments, subsequences, complementarity determining regions (CDRs)) that retain capacity to bind antigen, including (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CHl domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CHl domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Single chain antibodies are also included by reference in the term "antibody."

[0078] Antibodies used in the immunoassays described herein preferably specifically bind to a kidney injury marker of the present invention. The term "specifically binds" is not intended to indicate that an antibody binds exclusively to its intended target since, as noted above, an antibody binds to any polypeptide displaying the epitope(s) to which the antibody binds. Rather, an antibody "specifically binds" if its affinity for its intended target is about 5-fold greater when compared to its affinity for a non-target molecule which does not display the appropriate epitope(s). Preferably the affinity of the antibody will be at least about 5 fold, preferably 10 fold, more preferably 25-fold, even more preferably 50-fold, and most preferably 100-fold or more, greater for a target molecule than its affinity for a non-target molecule. In preferred embodiments, Preferred antibodies bind with affinities of at least about 10^7 M^{-1}, and preferably between about 10^8 M^{-1} to about 10^9 M^{-1}, about 10^9 M^{-1} to about 10^{10} M^{-1}, or about 10^{10} M^{-1} to about 10^{12} M^{-1} .

[0079] Affinity is calculated as $K_d = k_{off}/k_{on}$ (k_{off} is the dissociation rate constant, K_{on} is the association rate constant and K_d is the equilibrium constant). Affinity can be

determined at equilibrium by measuring the fraction bound (r) of labeled ligand at various concentrations (c). The data are graphed using the Scatchard equation: r/c = K(n-r): where r = moles of bound ligand/mole of receptor at equilibrium; c = free ligand concentration at equilibrium; K = equilibrium association constant; and n = number of ligand binding sites per receptor molecule. By graphical analysis, r/c is plotted on the Y-axis versus r on the X-axis, thus producing a Scatchard plot. Antibody affinity measurement by Scatchard analysis is well known in the art. *See, e.g.*, van Erp *et al., J. Immunoassay* 12: 425-43, 1991; Nelson and Griswold, *Comput. Methods Programs Biomed.* 27: 65-8, 1988.

[0080] The term "epitope" refers to an antigenic determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and nonconformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

[0081] Numerous publications discuss the use of phage display technology to produce and screen libraries of polypeptides for binding to a selected analyte. *See, e.g*, Cwirla *et al., Proc. Natl. Acad. Sci. USA* 87, 6378-82, 1990; Devlin *et al., Science* 249, 404-6, 1990, Scott and Smith, *Science* 249, 386-88, 1990; and Ladner *et al.*, U.S. Pat. No. 5,571,698. A basic concept of phage display methods is the establishment of a physical association between DNA encoding a polypeptide to be screened and the polypeptide. This physical association is provided by the phage particle, which displays a polypeptide as part of a capsid enclosing the phage genome which encodes the polypeptide. The establishment of a physical association between polypeptides and their genetic material allows simultaneous mass screening of very large numbers of phage bearing different polypeptides. Phage displaying a polypeptide with affinity to a target bind to the target and these phage are enriched by affinity screening to the target. The identity of polypeptides displayed from these phage can be determined from their respective genomes. Using these methods a polypeptide identified as having a binding affinity for a desired target can then be synthesized in bulk by conventional means. *See, e.g.*, U.S. Patent No. 6,057,098, which is hereby incorporated in its entirety, including all tables, figures, and claims.

[0082] The antibodies that are generated by these methods may then be selected by first screening for affinity and specificity with the purified polypeptide of interest and, if

required, comparing the results to the affinity and specificity of the antibodies with polypeptides that are desired to be excluded from binding. The screening procedure can involve immobilization of the purified polypeptides in separate wells of microtiter plates. The solution containing a potential antibody or groups of antibodies is then placed into the respective microtiter wells and incubated for about 30 min to 2 h. The microtiter wells are then washed and a labeled secondary antibody (for example, an anti-mouse antibody conjugated to alkaline phosphatase if the raised antibodies are mouse antibodies) is added to the wells and incubated for about 30 min and then washed. Substrate is added to the wells and a color reaction will appear where antibody to the immobilized polypeptide(s) are present.

[0083] The antibodies so identified may then be further analyzed for affinity and specificity in the assay design selected. In the development of immunoassays for a target protein, the purified target protein acts as a standard with which to judge the sensitivity and specificity of the immunoassay using the antibodies that have been selected. Because the binding affinity of various antibodies may differ; certain antibody pairs (*e.g.*, in sandwich assays) may interfere with one another sterically, *etc.*, assay performance of an antibody may be a more important measure than absolute affinity and specificity of an antibody.

[0084] Assay Correlations

[0085] The term "correlating" as used herein in reference to the use of biomarkers refers to comparing the presence or amount of the biomarker(s) in a patient to its presence or amount in persons known to suffer from, or known to be at risk of, a given condition; or in persons known to be free of a given condition. Often, this takes the form of comparing an assay result in the form of a biomarker concentration to a predetermined threshold selected to be indicative of the occurrence or nonoccurrence of a disease or the likelihood of some future outcome.

[0086] Selecting a diagnostic threshold involves, among other things, consideration of the probability of disease, distribution of true and false diagnoses at different test thresholds, and estimates of the consequences of treatment (or a failure to treat) based on the diagnosis. For example, when considering administering a specific therapy which is highly efficacious and has a low level of risk, few tests are needed because clinicians can accept substantial diagnostic uncertainty. On the other hand, in situations where treatment

options are less effective and more risky, clinicians often need a higher degree of diagnostic certainty. Thus, cost/benefit analysis is involved in selecting a diagnostic threshold.

[0087] Suitable thresholds may be determined in a variety of ways. For example, one recommended diagnostic threshold for the diagnosis of acute myocardial infarction using cardiac troponin is the 97.5th percentile of the concentration seen in a normal population. Another method may be to look at serial samples from the same patient, where a prior "baseline" result is used to monitor for temporal changes in a biomarker level.

[0088] Population studies may also be used to select a decision threshold. Reciever Operating Characteristic ("ROC") arose from the field of signal dectection therory developed during World War II for the analysis of radar images, and ROC analysis is often used to select a threshold able to best distinguish a "diseased" subpopulation from a "nondiseased" subpopulation. A false positive in this case occurs when the person tests positive, but actually does not have the disease. A false negative, on the other hand, occurs when the person tests negative, suggesting they are healthy, when they actually do have the disease. To draw a ROC curve, the true positive rate (TPR) and false positive rate (FPR) are determined as the decision threshold is varied continuously. Since TPR is equivalent with sensitivity and FPR is equal to 1 - specificity, the ROC graph is sometimes called the sensitivity vs (1 - specificity) plot. A perfect test will have an area under the ROC curve of 1.0; a random test will have an area of 0.5. A threshold is selected to provide an acceptable level of specificity and sensitivity.

[0089] In this context, "diseased" is meant to refer to a population having one characteristic (the presence of a disease or condition or the occurrence of some outcome) and "nondiseased" is meant to refer to a population lacking the characteristic. While a single decision threshold is the simplest application of such a method, multiple decision thresholds may be used. For example, below a first threshold, the absence of disease may be assigned with relatively high confidence, and above a second threshold the presence of disease may also be assigned with relatively high confidence. Between the two thresholds may be considered indeterminate. This is meant to be exemplary in nature only.

[0090] In addition to threshold comparisons, other methods for correlating assay results to a patient classification (occurrence or nonoccurrence of disease, likelihood of an outcome, *etc.*) include decision trees, rule sets, Bayesian methods, and neural network

methods. These methods can produce probability values representing the degree to which a subject belongs to one classification out of a plurality of classifications.

[0091] Measures of test accuracy may be obtained as described in Fischer *et al., Intensive Care Med.* 29: 1043-51, 2003, and used to determine the effectiveness of a given biomarker. These measures include sensitivity and specificity, predictive values, likelihood ratios, diagnostic odds ratios, and ROC curve areas. The area under the curve ("AUC") of a ROC plot is equal to the probability that a classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one. The area under the ROC curve may be thought of as equivalent to the Mann-Whitney U test, which tests for the median difference between scores obtained in the two groups considered if the groups are of continuous data, or to the Wilcoxon test of ranks.

[0092] As discussed above, suitable tests may exhibit one or more of the following results on these various measures: a specificity of greater than 0.5, preferably at least 0.6, more preferably at least 0.7, still more preferably at least 0.8, even more preferably at least 0.9 and most preferably at least 0.95, with a corresponding sensitivity greater than 0.2, preferably greater than 0.3, more preferably greater than 0.4, still more preferably at least 0.5, even more preferably 0.6, yet more preferably greater than 0.7, still more preferably greater than 0.8, more preferably greater than 0.9, and most preferably greater than 0.95; a sensitivity of greater than 0.5, preferably at least 0.6, more preferably at least 0.7, still more preferably at least 0.8, even more preferably at least 0.9 and most preferably at least 0.95, with a corresponding specificity greater than 0.2, preferably greater than 0.3, more preferably greater than 0.4, still more preferably at least 0.5, even more preferably 0.6, yet more preferably greater than 0.7, still more preferably greater than 0.8, more preferably greater than 0.9, and most preferably greater than 0.95; at least 75% sensitivity, combined with at least 75% specificity; a ROC curve area of greater than 0.5, preferably at least 0.6, more preferably 0.7, still more preferably at least 0.8, even more preferably at least 0.9, and most preferably at least 0.95; an odds ratio different from 1, preferably at least about 2 or more or about 0.5 or less, more preferably at least about 3 or more or about 0.33 or less, still more preferably at least about 4 or more or about 0.25 or less, even more preferably at least about 5 or more or about 0.2 or less, and most preferably at least about 10 or more or about 0.1 or less; a positive likelihood ratio (calculated as sensitivity/(1-specificity)) of greater than 1, at least 2, more preferably at least 3, still more preferably at least 5, and most preferably at least 10; and or a negative

likelihood ratio (calculated as (1-sensitivity)/specificity) of less than 1, less than or equal to 0.5, more preferably less than or equal to 0.3, and most preferably less than or equal to 0.1

[0093] Additional clinical indicia may be combined with the kidney injury marker assay result(s) of the present invention. These include other biomarkers related to renal status. Examples include the following, which recite the common biomarker name, followed by the Swiss-Prot entry number for that biomarker or its parent: Actin (P68133); Adenosine deaminase binding protein (DPP4, P27487); Alpha-1-acid glycoprotein 1 (P02763); Alpha-1-microglobulin (P02760); Albumin (P02768); Angiotensinogenase (Renin, P00797); Nidogen-1 (P07355); Beta-glucuronidase (P08236); B-2-microglobulin (P61769); Beta-galactosidase (P16278); BMP-7 (P18075); Brain natriuretic peptide (proBNP, BNP-32, NTproBNP; P16860); Calcium-binding protein Beta (S100-beta, P04271); Carbonic anhydrase 9 (Q16790); Casein Kinase 2 (P68400); Clusterin (P10909); Complement C3 (P01024); Cysteine-rich protein (CYR61, O00622); Cytochrome C (P99999); Epidermal growth factor (EGF, P01133); Endothelin-1 (P05305); Exosomal Fetuin-A (P02765); Fatty acid-binding protein, heart (FABP3, P05413); Fatty acid-binding protein, liver (P07148); Ferritin (light chain, P02792; heavy chain P02794); Fructose-1,6-biphosphatase (P09467); GRO-alpha (CXCL1, (P09341); Growth Hormone (P01241); Hepatocyte growth factor (P14210); Insulin-like growth factor I (P05019); Immunoglobulin G; Immunoglobulin Light Chains (Kappa and Lambda); Interferon gamma (P01308); Lysozyme (P61626); Interleukin-1alpha (P01583); Interleukin-2 (P60568); Interleukin-4 (P05112); Interleukin-9 (P15248); Interleukin-12p40 (P29460); Interleukin-13 (P35225); Interleukin-16 (Q14005); L1 cell adhesion molecule (P32004); Lactate dehydrogenase (P00338); Leucine Aminopeptidase (P28838); Meprin A-alpha subunit (Q16819); Meprin A-beta subunit (Q16820); Midkine (P21741); MIP2-alpha (CXCL2, P19875); MMP-2 (P08253); MMP-9 (P14780); Netrin-1 (O95631); Neutral endopeptidase (P08473); Osteopontin (O14788); Renal papillary antigen 1 (RPA1); Renal papillary antigen 2 (RPA2); Retinol binding protein (P09455); Ribonuclease; S100 calcium-binding protein A6 (P06703); Serum Amyloid P Component (P02743); Sodium/Hydrogen exchanger isoform (NHE3, P48764); Spermidine/spermine N1-acetyltransferase (P21673); TGF-Beta1 (P01137); Transferrin (P02787); Trefoil factor 3 (TFF3, Q07654); Toll-Like protein 4 (O00206); Total protein; Tubulointerstitial nephritis antigen (Q9UJW2); Uromodulin (Tamm-Horsfall protein, P07911).

[0094] For purposes of risk stratification, Adiponectin (Q15848); Alkaline phosphatase (P05186); Aminopeptidase N (P15144); CalbindinD28k (P05937); Cystatin C (P01034); 8 subunit of F1FO ATPase (P03928); Gamma-glutamyltransferase (P19440); GSTa (alpha-glutathione-S-transferase, P08263); GSTpi (Glutathione-S-transferase P; GST class-pi; P09211); IGFBP-1 (P08833); IGFBP-2 (P18065); IGFBP-6 (P24592); Integral membrane protein 1 (Itm1, P46977); Interleukin-6 (P05231); Interleukin-8 (P10145); Interleukin-18 (Q14116); IP-10 (10 kDa interferon-gamma-induced protein, P02778); IRPR (IFRD1, O00458); Isovaleryl-CoA dehydrogenase (IVD, P26440); I-TAC/CXCL11 (O14625); Keratin 19 (P08727); Kim-1 (Hepatitis A virus cellular receptor 1, O43656); L-arginine:glycine amidinotransferase (P50440); Leptin (P41159); Lipocalin2 (NGAL, P80188); MCP-1 (P13500); MIG (Gamma-interferon-induced monokine Q07325); MIP-1a (P10147); MIP-3a (P78556); MIP-1beta (P13236); MIP-1d (Q16663); NAG (N-acetyl-beta-D-glucosaminidase, P54802); Organic ion transporter (OCT2, O15244); Osteoprotegerin (O14788); P8 protein (O60356); Plasminogen activator inhibitor 1 (PAI-1, P05121); ProANP(1-98) (P01160); Protein phosphatase 1-beta (PPI-beta, P62140); Rab GDI-beta (P50395); Renal kallikrein (P06870); RT1.B-1 (alpha) chain of the integral membrane protein (Q5Y7A8); soluble tumor necrosis factor receptor superfamily member 1A (sTNFR-I, P19438); soluble tumor necrosis factor receptor superfamily member 1B (sTNFR-II, P20333); Tissue inhibitor of metalloproteinases 3 (TIMP-3, P35625); uPAR (Q03405) may be combined with the kidney injury marker assay result(s) of the present invention.

[0095] Other clinical indicia which may be combined with the kidney injury marker assay result(s) of the present invention includes demographic information (e.g., weight, sex, age, race), medical history (e.g., family history, type of surgery, pre-existing disease such as aneurism, congestive heart failure, preeclampsia, eclampsia, diabetes mellitus, hypertension, coronary artery disease, proteinuria, renal insufficiency, or sepsis, type of toxin exposure such as NSAIDs, cyclosporines, tacrolimus, aminoglycosides, foscarnet, ethylene glycol, hemoglobin, myoglobin, ifosfamide, heavy metals, methotrexate, radiopaque contrast agents, or streptozotocin), clinical variables (*e.g.*, blood pressure, temperature, respiration rate), risk scores (APACHE score, PREDICT score, TIMI Risk Score for UA/NSTEMI, Framingham Risk Score), a urine total protein measurement, a glomerular filtration rate, an estimated glomerular filtration rate, a urine production rate, a serum or plasma creatinine concentration, a renal papillary antigen 1 (RPA1)

measurement; a renal papillary antigen 2 (RPA2) measurement; a urine creatinine concentration, a fractional excretion of sodium, a urine sodium concentration, a urine creatinine to serum or plasma creatinine ratio, a urine specific gravity, a urine osmolality, a urine urea nitrogen to plasma urea nitrogen ratio, a plasma BUN to creatnine ratio, and/or a renal failure index calculated as urine sodium / (urine creatinine / plasma creatinine). Other measures of renal function which may be combined with the kidney injury marker assay result(s) are described hereinafter and in Harrison's Principles of Internal Medicine, 17th Ed., McGraw Hill, New York, pages 1741-1830, and Current Medical Diagnosis & Treatment 2008, 47th Ed, McGraw Hill, New York, pages 785-815, each of which are hereby incorporated by reference in their entirety.

[0096] Combining assay results/clinical indicia in this manner can comprise the use of multivariate logistical regression, loglinear modeling, neural network analysis, n-of-m analysis, decision tree analysis, etc. This list is not meant to be limiting.

[0097] Diagnosis of Acute Renal Failure

[0098] As noted above, the terms "acute renal (or kidney) injury" and "acute renal (or kidney) failure" as used herein are defined in part in terms of changes in serum creatinine from a baseline value. Most definitions of ARF have common elements, including the use of serum creatinine and, often, urine output. Patients may present with renal dysfunction without an available baseline measure of renal function for use in this comparison. In such an event, one may estimate a baseline serum creatinine value by assuming the patient initially had a normal GFR. Glomerular filtration rate (GFR) is the volume of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman's capsule per unit time. Glomerular filtration rate (GFR) can be calculated by measuring any chemical that has a steady level in the blood, and is freely filtered but neither reabsorbed nor secreted by the kidneys. GFR is typically expressed in units of ml/min:

$$GFR = \frac{\text{Urine Concentration} \times \text{Urine Flow}}{\text{Plasma Concentration}}$$

[0099] By normalizing the GFR to the body surface area, a GFR of approximately 75–100 ml/min per 1.73 m^2 can be assumed. The rate therefore measured is the quantity of the substance in the urine that originated from a calculable volume of blood.

[0100] There are several different techniques used to calculate or estimate the glomerular filtration rate (GFR or eGFR). In clinical practice, however, creatinine

clearance is used to measure GFR. Creatinine is produced naturally by the body (creatinine is a metabolite of creatine, which is found in muscle). It is freely filtered by the glomerulus, but also actively secreted by the renal tubules in very small amounts such that creatinine clearance overestimates actual GFR by 10-20%. This margin of error is acceptable considering the ease with which creatinine clearance is measured.

[0101] Creatinine clearance (CCr) can be calculated if values for creatinine's urine concentration (U_{Cr}), urine flow rate (V), and creatinine's plasma concentration (P_{Cr}) are known. Since the product of urine concentration and urine flow rate yields creatinine's excretion rate, creatinine clearance is also said to be its excretion rate ($U_{Cr} \times V$) divided by its plasma concentration. This is commonly represented mathematically as:

$$C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$$

[0102] Commonly a 24 hour urine collection is undertaken, from empty-bladder one morning to the contents of the bladder the following morning, with a comparative blood test then taken:

$$C_{Cr} = \frac{U_{Cr} \times \text{24-hour volume}}{P_{Cr} \times 24 \times 60 mins}$$

[0103] To allow comparison of results between people of different sizes, the CCr is often corrected for the body surface area (BSA) and expressed compared to the average sized man as ml/min/1.73 m2. While most adults have a BSA that approaches 1.7 (1.6-1.9), extremely obese or slim patients should have their CCr corrected for their actual BSA:

$$C_{Cr-corrected} = \frac{C_{Cr} \times 1.73}{BSA}$$

[0104] The accuracy of a creatinine clearance measurement (even when collection is complete) is limited because as glomerular filtration rate (GFR) falls creatinine secretion is increased, and thus the rise in serum creatinine is less. Thus, creatinine excretion is much greater than the filtered load, resulting in a potentially large overestimation of the GFR (as much as a twofold difference). However, for clinical purposes it is important to determine whether renal function is stable or getting worse or better. This is often determined by monitoring serum creatinine alone. Like creatinine clearance, the serum

creatinine will not be an accurate reflection of GFR in the non-steady-state condition of ARF. Nonetheless, the degree to which serum creatinine changes from baseline will reflect the change in GFR. Serum creatinine is readily and easily measured and it is specific for renal function.

[0105] For purposes of determining urine output on a Urine output on a mL/kg/hr basis, hourly urine collection and measurement is adequate. In the case where, for example, only a cumulative 24-h output was available and no patient weights are provided, minor modifications of the RIFLE urine output criteria have been described. For example, Bagshaw *et al., Nephrol. Dial. Transplant*. 23: 1203–1210, 2008, assumes an average patient weight of 70 kg, and patients are assigned a RIFLE classification based on the following: <35 mL/h (Risk), <21 mL/h (Injury) or <4 mL/h (Failure).

[0106] Selecting a Treatment Regimen

[0107] Once a diagnosis is obtained, the clinician can readily select a treatment regimen that is compatible with the diagnosis, such as initiating renal replacement therapy, withdrawing delivery of compounds that are known to be damaging to the kidney, kidney transplantation, delaying or avoiding procedures that are known to be damaging to the kidney, modifying diuretic administration, initiating goal directed therapy, etc. The skilled artisan is aware of appropriate treatments for numerous diseases discussed in relation to the methods of diagnosis described herein. See, e.g., Merck Manual of Diagnosis and Therapy, 17th Ed. Merck Research Laboratories, Whitehouse Station, NJ, 1999. In addition, since the methods and compositions described herein provide prognostic information, the markers of the present invention may be used to monitor a course of treatment. For example, improved or worsened prognostic state may indicate that a particular treatment is or is not efficacious.

[0108] One skilled in the art readily appreciates that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The examples provided herein are representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention.

[0109] Example 1: Contrast-induced nephropathy sample collection

[0110] The objective of this sample collection study is to collect samples of plasma and urine and clinical data from patients before and after receiving intravascular contrast

media. Approximately 250 adults undergoing radiographic/angiographic procedures involving intravascular administration of iodinated contrast media are enrolled. To be enrolled in the study, each patient must meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion Criteria

males and females 18 years of age or older;

undergoing a radiographic / angiographic procedure (such as a CT scan or coronary intervention) involving the intravascular administration of contrast media;

expected to be hospitalized for at least 48 hours after contrast administration.

able and willing to provide written informed consent for study participation and to comply with all study procedures.

Exclusion Criteria

renal transplant recipients;

acutely worsening renal function prior to the contrast procedure;

already receiving dialysis (either acute or chronic) or in imminent need of dialysis at enrollment;

expected to undergo a major surgical procedure (such as involving cardiopulmonary bypass) or an additional imaging procedure with contrast media with significant risk for further renal insult within the 48 hrs following contrast administration;

participation in an interventional clinical study with an experimental therapy within the previous 30 days;

known infection with human immunodeficiency virus (HIV) or a hepatitis virus.

[0111] Immediately prior to the first contrast administration (and after any pre-procedure hydration), an EDTA anti-coagulated blood sample (10 mL) and a urine sample (10 mL) are collected from each patient. Blood and urine samples are then collected at 4 (±0.5), 8 (±1), 24 (±2) 48 (±2), and 72 (±2) hrs following the last administration of contrast media during the index contrast procedure. Blood is collected via direct venipuncture or via other available venous access, such as an existing femoral sheath, central venous line, peripheral intravenous line or hep-lock. These study blood samples are processed to plasma at the clinical site, frozen and shipped to Astute Medical,

Inc., San Diego, CA. The study urine samples are frozen and shipped to Astute Medical, Inc.

[0112] Serum creatinine is assessed at the site immediately prior to the first contrast administration (after any pre-procedure hydration) and at 4 (±0.5), 8 (±1), 24 (±2) and 48 (±2)), and 72 (±2) hours following the last administration of contrast (ideally at the same time as the study samples are obtained). In addition, each patient's status is evaluated through day 30 with regard to additional serum and urine creatinine measurements, a need for dialysis, hospitalization status, and adverse clinical outcomes (including mortality).

[0113] Prior to contrast administration, each patient is assigned a risk based on the following assessment: systolic blood pressure <80 mm Hg = 5 points; intra-arterial balloon pump = 5 points; congestive heart failure (Class III-IV or history of pulmonary edema) = 5 points; age >75 yrs = 4 points; hematocrit level <39% for men, <35% for women = 3 points; diabetes = 3 points; contrast media volume = 1 point for each 100 mL; serum creatinine level >1.5 g/dL = 4 points OR estimated GFR 40–60 mL/min/1.73 m^2 = 2 points, 20–40 mL/min/1.73 m^2 = 4 points, < 20 mL/min/1.73 m^2 = 6 points. The risks assigned are as follows: risk for CIN and dialysis: 5 or less total points = risk of CIN - 7.5%, risk of dialysis - 0.04%; 6–10 total points = risk of CIN - 14%, risk of dialysis - 0.12%; 11–16 total points = risk of CIN - 26.1%, risk of dialysis - 1.09%; >16 total points = risk of CIN - 57.3%, risk of dialysis - 12.8%.

[0114] Example 2: Cardiac surgery sample collection

[0115] The objective of this sample collection study is to collect samples of plasma and urine and clinical data from patients before and after undergoing cardiovascular surgery, a procedure known to be potentially damaging to kidney function. Approximately 900 adults undergoing such surgery are enrolled. To be enrolled in the study, each patient must meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion Criteria

males and females 18 years of age or older;

undergoing cardiovascular surgery;

Toronto/Ottawa Predictive Risk Index for Renal Replacement risk score of at least 2 (Wijeysundera *et al., JAMA* 297: 1801-9, 2007); and

able and willing to provide written informed consent for study participation and to comply with all study procedures.

Exclusion Criteria

known pregnancy;

previous renal transplantation;

acutely worsening renal function prior to enrollment (e.g., any category of

RIFLE criteria);

already receiving dialysis (either acute or chronic) or in imminent need of dialysis at enrollment;

currently enrolled in another clinical study or expected to be enrolled in another clinical study within 7 days of cardiac surgery that involves drug infusion or a therapeutic intervention for AKI;

known infection with human immunodeficiency virus (HIV) or a hepatitis virus.

[0116] Within 3 hours prior to the first incision (and after any pre-procedure hydration), an EDTA anti-coagulated blood sample (10 mL), whole blood (3 mL), and a urine sample (35 mL) are collected from each patient. Blood and urine samples are then collected at 3 (±0.5), 6 (±0.5), 12 (±1), 24 (±2) and 48 (±2) hrs following the procedure and then daily on days 3 through 7 if the subject remains in the hospital. Blood is collected via direct venipuncture or via other available venous access, such as an existing femoral sheath, central venous line, peripheral intravenous line or hep-lock. These study blood samples are frozen and shipped to Astute Medical, Inc., San Diego, CA. The study urine samples are frozen and shipped to Astute Medical, Inc.

[0117] Example 3: Acutely ill subject sample collection

[0118] The objective of this study is to collect samples from acutely ill patients. Approximately 900 adults expected to be in the ICU for at least 48 hours will be enrolled. To be enrolled in the study, each patient must meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion Criteria

males and females 18 years of age or older;

Study population 1: approximately 300 patients that have at least one of:

shock (SBP < 90 mmHg and/or need for vasopressor support to maintain MAP > 60 mmHg and/or documented drop in SBP of at least 40 mmHg); and

sepsis;

Study population 2: approximately 300 patients that have at least one of:

IV antibiotics ordered in computerized physician order entry (CPOE) within 24 hours of enrollment;

contrast media exposure within 24 hours of enrollment;

increased Intra-Abdominal Pressure with acute decompensated heart failure; and

severe trauma as the primary reason for ICU admission and likely to be hospitalized in the ICU for 48 hours after enrollment;

Study population 3: approximately 300 patients

expected to be hospitalized through acute care setting (ICU or ED) with a known risk factor for acute renal injury (*e.g.* sepsis, hypotension/shock (Shock = systolic BP < 90 mmHg and/or the need for vasopressor support to maintain a MAP > 60 mmHg and/or a documented drop in SBP > 40 mmHg), major trauma, hemorrhage, or major surgery); and/or expected to be hospitalized to the ICU for at least 24 hours after enrollment.

Exclusion Criteria

known pregnancy;

institutionalized individuals;

previous renal transplantation;

known acutely worsening renal function prior to enrollment (e.g., any category of RIFLE criteria);

received dialysis (either acute or chronic) within 5 days prior to enrollment or in imminent need of dialysis at the time of enrollment;

known infection with human immunodeficiency virus (HIV) or a hepatitis virus;

meets only the SBP < 90 mmHg inclusion criterion set forth above, and does not have shock in the attending physician's or principal investigator's opinion.

[0119] After providing informed consent, an EDTA anti-coagulated blood sample (10 mL) and a urine sample (25-30 mL) are collected from each patient. Blood and urine samples are then collected at 4 (± 0.5) and 8 (± 1) hours after contrast administration (if applicable); at 12 (± 1), 24 (± 2), and 48 (± 2) hours after enrollment, and thereafter daily up to day 7 to day 14 while the subject is hospitalized. Blood is collected via direct venipuncture or via other available venous access, such as an existing femoral sheath, central venous line, peripheral intravenous line or hep-lock. These study blood samples are processed to plasma at the clinical site, frozen and shipped to Astute Medical, Inc., San Diego, CA. The study urine samples are frozen and shipped to Astute Medical, Inc.

[0120] Example 4. Immunoassay format

[0121] Analytes are measured using standard sandwich enzyme immunoassay techniques. A first antibody which binds the analyte is immobilized in wells of a 96 well polystyrene microplate. Analyte standards and test samples are pipetted into the appropriate wells and any analyte present is bound by the immobilized antibody. After washing away any unbound substances, a horseradish peroxidase-conjugated second antibody which binds the analyte is added to the wells, thereby forming sandwich complexes with the analyte (if present) and the first antibody. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution comprising tetramethylbenzidine and hydrogen peroxide is added to the wells. Color develops in proportion to the amount of analyte present in the sample. The color development is stopped and the intensity of the color is measured at 540 nm or 570 nm. An analyte concentration is assigned to the test sample by comparison to a standard curve determined from the analyte standards. Units for Follistatin-related protein 3, Basigin, and Tenascin reported herein are pg/mL; units for Cathepsin B are ng/mL.

[0122] Example 5. Apparently Healthy Donor and Chronic Disease Patient Samples

[0123] Human urine samples from donors with no known chronic or acute disease ("Apparently Healthy Donors") were purchased from two vendors (Golden West Biologicals, Inc., 27625 Commerce Center Dr., Temecula, CA 92590 and Virginia Medical Research, Inc., 915 First Colonial Rd., Virginia Beach, VA 23454). The urine samples were shipped and stored frozen at less than -20° C. The vendors supplied

demographic information for the individual donors including gender, race (Black /White), smoking status and age.

[0124] Human urine samples from donors with various chronic diseases ("Chronic Disease Patients") including congestive heart failure, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus and hypertension were purchased from Virginia Medical Research, Inc., 915 First Colonial Rd., Virginia Beach, VA 23454. The urine samples were shipped and stored frozen at less than -20 degrees centigrade. The vendor provided a case report form for each individual donor with age, gender, race (Black/White), smoking status and alcohol use, height, weight, chronic disease(s) diagnosis, current medications and previous surgeries.

[0125] Example 6. Use of Follistatin-related protein 3 for evaluating renal status in patients admitted to the ICU: Recovery to RIFLE 0 from RIFLE I and F

[0126] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Follistatin-related protein 3 is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0127] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output during a period starting at 12, 24, 48, or 72 hours after sample collection or at any time within 7 days after sample collection. Two cohorts are defined to represent a "recovered" and a "non-recovered" population. "Recovered" indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0). "Non-recovered" indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is risk of injury (R), injury (I) or failure (F). If a patient dies or is placed on renal replacement therapy (RRT) within 9 days of enrollment, the patient is considered "non-recovered".

[0128] The ability to distinguish the "recovered" and "non-recovered" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0129] Table 6.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum

creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	36900	64700	36400	64500	36400	64500
Average	43900	86000	44100	85700	44100	85700
Stdev	21100	118000	22600	118000	22600	118000
p (t-test)		0.29		0.32		0.32
Min	24900	10500	24900	10500	24900	10500
Max	89300	1230000	89300	1230000	89300	1230000
n (Patient)	9	141	8	142	8	142

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	39100	65900	37800	65800	37800	65800
Average	83200	83500	85400	83200	85400	83200
Stdev	154000	110000	158000	109000	158000	109000
p (t-test)		0.99		0.94		0.94
Min	10500	15100	10500	15100	10500	15100
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	18	132	17	133	17	133

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	47500	77400	47700	74000	47500	73900
Average	58600	102000	59000	100000	58700	99200
Stdev	42400	145000	42900	143000	43700	141000
p (t-test)		0.023		0.031		0.037
Min	15100	10500	15100	10500	15100	10500
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	63	86	60	89	57	92

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.74	0.68	0.70	0.74	0.68	0.69	0.74	0.68	0.70
SE	0.070	0.060	0.042	0.075	0.062	0.043	0.075	0.062	0.043
p Value	5.3E-4	0.0025	1.2E-6	0.0013	0.0036	4.9E-6	0.0013	0.0036	4.4E-6
nCohort Recovered	9	18	63	8	17	60	8	17	57
nCohort Non-recovered	141	132	86	142	133	89	142	133	92
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	77%	79%	86%	77%	79%	85%	77%	79%	85%
Specificity	67%	56%	40%	75%	59%	40%	75%	59%	40%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	52%	53%	64%	51%	53%	63%	51%	53%	63%
Specificity	78%	72%	68%	75%	71%	68%	75%	71%	70%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	27%	27%	36%	27%	26%	36%	27%	26%	36%
Specificity	100%	83%	89%	100%	82%	90%	100%	82%	91%
OR Quartile 2	6.81	4.64	4.06	10.3	5.36	3.90	10.3	5.36	3.77
p Value	0.0091	0.0031	5.3E-4	0.0055	0.0018	6.6E-4	0.0055	0.0018	8.2E-4
Lower limit of 95% CI	1.61	1.68	1.84	1.98	1.87	1.78	1.98	1.87	1.73

Upper limit of 95% CI	28.8	12.9	8.95	53.6	15.3	8.53	53.6	15.3	8.20
OR Quartile 3	3.76	2.94	3.81	3.17	2.67	3.66	3.17	2.67	4.01
p Value	0.11	0.052	1.4E-4	0.17	0.080	2.4E-4	0.17	0.080	1.2E-4
Lower limit of 95% CI	0.754	0.990	1.91	0.619	0.890	1.83	0.619	0.890	1.98
Upper limit of 95% CI	18.7	8.70	7.60	16.3	7.99	7.33	16.3	7.99	8.15
OR Quartile 4	7.07	1.80	4.51	6.26	1.67	5.05	6.26	1.67	5.82
p Value	0.18	0.37	0.0010	0.21	0.44	8.1E-4	0.21	0.44	6.5E-4
Lower limit of 95% CI	0.402	0.492	1.83	0.353	0.452	1.96	0.353	0.452	2.11
Upper limit of 95% CI	124	6.61	11.1	111	6.15	13.0	111	6.15	16.0

[0130] Table 6.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	35900	68300	36000	67200	36100	66600
Average	49400	89000	51500	87800	52800	87400
Stdev	52400	122000	56500	120000	58000	120000
p (t-test)		0.14		0.21		0.25
Min	10500	15100	10500	15100	10500	15100
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	21	129	18	132	17	133

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	37400	68400	37400	68100	37800	67900
Average	74800	85400	77500	84700	79400	84300
Stdev	130000	112000	134000	111000	137000	111000
p (t-test)		0.66		0.77		0.85
Min	10500	15100	10500	15100	10500	15100
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	28	122	26	124	25	125

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	49100	81200	49500	74000	48800	74000
Average	59200	108000	59800	105000	59400	104000
Stdev	39700	155000	40600	151000	41000	149000
p (t-test)		0.011		0.021		0.022
Min	10500	21500	10500	21500	10500	21500
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	71	74	66	79	64	81

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only

AUC	0.78	0.72	0.71	0.76	0.71	0.69	0.75	0.70	0.70
SE	0.046	0.048	0.043	0.051	0.050	0.043	0.054	0.051	0.043
p Value	1.0E-9	2.7E-6	7.2E-7	3.0E-7	1.6E-5	1.2E-5	3.6E-6	8.3E-5	5.2E-6
nCohort Recovered	21	28	71	18	26	66	17	25	64
nCohort Non-recovered	129	122	74	132	124	79	133	125	81
Cutoff Quartile 2	40800	40800	41800	40800	40800	41800	40800	40800	41800
Sensitivity	81%	82%	86%	80%	81%	85%	80%	81%	85%
Specificity	67%	57%	37%	67%	58%	36%	65%	56%	38%
Cutoff Quartile 3	63600	63600	64300	63600	63600	64300	63600	63600	64300
Sensitivity	56%	57%	65%	55%	56%	63%	54%	55%	63%
Specificity	86%	79%	65%	83%	77%	65%	82%	76%	66%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	29%	28%	38%	28%	27%	37%	28%	27%	37%
Specificity	95%	86%	87%	94%	85%	88%	94%	84%	89%
OR Quartile 2	8.75	6.06	3.70	8.15	5.99	3.19	7.20	5.36	3.45
p Value	2.6E-5	5.9E-5	0.0018	1.2E-4	9.7E-5	0.0041	3.4E-4	2.8E-4	0.0023
Lower limit of 95% CI	3.19	2.52	1.62	2.80	2.43	1.44	2.44	2.16	1.56
Upper limit of 95% CI	24.0	14.6	8.42	23.8	14.7	7.05	21.2	13.3	7.64
OR Quartile 3	7.58	4.77	3.40	6.00	4.18	3.22	5.51	3.90	3.25
p Value	0.0018	0.0016	4.4E-4	0.0063	0.0042	7.7E-4	0.0097	0.0066	7.6E-4
Lower limit of 95% CI	2.13	1.81	1.72	1.66	1.57	1.63	1.51	1.46	1.64
Upper limit of 95% CI	27.0	12.6	6.72	21.7	11.1	6.38	20.1	10.4	6.44
OR Quartile 4	8.04	2.32	4.19	6.62	2.08	4.20	6.17	1.96	4.79
p Value	0.046	0.14	8.5E-4	0.071	0.21	0.0012	0.083	0.25	7.0E-4
Lower limit of 95% CI	1.04	0.749	1.81	0.850	0.667	1.76	0.789	0.628	1.94
Upper limit of 95% CI	62.1	7.18	9.74	51.5	6.47	10.0	48.2	6.13	11.8

[0131] Table 6.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	42000	68700	43700	68400	43600	68600
Average	56500	91300	57900	90400	56600	89900
Stdev	49700	127000	51100	126000	53200	124000
p (t-test)		0.13		0.17		0.18
Min	10500	15100	10500	15100	10500	15100
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	32	117	30	119	27	122

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	42700	69300	43600	68700	43600	68700
Average	74500	87400	75700	86900	75700	86900
Stdev	113000	117000	114000	117000	114000	117000
p (t-test)		0.56		0.61		0.61
Min	10500	15100	10500	15100	10500	15100
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	38	110	37	111	37	111

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	54200	73800	55100	72700	55100	72700
Average	62900	109000	62900	107000	63200	103000
Stdev	33800	161000	34300	158000	35100	152000
p (t-test)		0.026		0.034		0.056
Min	15100	23300	15100	23300	15100	23300
Max	181000	1230000	181000	1230000	181000	1230000
n (Patient)	64	69	61	72	55	78

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.68	0.66	0.69	0.67	0.66	0.71	0.67	0.64
SE	0.047	0.047	0.047	0.049	0.048	0.047	0.049	0.048	0.048
p Value	1.1E-5	1.7E-4	5.5E-4	1.1E-4	5.5E-4	7.7E-4	1.8E-5	5.5E-4	0.0026
nCohort Recovered	32	38	64	30	37	61	27	37	55
nCohort Non-recovered	117	110	69	119	111	72	122	111	78
Cutoff Quartile 2	41800	41500	43900	41800	41500	43900	41800	41500	43900
Sensitivity	82%	82%	83%	81%	81%	82%	80%	81%	79%
Specificity	50%	45%	33%	47%	43%	33%	48%	43%	31%
Cutoff Quartile 3	63900	64100	66600	63900	64100	66600	63900	64100	66600
Sensitivity	58%	58%	61%	57%	58%	60%	57%	58%	59%
Specificity	78%	74%	61%	77%	73%	61%	81%	73%	62%
Cutoff Quartile 4	91300	91400	93500	91300	91400	93500	91300	91400	93500
Sensitivity	30%	28%	35%	29%	28%	35%	29%	28%	32%
Specificity	91%	84%	84%	90%	84%	85%	89%	84%	84%
OR Quartile 2	4.57	3.64	2.32	3.65	3.27	2.21	3.79	3.27	1.73
p Value	3.8E-4	0.0016	0.042	0.0028	0.0040	0.053	0.0029	0.0040	0.17
Lower limit of 95% CI	1.98	1.63	1.03	1.56	1.46	0.991	1.58	1.46	0.784
Upper limit of 95% CI	10.6	8.13	5.23	8.54	7.31	4.95	9.11	7.31	3.83
OR Quartile 3	4.96	3.90	2.43	4.38	3.68	2.29	5.92	3.68	2.33
p Value	6.1E-4	0.0011	0.013	0.0017	0.0018	0.020	7.6E-4	0.0018	0.019
Lower limit of 95% CI	1.98	1.72	1.21	1.74	1.62	1.14	2.10	1.62	1.15
Upper limit of 95% CI	12.4	8.80	4.87	11.0	8.33	4.59	16.7	8.33	4.72
OR Quartile 4	4.13	2.09	2.88	3.75	2.00	3.07	3.22	2.00	2.41
p Value	0.027	0.13	0.013	0.039	0.16	0.010	0.070	0.16	0.044
Lower limit of 95% CI	1.18	0.797	1.25	1.07	0.761	1.30	0.910	0.761	1.02
Upper limit of 95% CI	14.4	5.50	6.65	13.2	5.27	7.25	11.4	5.27	5.69

[0132] Table 6.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	44700	70200	43900	70500	43600	70500
Average	59300	94800	58100	93500	58000	92900
Stdev	46200	133000	48800	130000	50200	129000
p (t-test)		0.11		0.13		0.14
Min	10500	15100	10500	15100	10500	15100
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	38	106	33	111	31	113

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	45400	70500	45400	70500	45400	70500
Average	73600	90800	73600	90800	74300	90100
Stdev	104000	123000	104000	123000	106000	122000
p (t-test)		0.42		0.42		0.46
Min	10500	15100	10500	15100	10500	15100
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	45	99	45	99	43	101

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	60900	73800	60900	71700	50700	74200
Average	66000	111000	67200	105000	62000	105000
Stdev	35600	165000	37000	157000	35000	151000
p (t-test)		0.042		0.091		0.059
Min	15100	23300	15100	23300	15100	23300
Max	181000	1230000	181000	1230000	181000	1230000
n (Patient)	60	65	52	73	47	79

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.68	0.67	0.64	0.70	0.67	0.61	0.70	0.67	0.67
SE	0.047	0.046	0.049	0.048	0.046	0.050	0.048	0.047	0.048
p Value	1.4E-4	3.7E-4	0.0035	3.4E-5	3.7E-4	0.022	2.4E-5	3.6E-4	4.1E-4
nCohort Recovered	38	45	60	33	45	52	31	43	47
nCohort Non-recovered	106	99	65	111	99	73	113	101	79
Cutoff Quartile 2	41800	41800	45200	41800	41800	45200	41800	41800	44800
Sensitivity	82%	83%	83%	81%	83%	79%	81%	83%	81%
Specificity	45%	42%	33%	45%	42%	31%	48%	44%	36%
Cutoff Quartile 3	65200	65200	68200	65200	65200	68200	65200	65200	68000
Sensitivity	57%	58%	58%	57%	58%	56%	57%	57%	58%
Specificity	68%	67%	58%	73%	67%	58%	74%	67%	64%
Cutoff Quartile 4	92300	92300	95500	92300	92300	95500	92300	92300	95100
Sensitivity	31%	30%	35%	30%	30%	32%	29%	30%	32%
Specificity	92%	87%	85%	91%	87%	83%	90%	86%	85%
OR Quartile 2	3.71	3.52	2.45	3.57	3.52	1.72	4.11	3.91	2.42
p Value	0.0015	0.0018	0.037	0.0028	0.0018	0.19	0.0011	7.9E-4	0.035
Lower limit of 95% CI	1.65	1.60	1.06	1.55	1.60	0.758	1.76	1.76	1.07
Upper limit of 95% CI	8.33	7.76	5.70	8.22	7.76	3.89	9.60	8.67	5.48
OR Quartile 3	2.83	2.71	1.97	3.50	2.71	1.75	3.76	2.79	2.46
p Value	0.0094	0.0079	0.062	0.0040	0.0079	0.13	0.0034	0.0072	0.018
Lower limit of 95% CI	1.29	1.30	0.967	1.49	1.30	0.852	1.55	1.32	1.17
Upper limit of 95% CI	6.19	5.67	4.02	8.21	5.67	3.58	9.11	5.91	5.18
OR Quartile 4	5.27	2.83	3.10	4.23	2.83	2.20	3.85	2.61	2.65
p Value	0.0091	0.034	0.011	0.024	0.034	0.077	0.036	0.051	0.041
Lower limit of 95% CI	1.51	1.08	1.30	1.21	1.08	0.919	1.09	0.995	1.04
Upper limit of 95% CI	18.4	7.38	7.42	14.8	7.38	5.26	13.5	6.82	6.72

[0133] Table 6.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	48400	73800	48200	73900	48200	73900
Average	68600	101000	60800	109000	60800	109000
Stdev	80100	145000	39500	160000	39500	160000
p (t-test)		0.087		0.0096		0.0096
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	265000	1230000	265000	1230000
n (Patient)	81	69	80	70	80	70

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	45400	70900	45400	70900	45400	70900
Average	68200	95700	67500	95600	67500	95600
Stdev	87400	133000	88200	131000	88200	131000
p (t-test)		0.15		0.14		0.14
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	67	83	65	85	65	85

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	50700	72700	50300	77200	49800	81200
Average	70300	107000	63200	118000	62000	118000
Stdev	76000	162000	40800	177000	40100	174000
p (t-test)		0.059		0.0048		0.0037
Min	10500	21500	10500	21500	10500	21500
Max	689000	1230000	265000	1230000	265000	1230000
n (Patient)	95	54	93	56	91	58

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.67	0.69	0.67	0.69	0.70	0.69	0.69	0.70	0.71
SE	0.044	0.043	0.047	0.044	0.042	0.046	0.044	0.042	0.045
p Value	8.3E-5	8.4E-6	2.7E-4	1.8E-5	3.3E-6	3.0E-5	1.8E-5	3.3E-6	3.6E-6
nCohort Recovered	81	67	95	80	65	93	80	65	91
nCohort Non-recovered	69	83	54	70	85	56	70	85	58
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	86%	86%	89%	86%	86%	89%	86%	86%	90%
Specificity	35%	39%	33%	35%	40%	33%	35%	40%	34%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	62%	63%	65%	63%	62%	66%	63%	62%	67%
Specificity	60%	66%	58%	61%	66%	59%	61%	66%	60%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	36%	34%	37%	37%	34%	39%	37%	34%	40%
Specificity	84%	85%	81%	85%	86%	83%	85%	86%	84%
OR Quartile 2	3.12	3.75	3.88	3.23	4.06	4.17	3.23	4.06	4.48
p Value	0.0061	9.6E-4	0.0052	0.0046	4.9E-4	0.0032	0.0046	4.9E-4	0.0020
Lower limit of 95% CI	1.38	1.71	1.50	1.43	1.85	1.61	1.43	1.85	1.73
Upper limit of 95% CI	7.02	8.22	10.0	7.28	8.91	10.8	7.28	8.91	11.6
OR Quartile 3	2.53	3.21	2.53	2.67	3.24	2.82	2.67	3.24	3.14
p Value	0.0058	6.8E-4	0.0084	0.0035	6.5E-4	0.0033	0.0035	6.5E-4	0.0012
Lower limit of 95% CI	1.31	1.64	1.27	1.38	1.65	1.41	1.38	1.65	1.57
Upper limit of 95% CI	4.90	6.29	5.06	5.18	6.36	5.62	5.18	6.36	6.26

OR Quartile 4	2.97	2.90	2.52	3.35	3.22	3.11	3.35	3.22	3.33
p Value	0.0056	0.010	0.016	0.0025	0.0060	0.0034	0.0025	0.0060	0.0020
Lower limit of 95% CI	1.38	1.29	1.18	1.53	1.40	1.46	1.53	1.40	1.55
Upper limit of 95% CI	6.42	6.53	5.35	7.32	7.42	6.66	7.32	7.42	7.15

[0134] Example 7. Use of Follistatin-related protein 3 for evaluating renal status in patients admitted to the ICU: Recovery to RIFLE 0 and R from RIFLE I and F

[0135] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Follistatin-related protein 3 is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0136] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output during a period starting at 12, 24, 48, or 72 hours after sample collection or at any time within 7 days after sample collection. Two cohorts are defined to represent a “recovered” and a “non-recovered” population. “Recovered” indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0) or risk of injury (R). “Non-recovered” indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is injury (I) or failure (F). If a patient dies or is placed on renal replacement therapy (RRT) within 9 days of enrollment, the patient is considered “non-recovered”.

[0137] The ability to distinguish the “recovered” and “non-recovered” cohorts is determined using receiver operating characteristic (ROC) analysis.

[0138] Table 7.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	37600	70200	37100	70200	36900	70000
Average	50400	92400	48900	92100	49000	91700
Stdev	45400	126000	45900	125000	46700	125000
p (t-test)		0.067		0.066		0.073
Min	10500	20700	10500	20700	10500	20700

Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	32	118	30	120	29	121

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	40400	70500	40400	70500	39100	70200
Average	67200	89500	67200	89500	67800	89100
Stdev	108000	118000	108000	118000	110000	117000
p (t-test)		0.29		0.29		0.32
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	41	109	41	109	40	110

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	48200	81800	48200	81800	47900	81200
Average	60200	108000	59900	107000	59800	107000
Stdev	41300	156000	41500	154000	41800	154000
p (t-test)		0.011		0.012		0.013
Min	10500	21500	10500	21500	10500	21500
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	76	73	74	75	73	76

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.76	0.74	0.70	0.78	0.74	0.71	0.78	0.74	0.71
SE	0.042	0.042	0.043	0.041	0.042	0.042	0.041	0.042	0.042
p Value	3.4E-10	8.9E-9	2.0E-6	5.3E-12	8.9E-9	1.2E-6	1.0E-11	1.8E-8	1.0E-6
nCohort Recovered	32	41	76	30	41	74	29	40	73
nCohort Non-recovered	118	109	73	120	109	75	121	110	76
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	83%	84%	86%	83%	84%	87%	83%	85%	87%
Specificity	56%	51%	36%	60%	51%	36%	62%	52%	37%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	59%	61%	67%	59%	61%	67%	59%	60%	67%
Specificity	84%	78%	66%	87%	78%	66%	86%	78%	67%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	30%	30%	37%	30%	30%	37%	30%	30%	37%
Specificity	91%	88%	86%	93%	88%	86%	93%	88%	86%
OR Quartile 2	6.30	5.68	3.47	7.50	5.68	3.73	8.26	6.05	3.87
p Value	2.1E-5	2.2E-5	0.0028	6.2E-6	2.2E-5	0.0016	3.3E-6	1.3E-5	0.0012
Lower limit of 95% CI	2.70	2.55	1.54	3.13	2.55	1.65	3.39	2.70	1.71
Upper limit of 95% CI	14.7	12.7	7.85	18.0	12.7	8.45	20.1	13.6	8.77
OR Quartile 3	7.88	5.46	3.93	9.42	5.46	3.92	8.88	5.17	4.16
p Value	7.6E-5	6.6E-5	8.2E-5	7.9E-5	6.6E-5	8.3E-5	1.3E-4	1.1E-4	4.3E-5
Lower limit of 95% CI	2.83	2.37	1.99	3.09	2.37	1.99	2.91	2.24	2.10
Upper limit of 95% CI	21.9	12.6	7.75	28.7	12.6	7.74	27.1	11.9	8.25
OR Quartile 4	4.08	3.13	3.47	6.00	3.13	3.81	5.72	3.00	3.68
p Value	0.028	0.029	0.0022	0.018	0.029	0.0013	0.022	0.035	0.0017
Lower limit of 95% CI	1.16	1.13	1.56	1.36	1.13	1.69	1.29	1.08	1.63
Upper limit of 95% CI	14.3	8.68	7.69	26.5	8.68	8.61	25.3	8.34	8.29

[0139] Table 7.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum

creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	40400	71700	38700	71700	38700	71700
Average	49900	97800	48800	97400	48800	97400
Stdev	39700	133000	39800	132000	39800	132000
p (t-test)		0.019		0.019		0.019
Min	10500	20700	10500	20700	10500	20700
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	45	105	43	107	43	107

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	41800	71900	41800	71700	41800	71700
Average	63300	93500	63700	93000	63700	93000
Stdev	98400	122000	99400	121000	99400	121000
p (t-test)		0.13		0.14		0.14
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	50	100	49	101	49	101

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	49100	81200	48400	81200	48400	81200
Average	60500	113000	59900	112000	59900	112000
Stdev	39600	164000	39800	161000	39800	161000
p (t-test)		0.0069		0.0071		0.0071
Min	10500	21500	10500	21500	10500	21500
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	79	66	77	68	77	68

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.78	0.76	0.71	0.79	0.76	0.72	0.79	0.76	0.72
SE	0.038	0.039	0.043	0.037	0.039	0.043	0.037	0.039	0.043
p Value	1.6E-13	8.2E-12	8.2E-7	5.6E-15	2.1E-11	2.2E-7	5.6E-15	2.1E-11	2.2E-7
nCohort Recovered	45	50	79	43	49	77	43	49	77
nCohort Non-recovered	105	100	66	107	101	68	107	101	68
Cutoff Quartile 2	40800	40800	41800	40800	40800	41800	40800	40800	41800
Sensitivity	86%	86%	89%	86%	86%	90%	86%	86%	90%
Specificity	51%	48%	37%	53%	49%	38%	53%	49%	38%
Cutoff Quartile 3	63600	63600	64300	63600	63600	64300	63600	63600	64300
Sensitivity	64%	65%	67%	64%	64%	68%	64%	64%	68%
Specificity	82%	80%	63%	84%	80%	65%	84%	80%	65%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	33%	33%	38%	34%	33%	38%	34%	33%	38%
Specificity	93%	90%	85%	95%	90%	86%	95%	90%	86%
OR Quartile 2	6.27	5.67	4.89	7.05	5.97	5.26	7.05	5.97	5.26
p Value	6.9E-6	1.7E-5	6.1E-4	2.3E-6	1.1E-5	3.4E-4	2.3E-6	1.1E-5	3.4E-4
Lower limit of 95% CI	2.82	2.57	1.97	3.14	2.69	2.12	3.14	2.69	2.12

Upper limit of 95% CI	14.0	12.5	12.1	15.9	13.2	13.1	15.9	13.2	13.1
OR Quartile 3	8.15	7.43	3.45	8.97	7.04	3.87	8.97	7.04	3.87
p Value	1.8E-6	1.1E-6	4.1E-4	1.8E-6	2.0E-6	1.2E-4	1.8E-6	2.0E-6	1.2E-4
Lower limit of 95% CI	3.44	3.32	1.74	3.64	3.15	1.94	3.64	3.15	1.94
Upper limit of 95% CI	19.3	16.6	6.85	22.1	15.8	7.73	22.1	15.8	7.73
OR Quartile 4	7.00	4.43	3.40	10.4	4.27	3.71	10.4	4.27	3.71
p Value	0.0021	0.0040	0.0024	0.0019	0.0050	0.0014	0.0019	0.0050	0.0014
Lower limit of 95% CI	2.03	1.61	1.54	2.38	1.55	1.66	2.38	1.55	1.66
Upper limit of 95% CI	24.2	12.2	7.50	45.4	11.8	8.30	45.4	11.8	8.30

[0140] Table 7.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	43500	72000	43500	72000	43600	71900
Average	55600	102000	55600	102000	56000	101000
Stdev	40500	142000	40500	142000	40700	141000
p (t-test)		0.017		0.017		0.020
Min	10500	20700	10500	20700	10500	20700
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	58	91	58	91	57	92

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	43900	71700	43900	71700	43900	71700
Average	67700	95600	67700	95600	67700	95600
Stdev	90500	130000	90500	130000	90500	130000
p (t-test)		0.15		0.15		0.15
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	61	87	61	87	61	87

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	52000	81800	52000	81800	52000	81800
Average	62100	116000	62100	116000	61900	114000
Stdev	33300	169000	33300	169000	33100	167000
p (t-test)		0.0094		0.0094		0.011
Min	15100	24400	15100	24400	15100	24400
Max	181000	1230000	181000	1230000	181000	1230000
n (Patient)	72	61	72	61	70	63

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only

AUC	0.74	0.71	0.70	0.74	0.71	0.70	0.73	0.71	0.69
SE	0.040	0.042	0.046	0.040	0.042	0.046	0.041	0.042	0.046
p Value	3.8E-9	1.2E-6	1.8E-5	3.8E-9	1.2E-6	1.8E-5	2.7E-8	1.2E-6	2.8E-5
nCohort Recovered	58	61	72	58	61	72	57	61	70
nCohort Non-recovered	91	87	61	91	87	61	92	87	63
Cutoff Quartile 2	41800	41500	43900	41800	41500	43900	41800	41500	43900
Sensitivity	87%	86%	87%	87%	86%	87%	86%	86%	86%
Specificity	43%	41%	35%	43%	41%	35%	42%	41%	34%
Cutoff Quartile 3	63900	64100	66600	63900	64100	66600	63900	64100	66600
Sensitivity	64%	62%	66%	64%	62%	66%	63%	62%	65%
Specificity	71%	67%	62%	71%	67%	62%	70%	67%	63%
Cutoff Quartile 4	91300	91400	93500	91300	91400	93500	91300	91400	93500
Sensitivity	37%	34%	38%	37%	34%	38%	37%	34%	38%
Specificity	93%	89%	85%	93%	89%	85%	93%	89%	86%
OR Quartile 2	4.99	4.34	3.52	4.99	4.34	3.52	4.42	4.34	3.13
p Value	8.1E-5	2.9E-4	0.0054	8.1E-5	2.9E-4	0.0054	2.2E-4	2.9E-4	0.0094
Lower limit of 95% CI	2.24	1.96	1.45	2.24	1.96	1.45	2.01	1.96	1.32
Upper limit of 95% CI	11.1	9.61	8.56	11.1	9.61	8.56	9.72	9.61	7.41
OR Quartile 3	4.24	3.35	3.17	4.24	3.35	3.17	4.01	3.35	3.15
p Value	6.5E-5	5.6E-4	0.0015	6.5E-5	5.6E-4	0.0015	1.2E-4	5.6E-4	0.0015
Lower limit of 95% CI	2.09	1.69	1.56	2.09	1.69	1.56	1.98	1.69	1.55
Upper limit of 95% CI	8.61	6.67	6.47	8.61	6.67	6.47	8.15	6.67	6.41
OR Quartile 4	8.05	4.06	3.36	8.05	4.06	3.36	7.77	4.06	3.69
p Value	2.0E-4	0.0024	0.0040	2.0E-4	0.0024	0.0040	2.6E-4	0.0024	0.0023
Lower limit of 95% CI	2.68	1.65	1.47	2.68	1.65	1.47	2.58	1.65	1.59
Upper limit of 95% CI	24.2	10.0	7.66	24.2	10.0	7.66	23.4	10.0	8.56

[0141] Table 7.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	44700	80700	44300	80900	44700	80700
Average	67200	100000	57100	107000	56400	106000
Stdev	88100	135000	40700	148000	40000	146000
p (t-test)		0.090		0.011		0.013
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	265000	1230000	265000	1230000
n (Patient)	65	79	62	82	59	85

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	45400	74000	45400	74000	45600	73900
Average	68500	100000	68500	100000	69000	99300
Stdev	87100	137000	87100	137000	87600	136000
p (t-test)		0.11		0.11		0.12
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	67	77	67	77	66	78

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	60900	80700	55400	81200	55200	81200
Average	74300	108000	65100	115000	63700	115000
Stdev	82100	160000	34900	171000	33900	168000
p (t-test)		0.13		0.022		0.019
Min	15100	24400	15100	24400	15100	24400
Max	689000	1230000	181000	1230000	181000	1230000
n (Patient)	70	55	65	60	64	62

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.73	0.71	0.66	0.74	0.71	0.67	0.74	0.70	0.68
SE	0.041	0.042	0.050	0.040	0.042	0.048	0.040	0.043	0.048
p Value	1.8E-8	3.9E-7	0.0015	1.2E-9	3.9E-7	5.0E-4	2.3E-9	1.9E-6	2.1E-4
nCohort Recovered	65	67	70	62	67	65	59	66	64
nCohort Non-recovered	79	77	55	82	77	60	85	78	62
Cutoff Quartile 2	41800	41800	45200	41800	41800	45200	41800	41800	44800
Sensitivity	89%	88%	85%	88%	88%	85%	87%	87%	84%
Specificity	42%	40%	33%	42%	40%	34%	42%	39%	34%
Cutoff Quartile 3	65200	65200	68200	65200	65200	68200	65200	65200	68000
Sensitivity	65%	64%	62%	65%	64%	62%	64%	63%	61%
Specificity	68%	66%	59%	69%	66%	60%	69%	65%	61%
Cutoff Quartile 4	92300	92300	95500	92300	92300	95500	92300	92300	95100
Sensitivity	37%	35%	38%	38%	35%	38%	38%	35%	39%
Specificity	89%	87%	84%	92%	87%	86%	93%	86%	88%
OR Quartile 2	5.53	5.10	2.88	5.20	5.10	2.90	4.95	4.42	2.72
p Value	8.3E-5	1.7E-4	0.022	1.0E-4	1.7E-4	0.017	1.3E-4	4.3E-4	0.021
Lower limit of 95% CI	2.36	2.18	1.17	2.26	2.18	1.21	2.18	1.93	1.16
Upper limit of 95% CI	12.9	11.9	7.07	11.9	11.9	6.96	11.2	10.1	6.38
OR Quartile 3	3.82	3.35	2.29	4.14	3.35	2.41	3.97	3.16	2.47
p Value	1.6E-4	5.5E-4	0.025	7.8E-5	5.5E-4	0.016	1.4E-4	9.7E-4	0.013
Lower limit of 95% CI	1.90	1.69	1.11	2.04	1.69	1.18	1.95	1.59	1.21
Upper limit of 95% CI	7.65	6.64	4.71	8.37	6.64	4.95	8.06	6.26	5.06
OR Quartile 4	4.81	3.48	3.31	6.93	3.48	3.87	8.30	3.35	4.42
p Value	7.0E-4	0.0038	0.0053	1.9E-4	0.0038	0.0025	1.8E-4	0.0049	0.0012
Lower limit of 95% CI	1.94	1.50	1.43	2.51	1.50	1.61	2.75	1.44	1.80
Upper limit of 95% CI	11.9	8.09	7.70	19.2	8.09	9.28	25.1	7.80	10.9

[0142] Table 7.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	48400	74000	48200	77400	47900	80700
Average	68400	105000	68000	105000	60800	115000
Stdev	77400	153000	77700	151000	39700	167000
p (t-test)		0.054		0.050		0.0044
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	265000	1230000
n (Patient)	89	61	88	62	87	63

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	47100	74000	47100	74000	47100	74000
Average	67300	101000	67300	101000	67300	101000
Stdev	81300	142000	81300	142000	81300	142000
p (t-test)		0.070		0.070		0.070
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	79	71	79	71	79	71

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	50500	73800	50500	73800	50100	80700
Average	70000	110000	70000	110000	63100	121000
Stdev	75100	166000	75100	166000	40800	181000
p (t-test)		0.044		0.044		0.0031
Min	10500	33600	10500	33600	10500	33600
Max	689000	1230000	689000	1230000	265000	1230000
n (Patient)	98	51	98	51	96	53

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.69	0.71	0.69	0.70	0.71	0.69	0.71	0.71	0.71
SE	0.045	0.043	0.048	0.044	0.043	0.048	0.044	0.043	0.046
p Value	1.8E-5	1.4E-6	9.0E-5	6.8E-6	1.4E-6	9.0E-5	1.1E-6	1.4E-6	8.1E-6
nCohort Recovered	89	79	98	88	79	98	87	79	96
nCohort Non-recovered	61	71	51	62	71	51	63	71	53
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	89%	87%	90%	89%	87%	90%	89%	87%	91%
Specificity	35%	37%	33%	35%	37%	33%	36%	37%	33%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	66%	68%	67%	66%	68%	67%	67%	68%	68%
Specificity	61%	66%	58%	61%	66%	58%	62%	66%	59%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	38%	37%	37%	39%	37%	37%	40%	37%	40%
Specificity	83%	85%	81%	84%	85%	81%	85%	85%	82%
OR Quartile 2	4.12	4.00	4.46	4.27	4.00	4.46	4.43	4.00	4.80
p Value	0.0020	0.0012	0.0039	0.0016	0.0012	0.0039	0.0012	0.0012	0.0024
Lower limit of 95% CI	1.68	1.73	1.62	1.74	1.73	1.62	1.80	1.73	1.74
Upper limit of 95% CI	10.1	9.21	12.3	10.5	9.21	12.3	10.9	9.21	13.2
OR Quartile 3	2.94	4.02	2.78	3.10	4.02	2.78	3.27	4.02	3.10
p Value	0.0018	6.2E-5	0.0046	0.0011	6.2E-5	0.0046	6.3E-4	6.2E-5	0.0017
Lower limit of 95% CI	1.49	2.04	1.37	1.57	2.04	1.37	1.66	2.04	1.53
Upper limit of 95% CI	5.79	7.94	5.64	6.11	7.94	5.64	6.46	7.94	6.27
OR Quartile 4	2.99	3.23	2.47	3.34	3.23	2.47	3.74	3.23	3.05
p Value	0.0047	0.0033	0.019	0.0021	0.0033	0.019	8.5E-4	0.0033	0.0040
Lower limit of 95% CI	1.40	1.48	1.16	1.55	1.48	1.16	1.72	1.48	1.43
Upper limit of 95% CI	6.38	7.05	5.26	7.18	7.05	5.26	8.14	7.05	6.52

[0143] Example 8. Use of Basigin for evaluating renal status in patients admitted to the ICU: Recovery to RIFLE 0 from RIFLE I and F

[0144] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10

mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Basigin is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0145] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output during a period starting at 12, 24, 48, or 72 hours after sample collection or at any time within 7 days after sample collection. Two cohorts are defined to represent a "recovered" and a "non-recovered" population. "Recovered" indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0). "Non-recovered" indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is risk of injury (R), injury (I) or failure (F). If a patient dies or is placed on renal replacement therapy (RRT) within 9 days of enrollment, the patient is considered "non-recovered".

[0146] The ability to distinguish the "recovered" and "non-recovered" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0147] Table 8.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	4230	11600	4090	11500	4090	11500
Average	4730	16600	4430	16500	4430	16500
Stdev	1860	14100	1730	14100	1730	14100
p (t-test)		0.013		0.017		0.017
Min	1970	2640	1970	2640	1970	2640
Max	7150	72100	7010	72100	7010	72100
n (Patient)	9	141	8	142	8	142

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	4670	12000	4930	11800	4930	11800
Average	9050	16800	9330	16700	9330	16700
Stdev	11700	14000	12000	14000	12000	14000
p (t-test)		0.027		0.040		0.040
Min	1970	3040	1970	3040	1970	3040

Max	42400	72100	42400	72100	42400	72100
n (Patient)	18	132	17	133	17	133

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7550	14000	7740	13900	7550	13900
Average	10700	19700	10700	19400	10500	19300
Stdev	10100	15200	10200	15100	10000	15000
p (t-test)		7.3E-5		1.4E-4		1.3E-4
Min	1970	2640	1970	2640	1970	2640
Max	60400	72100	60400	72100	60400	72100
n (Patient)	63	86	60	89	57	92

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.89	0.79	0.73	0.91	0.78	0.72	0.91	0.78	0.73
SE	0.038	0.046	0.041	0.034	0.049	0.041	0.034	0.049	0.041
p Value	0	2.5E-10	1.7E-8	0	1.3E-8	5.6E-8	0	1.3E-8	3.9E-8
nCohort Recovered	9	18	63	8	17	60	8	17	57
nCohort Non-recovered	141	132	86	142	133	89	142	133	92
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	78%	80%	84%	78%	80%	83%	78%	80%	83%
Specificity	78%	67%	37%	88%	65%	37%	88%	65%	37%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	53%	55%	70%	53%	54%	69%	53%	54%	67%
Specificity	100%	83%	76%	100%	82%	77%	100%	82%	77%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	27%	27%	35%	27%	27%	35%	27%	27%	35%
Specificity	100%	89%	87%	100%	88%	88%	100%	88%	89%
OR Quartile 2	12.4	8.15	2.96	25.1	7.20	2.86	25.1	7.20	2.77
p Value	0.0023	1.2E-4	0.0057	0.0031	3.4E-4	0.0071	0.0031	3.4E-4	0.0087
Lower limit of 95% CI	2.45	2.80	1.37	2.97	2.44	1.33	2.97	2.44	1.29
Upper limit of 95% CI	62.8	23.8	6.38	212	21.2	6.13	212	21.2	5.94
OR Quartile 3	21.6	6.00	7.38	19.0	5.51	7.16	19.0	5.51	6.99
p Value	0.035	0.0063	1.2E-7	0.044	0.0097	2.4E-7	0.044	0.0097	4.7E-7
Lower limit of 95% CI	1.23	1.66	3.52	1.08	1.51	3.39	1.08	1.51	3.28
Upper limit of 95% CI	378	21.7	15.5	336	20.1	15.1	336	20.1	14.9
OR Quartile 4	7.07	3.00	3.68	6.26	2.78	4.05	6.26	2.78	4.53
p Value	0.18	0.16	0.0031	0.21	0.19	0.0024	0.21	0.19	0.0018
Lower limit of 95% CI	0.402	0.657	1.55	0.353	0.606	1.64	0.353	0.606	1.76
Upper limit of 95% CI	124	13.7	8.74	111	12.8	9.96	111	12.8	11.7

[0148] Table 8.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	4390	12400	4260	12300	4230	12300
Average	4740	17700	4600	17400	4620	17300
Stdev	1650	14200	1680	14200	1730	14200

p (t-test)		5.7E-5		2.0E-4		3.3E-4
Min	1970	3040	1970	3040	1970	3040
Max	7920	72100	7920	72100	7920	72100
n (Patient)	21	129	18	132	17	133

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	4660	12800	4850	12600	4930	12400
Average	7670	17700	7930	17500	8070	17400
Stdev	9500	14200	9820	14100	10000	14100
p (t-test)		4.7E-4		0.0012		0.0020
Min	1970	3040	1970	3040	1970	3040
Max	42400	72100	42400	72100	42400	72100
n (Patient)	28	122	26	124	25	125

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7920	14300	8010	13900	7740	13900
Average	11600	20500	11800	19800	11500	19800
Stdev	10500	15700	10800	15500	10600	15400
p (t-test)		1.0E-4		5.1E-4		3.1E-4
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	71	74	66	79	64	81

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.93	0.85	0.73	0.93	0.84	0.70	0.93	0.83	0.71
SE	0.022	0.033	0.042	0.022	0.035	0.043	0.023	0.037	0.042
p Value	0	0	6.7E-8	0	0	1.6E-6	0	0	3.3E-7
nCohort Recovered	21	28	71	18	26	66	17	25	64
nCohort Non-recovered	129	122	74	132	124	79	133	125	81
Cutoff Quartile 2	6820	6820	6850	6820	6820	6850	6820	6820	6850
Sensitivity	84%	85%	88%	83%	84%	86%	82%	83%	86%
Specificity	81%	71%	38%	83%	69%	38%	82%	68%	39%
Cutoff Quartile 3	11000	11000	11200	11000	11000	11200	11000	11000	11200
Sensitivity	58%	59%	73%	57%	58%	70%	56%	58%	69%
Specificity	100%	89%	72%	100%	88%	71%	100%	88%	72%
Cutoff Quartile 4	19900	19900	21500	19900	19900	21500	19900	19900	21500
Sensitivity	29%	30%	35%	29%	29%	34%	29%	29%	35%
Specificity	100%	93%	85%	100%	92%	85%	100%	92%	86%
OR Quartile 2	21.9	14.4	4.43	23.7	11.7	3.77	21.2	10.5	4.08
p Value	3.4E-7	5.1E-8	5.6E-4	2.5E-6	5.2E-7	0.0013	6.1E-6	1.6E-6	6.7E-4
Lower limit of 95% CI	6.68	5.53	1.90	6.34	4.48	1.68	5.65	4.02	1.81
Upper limit of 95% CI	71.5	37.7	10.3	88.6	30.6	8.46	79.6	27.5	9.17
OR Quartile 3	59.6	12.0	6.88	48.6	10.6	5.67	45.2	9.96	5.72
p Value	0.0046	9.9E-5	2.1E-7	0.0072	2.2E-4	2.1E-6	0.0084	3.4E-4	2.1E-6
Lower limit of 95% CI	3.53	3.44	3.32	2.87	3.03	2.77	2.66	2.83	2.78
Upper limit of 95% CI	1000	41.9	14.3	823	37.2	11.6	767	35.0	11.8
OR Quartile 4	18.1	5.44	2.95	15.1	4.91	2.91	14.1	4.65	3.23
p Value	0.045	0.026	0.0080	0.061	0.037	0.011	0.067	0.044	0.0063
Lower limit of 95% CI	1.07	1.23	1.33	0.886	1.10	1.28	0.828	1.04	1.39
Upper limit of 95% CI	306	24.1	6.58	256	21.9	6.59	241	20.8	7.48

[0149] Table 8.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where

recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	6250	12900	6250	12700	5550	12600
Average	8350	18000	8490	17800	7790	17700
Stdev	7550	14600	7770	14500	7410	14400
p (t-test)		4.1E-4		9.0E-4		6.6E-4
Min	1970	3580	1970	3580	1970	3580
Max	33400	72100	33400	72100	33400	72100
n (Patient)	32	117	30	119	27	122

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7010	13200	7010	13100	7010	13100
Average	10000	18100	10200	18000	10200	18000
Stdev	10000	14500	10100	14500	10100	14500
p (t-test)		0.0019		0.0031		0.0031
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	42400	72100	42400	72100
n (Patient)	38	110	37	111	37	111

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	9030	13900	9000	13900	9000	13600
Average	13300	20300	13200	20200	13400	19500
Stdev	11300	16000	11300	15900	11700	15600
p (t-test)		0.0045		0.0046		0.016
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	64	69	61	72	55	78

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.79	0.75	0.66	0.78	0.74	0.66	0.81	0.74	0.64
SE	0.039	0.041	0.047	0.041	0.042	0.047	0.039	0.042	0.048
p Value	1.1E-13	9.2E-10	6.0E-4	4.3E-12	1.1E-8	4.2E-4	8.9E-16	1.1E-8	0.0024
nCohort Recovered	32	38	64	30	37	61	27	37	55
nCohort Non-recovered	117	110	69	119	111	72	122	111	78
Cutoff Quartile 2	6850	6960	7010	6850	6960	7010	6850	6960	7010
Sensitivity	83%	83%	84%	82%	82%	85%	83%	82%	82%
Specificity	53%	47%	33%	53%	46%	34%	59%	46%	33%
Cutoff Quartile 3	11000	11100	11800	11000	11100	11800	11000	11100	11800
Sensitivity	60%	60%	65%	59%	59%	64%	59%	59%	60%
Specificity	84%	79%	66%	83%	78%	66%	89%	78%	64%
Cutoff Quartile 4	20100	20400	23200	20100	20400	23200	20100	20400	23200
Sensitivity	30%	29%	33%	29%	29%	33%	30%	29%	32%
Specificity	91%	87%	83%	90%	86%	84%	93%	86%	84%
OR Quartile 2	5.50	4.31	2.58	5.33	3.87	2.91	7.00	3.87	2.22

p Value	7.7E-5	3.8E-4	0.025	1.3E-4	0.0010	0.012	2.3E-5	0.0010	0.052
Lower limit of 95% CI	2.36	1.92	1.12	2.26	1.72	1.27	2.84	1.72	0.992
Upper limit of 95% CI	12.8	9.65	5.90	12.6	8.67	6.69	17.2	8.67	4.99
OR Quartile 3	8.04	5.62	3.58	7.14	5.32	3.37	11.5	5.32	2.65
p Value	6.5E-5	9.6E-5	4.7E-4	1.8E-4	1.7E-4	8.6E-4	1.3E-4	1.7E-4	0.0073
Lower limit of 95% CI	2.89	2.36	1.75	2.56	2.23	1.65	3.29	2.23	1.30
Upper limit of 95% CI	22.4	13.4	7.32	20.0	12.7	6.88	40.3	12.7	5.41
OR Quartile 4	4.13	2.71	2.41	3.75	2.59	2.55	5.23	2.59	2.41
p Value	0.027	0.057	0.036	0.039	0.069	0.028	0.030	0.069	0.044
Lower limit of 95% CI	1.18	0.970	1.06	1.07	0.927	1.10	1.18	0.927	1.02
Upper limit of 95% CI	14.4	7.56	5.47	13.2	7.25	5.89	23.3	7.25	5.69

[0150] Table 8.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7010	13600	6300	13400	6300	13100
Average	9170	18700	8670	18400	8830	18200
Stdev	8610	14800	8740	14600	8980	14600
p (t-test)		2.7E-4		3.8E-4		8.7E-4
Min	1970	3580	1970	3580	1970	3580
Max	40700	72100	40700	72100	40700	72100
n (Patient)	38	106	33	111	31	113

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7010	13700	7010	13700	7010	13600
Average	10400	18800	10400	18800	10600	18600
Stdev	10300	14800	10300	14800	10500	14800
p (t-test)		6.9E-4		6.9E-4		0.0015
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	42400	72100	42400	72100
n (Patient)	45	99	45	99	43	101

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	9380	15600	9380	13700	9000	13900
Average	13300	21200	13700	20100	12400	20200
Stdev	10700	16300	11200	15800	10600	15600
p (t-test)		0.0020		0.014		0.0031
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	60	65	52	73	47	79

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.78	0.76	0.67	0.80	0.76	0.64	0.79	0.75	0.68
SE	0.039	0.040	0.048	0.038	0.040	0.049	0.040	0.041	0.047
p Value	6.5E-13	5.8E-11	4.9E-4	1.1E-15	5.8E-11	0.0055	1.3E-13	1.7E-9	1.5E-4
nCohort Recovered	38	45	60	33	45	52	31	43	47
nCohort Non-recovered	106	99	65	111	99	73	113	101	79
Cutoff Quartile 2	7010	7010	7530	7010	7010	7530	7010	7010	7250
Sensitivity	83%	84%	85%	84%	84%	81%	83%	83%	82%
Specificity	47%	44%	35%	55%	44%	33%	55%	44%	38%
Cutoff Quartile 3	11100	11100	12400	11100	11100	12400	11100	11100	12300
Sensitivity	62%	64%	63%	61%	64%	59%	60%	62%	59%
Specificity	84%	80%	63%	88%	80%	62%	87%	79%	66%
Cutoff Quartile 4	21600	21600	23800	21600	21600	23800	21600	21600	23600
Sensitivity	30%	30%	35%	30%	30%	33%	29%	30%	34%
Specificity	89%	87%	85%	91%	87%	85%	90%	86%	89%
OR Quartile 2	4.40	4.15	2.96	6.20	4.15	2.05	6.01	3.91	2.88
p Value	3.6E-4	4.5E-4	0.013	2.6E-5	4.5E-4	0.088	4.6E-5	7.9E-4	0.012
Lower limit of 95% CI	1.95	1.87	1.26	2.65	1.87	0.900	2.54	1.76	1.26
Upper limit of 95% CI	9.93	9.19	6.98	14.5	9.19	4.66	14.2	8.67	6.57
OR Quartile 3	8.80	7.00	2.95	11.5	7.00	2.29	10.2	6.26	2.85
p Value	8.3E-6	5.3E-6	0.0036	1.7E-5	5.3E-6	0.025	4.5E-5	1.8E-5	0.0064
Lower limit of 95% CI	3.38	3.03	1.43	3.77	3.03	1.11	3.34	2.71	1.34
Upper limit of 95% CI	22.9	16.2	6.11	34.9	16.2	4.75	31.1	14.5	6.04
OR Quartile 4	3.68	2.83	3.10	4.23	2.83	2.69	3.85	2.61	4.36
p Value	0.022	0.034	0.011	0.024	0.034	0.031	0.036	0.051	0.0054
Lower limit of 95% CI	1.20	1.08	1.30	1.21	1.08	1.10	1.09	0.995	1.55
Upper limit of 95% CI	11.2	7.38	7.42	14.8	7.38	6.61	13.5	6.82	12.3

[0151] Table 8.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	8090	13900	8010	14000	8010	14000
Average	12200	20100	11800	20500	11800	20500
Stdev	11000	15800	10500	15900	10500	15900
p (t-test)		4.2E-4		1.2E-4		1.2E-4
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	81	69	80	70	80	70

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7530	13900	7500	13900	7500	13900
Average	10800	19900	10500	19900	10500	19900
Stdev	9540	15600	9400	15500	9400	15500
p (t-test)		4.5E-5		2.9E-5		2.9E-5
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	42400	72100	42400	72100
n (Patient)	67	83	65	85	65	85

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	8740	16800	8720	17000	8440	16800
Average	12500	21900	12000	22300	12000	22000
Stdev	10600	17000	10200	16900	10300	16700
p (t-test)		4.8E-5		7.5E-6		1.3E-5
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	95	54	93	56	91	58

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.70	0.74	0.71	0.72	0.75	0.73	0.72	0.75	0.73
SE	0.043	0.040	0.046	0.042	0.039	0.044	0.042	0.039	0.044
p Value	2.3E-6	1.7E-9	5.3E-6	3.7E-7	2.0E-10	3.5E-7	3.7E-7	2.0E-10	2.1E-7
nCohort Recovered	81	67	95	80	65	93	80	65	91
nCohort Non-recovered	69	83	54	70	85	56	70	85	58
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	88%	88%	91%	89%	88%	91%	89%	88%	91%
Specificity	37%	42%	34%	38%	43%	34%	38%	43%	35%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	68%	67%	72%	69%	67%	73%	69%	67%	74%
Specificity	65%	72%	62%	66%	72%	63%	66%	72%	65%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	33%	35%	37%	34%	35%	39%	34%	35%	38%
Specificity	81%	87%	81%	82%	88%	83%	82%	88%	82%
OR Quartile 2	4.49	5.24	4.98	4.65	5.68	5.35	4.65	5.68	5.75
p Value	6.6E-4	7.5E-5	0.0019	4.9E-4	3.5E-5	0.0012	4.9E-4	3.5E-5	7.1E-4
Lower limit of 95% CI	1.89	2.31	1.81	1.96	2.49	1.94	1.96	2.49	2.09
Upper limit of 95% CI	10.6	11.9	13.7	11.0	12.9	14.7	11.0	12.9	15.8
OR Quartile 3	4.04	5.24	4.26	4.28	5.32	4.74	4.28	5.32	5.29
p Value	6.0E-5	3.8E-6	9.0E-5	3.2E-5	3.6E-6	2.7E-5	3.2E-5	3.6E-6	7.5E-6
Lower limit of 95% CI	2.04	2.60	2.06	2.16	2.62	2.29	2.16	2.62	2.55
Upper limit of 95% CI	8.00	10.6	8.80	8.50	10.8	9.81	8.50	10.8	11.0
OR Quartile 4	2.20	3.46	2.52	2.46	3.89	3.11	2.46	3.89	2.86
p Value	0.040	0.0036	0.016	0.020	0.0021	0.0034	0.020	0.0021	0.0064
Lower limit of 95% CI	1.04	1.50	1.18	1.15	1.64	1.46	1.15	1.64	1.34
Upper limit of 95% CI	4.66	7.97	5.35	5.25	9.22	6.66	5.25	9.22	6.11

[0152] Example 9. Use of Basigin for evaluating renal status in patients admitted to the ICU: Recovery to RIFLE 0 and R from RIFLE I and F

[0153] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Basigin is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0154] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output during a period starting at 12, 24, 48, or

72 hours after sample collection or at any time within 7 days after sample collection. Two cohorts are defined to represent a "recovered" and a "non-recovered" population. "Recovered" indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0) or risk of injury (R). "Non-recovered" indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is injury (I) or failure (F). If a patient dies or is placed on renal replacement therapy (RRT) within 9 days of enrollment, the patient is considered "non-recovered".

[0155] The ability to distinguish the "recovered" and "non-recovered" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0156] Table 9.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	5080	13000	5080	12800	5060	12700
Average	6710	18300	6620	18200	6660	18100
Stdev	4750	14600	4790	14500	4870	14500
p (t-test)		1.7E-5		3.3E-5		5.2E-5
Min	1970	3040	1970	3040	1970	3040
Max	25700	72100	25700	72100	25700	72100
n (Patient)	32	118	30	120	29	121

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	5620	13600	5620	13600	5590	13500
Average	8410	18700	8410	18700	8480	18500
Stdev	8550	14600	8550	14600	8650	14600
p (t-test)		4.0E-5		4.0E-5		6.5E-5
Min	1970	3040	1970	3040	1970	3040
Max	42400	72100	42400	72100	42400	72100
n (Patient)	41	109	41	109	40	110

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	8160	14100	8160	13900	8090	13900
Average	11600	20400	11700	20100	11700	19900
Stdev	10500	15700	10600	15700	10600	15600

p (t-test)		8.3E-5		1.9E-4		2.6E-4
Min	1970	3170	1970	3170	1970	3170
Max	60400	72100	60400	72100	60400	72100
n (Patient)	76	73	74	75	73	76

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.85	0.82	0.72	0.85	0.82	0.71	0.85	0.81	0.71
SE	0.032	0.034	0.042	0.033	0.034	0.042	0.033	0.035	0.042
p Value	0	0	1.6E-7	0	0	7.2E-7	0	0	9.7E-7
nCohort Recovered	32	41	76	30	41	74	29	40	73
nCohort Non-recovered	118	109	73	120	109	75	121	110	76
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	86%	88%	86%	85%	88%	85%	84%	87%	86%
Specificity	66%	61%	36%	67%	61%	35%	66%	60%	36%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	60%	62%	71%	60%	62%	71%	60%	62%	70%
Specificity	88%	83%	70%	90%	83%	70%	90%	82%	70%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	31%	32%	36%	31%	32%	35%	31%	32%	34%
Specificity	97%	93%	84%	97%	93%	84%	97%	92%	84%
OR Quartile 2	11.3	11.5	3.47	11.3	11.5	3.15	10.2	10.3	3.27
p Value	9.6E-8	2.0E-8	0.0028	1.7E-7	2.0E-8	0.0048	5.5E-7	6.5E-8	0.0037
Lower limit of 95% CI	4.65	4.91	1.54	4.56	4.91	1.42	4.11	4.42	1.47
Upper limit of 95% CI	27.7	27.1	7.85	28.1	27.1	7.00	25.3	24.0	7.27
OR Quartile 3	10.6	8.06	5.71	13.5	8.06	5.69	12.7	7.63	5.34
p Value	3.2E-5	5.7E-6	1.3E-6	4.3E-5	5.7E-6	1.3E-6	6.5E-5	1.0E-5	2.7E-6
Lower limit of 95% CI	3.48	3.27	2.82	3.88	3.27	2.82	3.65	3.10	2.65
Upper limit of 95% CI	32.1	19.8	11.5	47.0	19.8	11.5	44.4	18.8	10.8
OR Quartile 4	14.2	5.99	2.95	12.9	5.99	2.74	12.3	5.76	2.64
p Value	0.010	0.0047	0.0066	0.014	0.0047	0.011	0.015	0.0058	0.015
Lower limit of 95% CI	1.86	1.73	1.35	1.70	1.73	1.26	1.62	1.66	1.21
Upper limit of 95% CI	108	20.8	6.44	98.5	20.8	5.98	94.1	20.0	5.76

[0157] Table 9.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	5750	13900	5750	13900	5750	13900
Average	6890	19700	6810	19500	6810	19500
Stdev	4220	14900	4250	14800	4250	14800
p (t-test)		7.3E-8		1.5E-7		1.5E-7
Min	1970	3580	1970	3580	1970	3580
Max	25700	72100	25700	72100	25700	72100
n (Patient)	45	105	43	107	43	107

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	5980	14000	6200	13900	6200	13900

Average	8130	19700	8180	19600	8180	19600
Stdev	7800	14700	7870	14700	7870	14700
p (t-test)		6.5E-7		1.2E-6		1.2E-6
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	42400	72100	42400	72100
n (Patient)	50	100	49	101	49	101

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	8220	15000	8090	14300	8090	14300
Average	12000	21100	12100	20800	12100	20800
Stdev	10700	16000	10800	15900	10800	15900
p (t-test)		7.9E-5		1.5E-4		1.5E-4
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	79	66	77	68	77	68

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.86	0.85	0.72	0.86	0.84	0.72	0.86	0.84	0.72
SE	0.029	0.031	0.043	0.029	0.032	0.043	0.029	0.032	0.043
p Value	0	0	2.7E-7	0	0	3.6E-7	0	0	3.6E-7
nCohort Recovered	45	50	79	43	49	77	43	49	77
nCohort Non-recovered	105	100	66	107	101	68	107	101	68
Cutoff Quartile 2	6820	6820	6850	6820	6820	6850	6820	6820	6850
Sensitivity	90%	91%	89%	89%	90%	90%	89%	90%	90%
Specificity	60%	58%	37%	60%	57%	38%	60%	57%	38%
Cutoff Quartile 3	11000	11000	11200	11000	11000	11200	11000	11000	11200
Sensitivity	67%	68%	74%	66%	67%	74%	66%	67%	74%
Specificity	89%	86%	68%	91%	86%	69%	91%	86%	69%
Cutoff Quartile 4	19900	19900	21500	19900	19900	21500	19900	19900	21500
Sensitivity	35%	35%	36%	35%	35%	35%	35%	35%	35%
Specificity	98%	94%	84%	98%	94%	83%	98%	94%	83%
OR Quartile 2	12.8	14.0	4.89	12.1	12.1	5.26	12.1	12.1	5.26
p Value	7.1E-9	5.4E-9	6.1E-4	1.2E-8	1.5E-8	3.4E-4	1.2E-8	1.5E-8	3.4E-4
Lower limit of 95% CI	5.40	5.76	1.97	5.14	5.11	2.12	5.14	5.11	2.12
Upper limit of 95% CI	30.4	33.9	12.1	28.5	28.8	13.1	28.5	28.8	13.1
OR Quartile 3	16.0	13.1	6.23	19.2	12.4	6.13	19.2	12.4	6.13
p Value	8.5E-8	2.4E-8	8.3E-7	1.5E-7	4.6E-8	8.8E-7	1.5E-7	4.6E-8	8.8E-7
Lower limit of 95% CI	5.80	5.29	3.01	6.37	5.02	2.98	6.37	5.02	2.98
Upper limit of 95% CI	44.1	32.2	12.9	58.0	30.5	12.6	58.0	30.5	12.6
OR Quartile 4	23.9	8.44	2.90	22.2	8.13	2.69	22.2	8.13	2.69
p Value	0.0021	7.3E-4	0.0073	0.0027	9.0E-4	0.013	0.0027	9.0E-4	0.013
Lower limit of 95% CI	3.17	2.45	1.33	2.94	2.36	1.24	2.94	2.36	1.24
Upper limit of 95% CI	181	29.1	6.32	168	28.0	5.84	168	28.0	5.84

[0158] Table 9.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered	Non-recovered	Recovered	Non-recovered	Recovered	Non-recovered

	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort
Median	7010	14100	7010	14100	7010	14000
Average	9750	19900	9750	19900	9810	19700
Stdev	8860	15200	8860	15200	8930	15100
p (t-test)		8.5E-6		8.5E-6		1.4E-5
Min	1970	3580	1970	3580	1970	3580
Max	40700	72100	40700	72100	40700	72100
n (Patient)	58	91	58	91	57	92

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7150	14100	7150	14100	7150	14100
Average	10900	19700	10900	19700	10900	19700
Stdev	10200	15100	10200	15100	10200	15100
p (t-test)		1.2E-4		1.2E-4		1.2E-4
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	42400	72100	42400	72100
n (Patient)	61	87	61	87	61	87

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	8970	15600	8970	15600	8970	15600
Average	13000	21600	13000	21600	13000	21400
Stdev	11000	16400	11000	16400	11100	16300
p (t-test)		4.6E-4		4.6E-4		5.9E-4
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	72	61	72	61	70	63

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.79	0.76	0.70	0.79	0.76	0.70	0.78	0.76	0.70
SE	0.036	0.039	0.046	0.036	0.039	0.046	0.037	0.039	0.046
p Value	2.9E-15	2.6E-11	1.4E-5	2.9E-15	2.6E-11	1.4E-5	2.2E-14	2.6E-11	1.6E-5
nCohort Recovered	58	61	72	58	61	72	57	61	70
nCohort Non-recovered	91	87	61	91	87	61	92	87	63
Cutoff Quartile 2	6850	6960	7010	6850	6960	7010	6850	6960	7010
Sensitivity	89%	89%	89%	89%	89%	89%	88%	89%	87%
Specificity	47%	44%	35%	47%	44%	35%	46%	44%	34%
Cutoff Quartile 3	11000	11100	11800	11000	11100	11800	11000	11100	11800
Sensitivity	69%	68%	69%	69%	68%	69%	68%	68%	68%
Specificity	79%	75%	65%	79%	75%	65%	79%	75%	66%
Cutoff Quartile 4	20100	20400	23200	20100	20400	23200	20100	20400	23200
Sensitivity	34%	33%	36%	34%	33%	36%	34%	33%	37%
Specificity	88%	87%	83%	88%	87%	83%	88%	87%	84%
OR Quartile 2	7.05	6.11	4.10	7.05	6.11	4.10	6.18	6.11	3.59
p Value	4.6E-6	1.9E-5	0.0028	4.6E-6	1.9E-5	0.0028	1.3E-5	1.9E-5	0.0050
Lower limit of 95% CI	3.06	2.67	1.63	3.06	2.67	1.63	2.73	2.67	1.47
Upper limit of 95% CI	16.3	14.0	10.3	16.3	14.0	10.3	14.0	14.0	8.74
OR Quartile 3	8.62	6.46	4.16	8.62	6.46	4.16	8.15	6.46	4.12
p Value	5.2E-8	6.8E-7	1.2E-4	5.2E-8	6.8E-7	1.2E-4	1.1E-7	6.8E-7	1.3E-4
Lower limit of 95% CI	3.97	3.09	2.01	3.97	3.09	2.01	3.76	3.09	2.00
Upper limit of 95% CI	18.7	13.5	8.60	18.7	13.5	8.60	17.7	13.5	8.50
OR Quartile 4	3.76	3.31	2.82	3.76	3.31	2.82	3.63	3.31	3.08
p Value	0.0039	0.0068	0.012	0.0039	0.0068	0.012	0.0051	0.0068	0.0073
Lower limit of 95% CI	1.53	1.39	1.25	1.53	1.39	1.25	1.47	1.39	1.35
Upper limit of 95% CI	9.27	7.88	6.34	9.27	7.88	6.34	8.94	7.88	7.02

[0159] Table 9.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7530	14500	7520	15000	7530	14500
Average	10800	20600	10200	20700	10000	20400
Stdev	9670	15600	8860	15600	8680	15500
p (t-test)		2.3E-5		5.0E-6		7.1E-6
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	40700	72100	40700	72100
n (Patient)	65	79	62	82	59	85

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7550	14500	7550	14500	7630	14300
Average	11300	20500	11300	20500	11400	20300
Stdev	10100	15600	10100	15600	10200	15600
p (t-test)		6.6E-5		6.6E-5		1.2E-4
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	42400	72100	42400	72100
n (Patient)	67	77	67	77	66	78

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	9320	16700	9260	16800	9160	16800
Average	13800	21900	13200	21900	13000	21800
Stdev	11100	16800	10700	16500	10600	16400
p (t-test)		0.0016		5.7E-4		4.3E-4
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	70	55	65	60	64	62

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.76	0.75	0.68	0.78	0.75	0.69	0.77	0.74	0.69
SE	0.039	0.040	0.049	0.038	0.040	0.047	0.038	0.041	0.047
p Value	2.2E-11	7.0E-10	3.2E-4	2.7E-13	7.0E-10	5.9E-5	1.3E-12	5.1E-9	3.6E-5
nCohort Recovered	65	67	70	62	67	65	59	66	64
nCohort Non-recovered	79	77	55	82	77	60	85	78	62
Cutoff Quartile 2	7010	7010	7530	7010	7010	7530	7010	7010	7250
Sensitivity	89%	88%	87%	88%	88%	87%	86%	87%	85%
Specificity	42%	40%	34%	42%	40%	35%	41%	39%	36%
Cutoff Quartile 3	11100	11100	12400	11100	11100	12400	11100	11100	12300
Sensitivity	71%	70%	67%	71%	70%	67%	69%	69%	66%
Specificity	75%	73%	63%	77%	73%	65%	78%	73%	66%

Cutoff Quartile 4	21600	21600	23800	21600	21600	23800	21600	21600	23600
Sensitivity	34%	34%	36%	35%	34%	37%	35%	33%	37%
Specificity	86%	85%	83%	89%	85%	85%	90%	85%	86%
OR Quartile 2	5.53	5.10	3.58	5.20	5.10	3.56	4.17	4.42	3.30
p Value	8.3E-5	1.7E-4	0.0075	1.0E-4	1.7E-4	0.0058	4.8E-4	4.3E-4	0.0072
Lower limit of 95% CI	2.36	2.18	1.41	2.26	2.18	1.45	1.87	1.93	1.38
Upper limit of 95% CI	12.9	11.9	9.10	11.9	11.9	8.77	9.30	10.1	7.90
OR Quartile 3	7.46	6.39	3.48	8.29	6.39	3.65	8.03	6.00	3.73
p Value	1.2E-7	5.9E-7	0.0010	5.4E-8	5.9E-7	5.9E-4	1.1E-7	1.2E-6	4.6E-4
Lower limit of 95% CI	3.54	3.09	1.65	3.87	3.09	1.74	3.72	2.91	1.78
Upper limit of 95% CI	15.7	13.2	7.31	17.8	13.2	7.65	17.3	12.4	7.79
OR Quartile 4	3.23	2.91	2.76	4.30	2.91	3.18	4.82	2.80	3.60
p Value	0.0064	0.011	0.016	0.0016	0.011	0.0079	0.0012	0.014	0.0040
Lower limit of 95% CI	1.39	1.28	1.20	1.73	1.28	1.36	1.86	1.23	1.51
Upper limit of 95% CI	7.51	6.61	6.33	10.7	6.61	7.48	12.5	6.37	8.63

[0160] Table 9.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	8090	16700	8010	16800	7920	16900
Average	12000	21400	11900	21500	11600	21800
Stdev	10600	16300	10600	16100	10200	16200
p (t-test)		3.4E-5		2.4E-5		5.0E-6
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	89	61	88	62	87	63

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	7550	14100	7550	14100	7550	14100
Average	11800	20400	11800	20400	11800	20400
Stdev	11100	15400	11100	15400	11100	15400
p (t-test)		1.3E-4		1.3E-4		1.3E-4
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	79	71	79	71	79	71

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	8730	16900	8730	16900	8580	17200
Average	12400	22600	12400	22600	12000	23000
Stdev	10500	17200	10500	17200	10100	17000
p (t-test)		1.4E-5		1.4E-5		1.9E-6
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	98	51	98	51	96	53

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.73	0.74	0.72	0.74	0.74	0.72	0.75	0.74	0.74
SE	0.043	0.041	0.046	0.042	0.041	0.046	0.042	0.041	0.044
p Value	8.5E-8	7.3E-9	9.3E-7	2.4E-8	7.3E-9	9.3E-7	2.4E-9	7.3E-9	4.5E-8
nCohort Recovered	89	79	98	88	79	98	87	79	96
nCohort Non-recovered	61	71	51	62	71	51	63	71	53
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	92%	92%	92%	92%	92%	92%	92%	92%	92%
Specificity	37%	41%	34%	38%	41%	34%	38%	41%	34%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	72%	72%	75%	73%	72%	75%	73%	72%	75%
Specificity	65%	70%	62%	66%	70%	62%	67%	70%	64%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	36%	35%	39%	37%	35%	39%	38%	35%	42%
Specificity	82%	84%	82%	83%	84%	82%	84%	84%	83%
OR Quartile 2	6.60	7.38	5.97	6.84	7.38	5.97	7.09	7.38	6.42
p Value	2.5E-4	3.7E-5	0.0015	1.9E-4	3.7E-5	0.0015	1.5E-4	3.7E-5	9.5E-4
Lower limit of 95% CI	2.40	2.85	1.98	2.49	2.85	1.98	2.58	2.85	2.13
Upper limit of 95% CI	18.1	19.1	18.0	18.8	19.1	18.0	19.5	19.1	19.3
OR Quartile 3	4.84	5.84	4.82	5.12	5.84	4.82	5.41	5.84	5.36
p Value	1.3E-5	9.3E-7	4.0E-5	6.8E-6	9.3E-7	4.0E-5	3.4E-6	9.3E-7	1.2E-5
Lower limit of 95% CI	2.38	2.89	2.28	2.51	2.89	2.28	2.65	2.89	2.53
Upper limit of 95% CI	9.85	11.8	10.2	10.4	11.8	10.2	11.0	11.8	11.4
OR Quartile 4	2.57	2.76	2.87	2.87	2.76	2.87	3.21	2.76	3.55
p Value	0.014	0.0097	0.0066	0.0064	0.0097	0.0066	0.0028	0.0097	0.0012
Lower limit of 95% CI	1.21	1.28	1.34	1.35	1.28	1.34	1.49	1.28	1.65
Upper limit of 95% CI	5.46	5.95	6.13	6.12	5.95	6.13	6.90	5.95	7.63

[0161] Example 10. Use of Cathepsin B for evaluating renal status in patients admitted to the ICU: Recovery to RIFLE 0 from RIFLE I and F

[0162] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Cathepsin B is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0163] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output during a period starting at 12, 24, 48, or 72 hours after sample collection or at any time within 7 days after sample collection. Two cohorts are defined to represent a “recovered” and a “non-recovered” population. “Recovered” indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0). “Non-recovered” indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is risk of injury (R), injury (I) or failure (F). If a patient dies or is placed on renal replacement therapy (RRT) within 9 days of enrollment, the patient is considered “non-recovered”.

[0164] The ability to distinguish the "recovered" and "non-recovered" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0165] Table 10.1: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "recovered" and "non-recovered" cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	0.826	3.83	0.678	3.81	0.678	3.81
Average	1.93	12.6	2.01	12.5	2.01	12.5
Stdev	2.20	20.8	2.34	20.7	2.34	20.7
p (t-test)		0.13		0.16		0.16
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	5.56	111	5.56	111	5.56	111
n (Patient)	9	139	8	140	8	140

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	0.917	4.84	0.863	4.83	0.863	4.83
Average	1.72	13.7	1.73	13.6	1.73	13.6
Stdev	1.82	21.5	1.86	21.4	1.86	21.4
p (t-test)		0.010		0.012		0.012
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	6.53	111	6.53	111	6.53	111
n (Patient)	22	126	21	127	21	127

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.60	4.28	3.61	3.83	3.60	4.28
Average	10.3	13.3	10.1	13.3	9.39	13.6
Stdev	17.5	22.2	17.5	22.1	17.1	22.1
p (t-test)		0.37		0.34		0.22
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	103	111	103	111	103	111
n (Patient)	63	84	60	87	57	90

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.76	0.78	0.54	0.76	0.78	0.54	0.76	0.78	0.55
SE	0.068	0.045	0.048	0.071	0.046	0.048	0.071	0.046	0.048
p Value	1.3E-4	7.3E-10	0.42	2.8E-4	1.1E-9	0.37	2.8E-4	1.1E-9	0.27
nCohort Recovered	9	22	63	8	21	60	8	21	57
nCohort Non-recovered	139	126	84	140	127	87	140	127	90
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	77%	80%	75%	77%	80%	76%	77%	80%	76%
Specificity	56%	55%	25%	62%	57%	27%	62%	57%	26%

Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	52%	56%	52%	51%	56%	52%	51%	56%	52%
Specificity	78%	86%	52%	75%	86%	52%	75%	86%	53%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	27%	29%	26%	26%	29%	26%	26%	29%	28%
Specificity	100%	100%	76%	100%	100%	77%	100%	100%	79%
OR Quartile 2	4.18	4.85	1.02	5.62	5.44	1.14	5.62	5.44	1.10
p Value	0.041	0.0011	0.96	0.023	6.1E-4	0.73	0.023	6.1E-4	0.80
Lower limit of 95% CI	1.06	1.88	0.481	1.27	2.06	0.538	1.27	2.06	0.516
Upper limit of 95% CI	16.5	12.5	2.17	24.8	14.3	2.43	24.8	14.3	2.36
OR Quartile 3	3.76	8.18	1.21	3.18	7.61	1.15	3.18	7.61	1.21
p Value	0.11	0.0012	0.57	0.17	0.0018	0.69	0.17	0.0018	0.57
Lower limit of 95% CI	0.755	2.30	0.629	0.620	2.13	0.593	0.620	2.13	0.625
Upper limit of 95% CI	18.7	29.0	2.33	16.3	27.1	2.21	16.3	27.1	2.36
OR Quartile 4	6.95	18.9	1.14	6.16	17.8	1.18	6.16	17.8	1.44
p Value	0.19	0.042	0.74	0.22	0.046	0.67	0.22	0.046	0.36
Lower limit of 95% CI	0.395	1.11	0.533	0.347	1.05	0.550	0.347	1.05	0.657
Upper limit of 95% CI	122	319	2.42	109	302	2.54	109	302	3.17

[0166] Table 10.2: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "recovered" and "non-recovered" cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	1.35	4.83	2.06	4.73	1.75	4.77
Average	2.15	13.7	2.40	13.3	2.26	13.3
Stdev	1.90	21.6	2.00	21.4	1.95	21.3
p (t-test)		0.011		0.028		0.031
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	6.09	111	6.09	111	6.09	111
n (Patient)	23	125	19	129	18	130

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	1.35	5.87	1.35	4.92	1.32	4.94
Average	2.21	14.7	2.27	14.5	2.18	14.4
Stdev	2.04	22.2	2.09	22.1	2.06	22.0
p (t-test)		0.0016		0.0026		0.0029
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	7.07	111	7.07	111	7.07	111
n (Patient)	33	115	31	117	30	118

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.46	4.81	3.61	4.73	3.61	4.73
Average	9.67	14.3	9.12	14.4	9.09	14.3
Stdev	16.6	23.5	16.1	23.3	16.3	23.0
p (t-test)		0.17		0.12		0.13
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	103	111	103	111	103	111

n (Patient)	70	73	64	79	62	81

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.72	0.74	0.55	0.69	0.73	0.55	0.70	0.74	0.55
SE	0.051	0.044	0.048	0.058	0.046	0.048	0.058	0.045	0.048
p Value	9.9E-6	5.7E-8	0.30	0.0010	4.2E-7	0.32	4.0E-4	1.2E-7	0.30
nCohort Recovered	23	33	70	19	31	64	18	30	62
nCohort Non-recovered	125	115	73	129	117	79	130	118	81
Cutoff Quartile 2	1.13	1.13	1.06	1.13	1.13	1.06	1.13	1.13	1.06
Sensitivity	78%	80%	75%	77%	79%	76%	77%	80%	75%
Specificity	39%	42%	26%	37%	42%	27%	39%	43%	26%
Cutoff Quartile 3	3.63	3.63	3.80	3.63	3.63	3.80	3.63	3.63	3.80
Sensitivity	55%	58%	53%	53%	57%	52%	54%	58%	52%
Specificity	78%	79%	53%	74%	77%	52%	78%	80%	52%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	30%	32%	27%	29%	32%	28%	28%	31%	28%
Specificity	100%	100%	77%	100%	100%	78%	100%	100%	79%
OR Quartile 2	2.23	2.95	1.06	1.92	2.80	1.14	2.12	3.00	1.06
p Value	0.094	0.010	0.88	0.21	0.017	0.73	0.15	0.011	0.88
Lower limit of 95% CI	0.873	1.29	0.497	0.696	1.20	0.535	0.756	1.28	0.496
Upper limit of 95% CI	5.68	6.74	2.25	5.33	6.50	2.44	5.95	7.01	2.27
OR Quartile 3	4.44	5.18	1.29	3.22	4.59	1.15	4.08	5.44	1.15
p Value	0.0055	4.1E-4	0.45	0.034	0.0011	0.68	0.018	5.9E-4	0.68
Lower limit of 95% CI	1.55	2.08	0.667	1.10	1.83	0.594	1.28	2.07	0.593
Upper limit of 95% CI	12.7	12.9	2.48	9.46	11.5	2.22	13.1	14.3	2.23
OR Quartile 4	19.9	32.0	1.27	15.8	29.3	1.38	14.8	28.1	1.49
p Value	0.038	0.016	0.53	0.056	0.019	0.41	0.062	0.021	0.31
Lower limit of 95% CI	1.18	1.91	0.596	0.931	1.75	0.638	0.872	1.67	0.686
Upper limit of 95% CI	336	537	2.72	269	493	2.98	253	471	3.26

[0167] Table 10.3: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "recovered" and "non-recovered" cohorts where recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	1.95	6.29	1.72	5.97	2.02	5.42
Average	2.27	14.9	2.18	14.7	2.34	14.3
Stdev	1.88	22.4	1.88	22.2	1.90	22.1
p (t-test)		0.0013		0.0019		0.0041
Min	0.0435	0.126	0.0435	0.126	0.208	0.0435
Max	7.19	111	7.19	111	7.19	111
n (Patient)	34	113	32	115	29	118

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	1.50	6.80	1.44	6.67	1.44	6.67
Average	2.33	16.0	2.26	15.9	2.26	15.9
Stdev	2.05	23.0	2.04	22.9	2.04	22.9
p (t-test)		1.9E-4		2.3E-4		2.3E-4
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	7.19	111	7.19	111	7.19	111
n (Patient)	42	104	41	105	41	105

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.62	5.36	3.71	4.85	4.14	4.73
Average	9.06	16.4	9.13	16.0	9.89	14.9
Stdev	15.9	24.9	16.2	24.5	16.9	23.8
p (t-test)		0.046		0.062		0.18
Min	0.0435	0.126	0.0435	0.126	0.156	0.0435
Max	103	111	103	111	103	111
n (Patient)	65	66	62	69	56	75

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.72	0.74	0.59	0.73	0.75	0.59	0.70	0.75	0.54
SE	0.045	0.041	0.050	0.045	0.041	0.050	0.049	0.041	0.051
p Value	1.3E-6	3.9E-9	0.079	4.3E-7	1.2E-9	0.084	5.1E-5	1.2E-9	0.43
nCohort Recovered	34	42	65	32	41	62	29	41	56
nCohort Non-recovered	113	104	66	115	105	69	118	105	75
Cutoff Quartile 2	1.13	1.12	1.16	1.13	1.12	1.16	1.13	1.12	1.16
Sensitivity	79%	81%	80%	79%	81%	80%	78%	81%	76%
Specificity	38%	40%	31%	41%	41%	31%	38%	41%	27%
Cutoff Quartile 3	3.62	3.63	4.38	3.62	3.63	4.38	3.62	3.63	4.38
Sensitivity	58%	61%	55%	58%	61%	54%	57%	61%	51%
Specificity	76%	76%	54%	78%	78%	53%	76%	78%	50%
Cutoff Quartile 4	13.1	13.3	14.2	13.1	13.3	14.2	13.1	13.3	14.2
Sensitivity	33%	36%	29%	32%	35%	29%	31%	35%	27%
Specificity	100%	100%	78%	100%	100%	79%	100%	100%	77%
OR Quartile 2	2.30	2.86	1.81	2.59	3.01	1.74	2.16	3.01	1.16
p Value	0.049	0.0089	0.15	0.026	0.0062	0.18	0.081	0.0062	0.72
Lower limit of 95% CI	1.01	1.30	0.811	1.12	1.37	0.782	0.908	1.37	0.524
Upper limit of 95% CI	5.24	6.27	4.05	5.99	6.63	3.85	5.15	6.63	2.56
OR Quartile 3	4.56	4.92	1.40	4.99	5.55	1.32	4.13	5.55	1.03
p Value	6.8E-4	1.2E-4	0.34	5.9E-4	6.0E-5	0.43	0.0027	6.0E-5	0.94
Lower limit of 95% CI	1.90	2.18	0.704	1.99	2.40	0.662	1.64	2.40	0.514
Upper limit of 95% CI	11.0	11.1	2.78	12.5	12.8	2.62	10.4	12.8	2.05
OR Quartile 4	33.8	47.2	1.47	31.1	45.4	1.54	27.1	45.4	1.20
p Value	0.014	0.0073	0.34	0.017	0.0079	0.29	0.022	0.0079	0.65
Lower limit of 95% CI	2.02	2.82	0.664	1.85	2.72	0.689	1.62	2.72	0.538
Upper limit of 95% CI	567	790	3.26	521	760	3.43	456	760	2.69

[0168] Table 10.4: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "recovered" and "non-recovered" cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	1.55	6.50	1.81	6.13	1.81	6.03
Average	4.26	15.4	4.54	14.7	4.60	14.5
Stdev	9.39	22.9	9.94	22.6	10.2	22.4
p (t-test)		0.0033		0.0097		0.014
Min	0.0435	0.126	0.208	0.0435	0.208	0.0435
Max	57.5	111	57.5	111	57.5	111
n (Patient)	41	101	36	106	34	108

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	1.81	6.80	1.81	6.80	1.81	6.58
Average	4.15	16.2	4.15	16.2	4.18	16.0
Stdev	8.71	23.5	8.71	23.5	8.88	23.4
p (t-test)		7.8E-4		7.8E-4		0.0012
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	57.5	111	57.5	111	57.5	111
n (Patient)	48	94	48	94	46	96

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.61	5.87	3.85	4.81	4.14	4.77
Average	9.26	16.7	9.70	15.5	10.2	14.9
Stdev	16.1	25.3	16.6	24.4	17.0	23.8
p (t-test)		0.056		0.14		0.23
Min	0.0435	0.126	0.156	0.0435	0.156	0.0435
Max	103	111	103	111	103	111
n (Patient)	60	61	52	69	48	74

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.71	0.60	0.69	0.71	0.56	0.69	0.71	0.53
SE	0.044	0.043	0.051	0.047	0.043	0.052	0.048	0.044	0.053
p Value	1.3E-6	8.0E-7	0.043	6.2E-5	8.0E-7	0.26	9.7E-5	1.5E-6	0.58
nCohort Recovered	41	48	60	36	48	52	34	46	48
nCohort Non-recovered	101	94	61	106	94	69	108	96	74
Cutoff Quartile 2	1.12	1.12	1.22	1.12	1.12	1.22	1.12	1.12	1.23
Sensitivity	80%	81%	80%	79%	81%	77%	79%	80%	73%
Specificity	39%	38%	30%	39%	38%	27%	38%	37%	23%
Cutoff Quartile 3	3.71	3.71	4.38	3.71	3.71	4.38	3.71	3.71	4.56
Sensitivity	60%	63%	56%	58%	63%	52%	58%	62%	51%
Specificity	76%	75%	55%	75%	75%	52%	76%	76%	52%
Cutoff Quartile 4	13.3	13.3	16.1	13.3	13.3	16.1	13.3	13.3	15.7
Sensitivity	33%	35%	30%	31%	35%	28%	31%	34%	27%
Specificity	93%	94%	78%	92%	94%	77%	91%	93%	77%
OR Quartile 2	2.59	2.53	1.75	2.43	2.53	1.22	2.29	2.38	0.803
p Value	0.019	0.019	0.19	0.033	0.019	0.64	0.051	0.030	0.61
Lower limit of 95% CI	1.17	1.16	0.756	1.07	1.16	0.532	0.997	1.09	0.344
Upper limit of 95% CI	5.74	5.52	4.05	5.51	5.52	2.80	5.25	5.19	1.87
OR Quartile 3	4.73	5.06	1.54	4.23	5.06	1.18	4.55	5.30	1.15
p Value	1.9E-4	4.2E-5	0.24	8.6E-4	4.2E-5	0.66	7.4E-4	3.8E-5	0.71
Lower limit of 95% CI	2.09	2.33	0.751	1.81	2.33	0.573	1.89	2.40	0.555
Upper limit of 95% CI	10.7	11.0	3.15	9.87	11.0	2.42	11.0	11.7	2.37
OR Quartile 4	6.15	8.11	1.51	4.97	8.11	1.27	4.55	7.51	1.25
p Value	0.0043	9.6E-4	0.32	0.012	9.6E-4	0.58	0.018	0.0015	0.61
Lower limit of 95% CI	1.77	2.34	0.663	1.42	2.34	0.550	1.30	2.16	0.534
Upper limit of 95% CI	21.4	28.1	3.45	17.4	28.1	2.92	15.9	26.0	2.90

[0169] Table 10.5: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	2.42	6.53	2.46	6.52	2.46	6.52
Average	8.34	16.7	8.43	16.5	8.43	16.5
Stdev	15.4	24.8	15.4	24.6	15.4	24.6
p (t-test)		0.012		0.016		0.016
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	103	111	103	111	103	111
n (Patient)	85	63	84	64	84	64

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	1.95	8.30	2.04	7.97	2.04	7.97
Average	4.59	18.5	4.71	18.0	4.71	18.0
Stdev	8.07	25.2	8.15	25.0	8.15	25.0
p (t-test)		1.9E-5		4.5E-5		4.5E-5
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	57.5	111	57.5	111	57.5	111
n (Patient)	70	78	68	80	68	80

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.05	6.20	3.05	5.36	3.05	5.36
Average	8.92	17.6	9.06	17.0	9.16	16.6
Stdev	15.1	26.7	15.2	26.3	15.4	26.0
p (t-test)		0.013		0.021		0.032
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	103	111	103	111	103	111
n (Patient)	95	52	93	54	91	56

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.64	0.71	0.60	0.63	0.69	0.59	0.63	0.69	0.58
SE	0.047	0.042	0.050	0.047	0.043	0.049	0.047	0.043	0.049
p Value	0.0030	3.3E-7	0.053	0.0063	1.0E-5	0.082	0.0063	1.0E-5	0.093
nCohort Recovered	85	70	95	84	68	93	84	68	91
nCohort Non-recovered	63	78	52	64	80	54	64	80	56
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	83%	83%	77%	81%	81%	76%	81%	81%	77%
Specificity	31%	34%	26%	30%	32%	26%	30%	32%	26%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	62%	65%	60%	61%	64%	59%	61%	64%	59%
Specificity	59%	67%	55%	58%	66%	55%	58%	66%	55%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	32%	40%	31%	31%	39%	30%	31%	39%	29%
Specificity	80%	91%	78%	80%	91%	77%	80%	91%	77%
OR Quartile 2	2.08	2.61	1.19	1.84	2.07	1.10	1.84	2.07	1.18
p Value	0.071	0.015	0.67	0.13	0.059	0.82	0.13	0.059	0.67
Lower limit of 95% CI	0.938	1.20	0.540	0.839	0.972	0.504	0.839	0.972	0.545
Upper limit of 95% CI	4.62	5.65	2.62	4.02	4.42	2.39	4.02	4.42	2.57
OR Quartile 3	2.32	3.86	1.79	2.18	3.44	1.77	2.18	3.44	1.75
p Value	0.013	1.1E-4	0.098	0.021	3.6E-4	0.10	0.021	3.6E-4	0.10
Lower limit of 95% CI	1.19	1.95	0.899	1.12	1.75	0.895	1.12	1.75	0.892
Upper limit of 95% CI	4.52	7.64	3.54	4.24	6.78	3.48	4.24	6.78	3.43

OR Quartile 4	1.86	7.04	1.57	1.79	6.54	1.44	1.79	6.54	1.33
p Value	0.11	5.9E-5	0.25	0.13	1.1E-4	0.34	0.13	1.1E-4	0.46
Lower limit of 95% CI	0.878	2.72	0.730	0.846	2.53	0.675	0.846	2.53	0.625
Upper limit of 95% CI	3.94	18.2	3.36	3.79	16.9	3.09	3.79	16.9	2.84

[0170] Table 10.6: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	62.2	104	58.6	103	58.6	103
Average	72.8	116	74.2	115	74.2	115
Stdev	33.3	66.6	35.3	66.6	35.3	66.6
p (t-test)		0.057		0.084		0.084
Min	41.1	13.2	41.1	13.2	41.1	13.2
Max	134	401	134	401	134	401
n (Patient)	9	141	8	142	8	142

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	65.2	105	68.2	104	68.2	104
Average	81.9	118	83.5	117	83.5	117
Stdev	44.3	67.3	45.1	67.2	45.1	67.2
p (t-test)		0.031		0.048		0.048
Min	23.6	13.2	23.6	13.2	23.6	13.2
Max	174	401	174	401	174	401
n (Patient)	18	132	17	133	17	133

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	91.4	115	92.8	114	94.2	112
Average	98.4	125	98.1	124	99.5	122
Stdev	51.1	73.2	50.5	73.0	51.2	72.4
p (t-test)		0.015		0.018		0.038
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	63	86	60	89	57	92

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.66	0.60	0.71	0.65	0.60	0.71	0.65	0.58
SE	0.076	0.062	0.046	0.081	0.064	0.047	0.081	0.064	0.047
p Value	0.0049	0.0075	0.032	0.012	0.018	0.037	0.012	0.018	0.082
nCohort Recovered	9	18	63	8	17	60	8	17	57
nCohort Non-recovered	141	132	86	142	133	89	142	133	92

Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	77%	78%	80%	76%	77%	79%	76%	77%	78%
Specificity	56%	50%	32%	50%	47%	30%	50%	47%	30%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	52%	52%	57%	51%	52%	56%	51%	52%	54%
Specificity	78%	67%	59%	75%	65%	58%	75%	65%	56%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	27%	27%	30%	27%	27%	30%	27%	27%	29%
Specificity	100%	89%	81%	100%	88%	82%	100%	88%	81%
OR Quartile 2	4.09	3.55	1.89	3.18	3.05	1.58	3.18	3.05	1.53
p Value	0.044	0.014	0.097	0.12	0.035	0.23	0.12	0.035	0.27
Lower limit of 95% CI	1.04	1.29	0.891	0.754	1.08	0.746	0.754	1.08	0.720
Upper limit of 95% CI	16.1	9.77	4.00	13.4	8.60	3.34	13.4	8.60	3.25
OR Quartile 3	3.76	2.19	1.88	3.17	1.98	1.79	3.17	1.98	1.52
p Value	0.11	0.14	0.059	0.17	0.20	0.083	0.17	0.20	0.21
Lower limit of 95% CI	0.754	0.776	0.975	0.619	0.691	0.925	0.619	0.691	0.784
Upper limit of 95% CI	18.7	6.18	3.64	16.3	5.66	3.48	16.3	5.66	2.96
OR Quartile 4	7.07	3.00	1.84	6.26	2.78	1.94	6.26	2.78	1.74
p Value	0.18	0.16	0.12	0.21	0.19	0.10	0.21	0.19	0.17
Lower limit of 95% CI	0.402	0.657	0.845	0.353	0.606	0.876	0.353	0.606	0.783
Upper limit of 95% CI	124	13.7	4.01	111	12.8	4.30	111	12.8	3.85

[0171] Table 10.7: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	54.6	111	60.9	105	67.1	104
Average	73.4	120	77.6	118	79.0	118
Stdev	42.2	66.8	44.0	67.0	45.0	66.9
p (t-test)		0.0025		0.014		0.022
Min	23.6	13.2	23.6	13.2	23.6	13.2
Max	170	401	170	401	170	401
n (Patient)	21	129	18	132	17	133

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	64.7	111	67.7	109	68.2	106
Average	81.1	121	84.1	119	85.2	119
Stdev	44.6	67.9	44.9	68.0	45.4	68.0
p (t-test)		0.0039		0.012		0.019
Min	23.6	13.2	23.6	13.2	23.6	13.2
Max	174	401	174	401	174	401
n (Patient)	28	122	26	124	25	125

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	88.6	120	90.0	118	90.0	113

Average	96.7	131	97.1	129	97.5	128
Stdev	52.3	73.9	52.2	73.4	52.9	72.8
p (t-test)		0.0016		0.0039		0.0061
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	71	74	66	79	64	81

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.73	0.68	0.64	0.70	0.66	0.63	0.69	0.65	0.62
SE	0.052	0.051	0.046	0.059	0.054	0.046	0.061	0.056	0.046
p Value	8.7E-6	3.2E-4	0.0024	7.8E-4	0.0033	0.0061	0.0022	0.0071	0.0094
nCohort Recovered	21	28	71	18	26	66	17	25	64
nCohort Non-recovered	129	122	74	132	124	79	133	125	81
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	80%	80%	84%	78%	79%	81%	77%	78%	81%
Specificity	57%	50%	34%	50%	46%	32%	47%	44%	33%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	53%	54%	59%	52%	53%	57%	52%	53%	56%
Specificity	71%	68%	59%	67%	65%	58%	65%	64%	56%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	29%	29%	34%	28%	28%	33%	28%	28%	32%
Specificity	95%	89%	83%	94%	88%	83%	94%	88%	83%
OR Quartile 2	5.28	4.08	2.64	3.55	3.23	1.99	3.05	2.85	2.15
p Value	7.3E-4	0.0014	0.016	0.014	0.0093	0.077	0.035	0.022	0.050
Lower limit of 95% CI	2.01	1.72	1.20	1.29	1.33	0.927	1.08	1.16	0.999
Upper limit of 95% CI	13.9	9.70	5.81	9.77	7.82	4.28	8.60	7.00	4.62
OR Quartile 3	2.88	2.49	2.12	2.19	2.15	1.80	1.98	1.99	1.61
p Value	0.040	0.040	0.026	0.14	0.089	0.082	0.20	0.13	0.16
Lower limit of 95% CI	1.05	1.04	1.09	0.776	0.890	0.928	0.691	0.818	0.830
Upper limit of 95% CI	7.88	5.94	4.12	6.18	5.19	3.48	5.66	4.84	3.11
OR Quartile 4	8.04	3.35	2.51	6.62	3.01	2.45	6.17	2.85	2.28
p Value	0.046	0.060	0.022	0.071	0.087	0.028	0.083	0.11	0.044
Lower limit of 95% CI	1.04	0.951	1.14	0.850	0.851	1.10	0.789	0.803	1.02
Upper limit of 95% CI	62.1	11.8	5.50	51.5	10.7	5.46	48.2	10.1	5.07

[0172] Table 10.8: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	76.1	106	76.1	106	84.0	105
Average	90.2	120	90.3	120	91.9	119
Stdev	51.3	68.1	52.3	67.8	54.0	67.5
p (t-test)		0.022		0.029		0.057
Min	23.6	13.2	23.6	13.2	23.6	13.2
Max	246	401	246	401	246	401
n (Patient)	32	117	30	119	27	122

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered	Non-recovered	Recovered	Non-recovered	Recovered	Non-recovered

	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort
Median	86.1	109	87.0	106	87.0	106
Average	95.9	121	97.0	120	97.0	120
Stdev	51.8	69.1	52.1	69.1	52.1	69.1
p (t-test)		0.047		0.067		0.067
Min	23.6	13.2	23.6	13.2	23.6	13.2
Max	246	401	246	401	246	401
n (Patient)	38	110	37	111	37	111

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	98.3	118	96.1	115	106	108
Average	105	130	106	128	111	123
Stdev	56.9	73.2	58.0	72.1	58.5	71.9
p (t-test)		0.034		0.050		0.28
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	260	401	260	401	260	401
n (Patient)	64	69	61	72	55	78

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.64	0.60	0.60	0.64	0.60	0.59	0.62	0.60	0.54
SE	0.052	0.051	0.049	0.053	0.052	0.049	0.056	0.052	0.051
p Value	0.0073	0.041	0.046	0.0095	0.067	0.060	0.027	0.067	0.41
nCohort Recovered	32	38	64	30	37	61	27	37	55
nCohort Non-recovered	117	110	69	119	111	72	122	111	78
Cutoff Quartile 2	66.7	66.8	69.2	66.7	66.8	69.2	66.7	66.8	69.2
Sensitivity	79%	80%	81%	79%	79%	81%	79%	79%	76%
Specificity	41%	39%	31%	40%	38%	31%	41%	38%	25%
Cutoff Quartile 3	101	101	106	101	101	106	101	101	106
Sensitivity	53%	53%	54%	53%	52%	53%	52%	52%	50%
Specificity	59%	58%	53%	60%	57%	52%	59%	57%	49%
Cutoff Quartile 4	142	143	148	142	143	148	142	143	148
Sensitivity	29%	27%	33%	29%	27%	32%	28%	27%	29%
Specificity	88%	82%	83%	87%	81%	82%	85%	81%	80%
OR Quartile 2	2.65	2.61	1.96	2.51	2.33	1.87	2.54	2.33	1.06
p Value	0.022	0.019	0.10	0.035	0.040	0.12	0.038	0.040	0.89
Lower limit of 95% CI	1.15	1.17	0.878	1.07	1.04	0.845	1.05	1.04	0.478
Upper limit of 95% CI	6.12	5.81	4.37	5.88	5.22	4.16	6.13	5.22	2.35
OR Quartile 3	1.65	1.53	1.31	1.69	1.44	1.23	1.61	1.44	0.964
p Value	0.22	0.26	0.44	0.21	0.34	0.55	0.27	0.34	0.92
Lower limit of 95% CI	0.745	0.728	0.663	0.747	0.679	0.623	0.689	0.679	0.484
Upper limit of 95% CI	3.64	3.23	2.59	3.81	3.04	2.44	3.74	3.04	1.92
OR Quartile 4	2.87	1.66	2.41	2.60	1.59	2.13	2.22	1.59	1.67
p Value	0.066	0.28	0.036	0.096	0.33	0.070	0.17	0.33	0.22
Lower limit of 95% CI	0.935	0.661	1.06	0.844	0.631	0.940	0.715	0.631	0.736
Upper limit of 95% CI	8.80	4.17	5.47	8.01	4.00	4.84	6.90	4.00	3.80

[0173] Table 10.9: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	77.9	118	84.0	113	87.0	113
Average	88.8	125	91.7	123	94.1	121
Stdev	49.9	68.6	52.1	68.3	52.5	68.3
p (t-test)		0.0033		0.018		0.041
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	38	106	33	111	31	113

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	85.2	118	85.2	118	87.0	113
Average	94.3	125	94.3	125	96.1	124
Stdev	50.5	70.1	50.5	70.1	50.7	70.2
p (t-test)		0.0088		0.0088		0.021
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	45	99	45	99	43	101

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	109	118	119	104	111	113
Average	111	131	119	124	116	125
Stdev	57.6	73.3	57.6	72.9	58.8	71.0
p (t-test)		0.091		0.67		0.46
Min	24.0	13.2	24.0	13.2	24.0	13.2
Max	260	401	260	401	260	401
n (Patient)	60	65	52	73	47	79

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.67	0.63	0.58	0.64	0.63	0.50	0.62	0.61	0.53
SE	0.048	0.048	0.051	0.052	0.048	0.053	0.054	0.049	0.053
p Value	4.2E-4	0.0062	0.13	0.0068	0.0062	0.99	0.025	0.020	0.61
nCohort Recovered	38	45	60	33	45	52	31	43	47
nCohort Non-recovered	106	99	65	111	99	73	113	101	79
Cutoff Quartile 2	67.0	67.0	75.7	67.0	67.0	75.7	67.0	67.0	75.8
Sensitivity	81%	81%	83%	78%	81%	75%	78%	80%	76%
Specificity	42%	38%	33%	36%	38%	25%	35%	37%	28%
Cutoff Quartile 3	103	103	113	103	103	113	103	103	112
Sensitivity	55%	55%	52%	53%	55%	48%	52%	53%	51%
Specificity	63%	60%	52%	61%	60%	46%	58%	58%	51%
Cutoff Quartile 4	146	146	152	146	146	152	146	146	152
Sensitivity	29%	28%	32%	28%	28%	29%	27%	28%	28%
Specificity	87%	82%	82%	85%	82%	79%	84%	81%	79%
OR Quartile 2	3.13	2.56	2.45	2.07	2.56	1.02	1.94	2.40	1.21
p Value	0.0056	0.019	0.037	0.090	0.019	0.97	0.13	0.030	0.65
Lower limit of 95% CI	1.40	1.17	1.06	0.893	1.17	0.447	0.820	1.09	0.531
Upper limit of 95% CI	7.01	5.59	5.70	4.80	5.59	2.32	4.57	5.28	2.75
OR Quartile 3	2.07	1.80	1.17	1.75	1.80	0.789	1.51	1.60	1.07
p Value	0.061	0.11	0.66	0.17	0.11	0.52	0.31	0.20	0.85
Lower limit of 95% CI	0.967	0.880	0.581	0.791	0.880	0.387	0.678	0.776	0.520
Upper limit of 95% CI	4.44	3.68	2.37	3.85	3.68	1.61	3.38	3.28	2.20
OR Quartile 4	2.73	1.82	2.13	2.17	1.82	1.51	1.97	1.68	1.43
p Value	0.056	0.18	0.077	0.14	0.18	0.34	0.20	0.25	0.41

Lower limit of 95% CI	0.974	0.756	0.922	0.769	0.756	0.652	0.693	0.694	0.608
Upper limit of 95% CI	7.64	4.40	4.90	6.13	4.40	3.47	5.58	4.06	3.36

[0174] Table 10.10: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	91.4	113	90.0	115	90.0	115
Average	101	128	100.0	128	100.0	128
Stdev	52.9	76.1	53.0	75.6	53.0	75.6
p (t-test)		0.010		0.0078		0.0078
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	253	401	253	401	253	401
n (Patient)	81	69	80	70	80	70

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	87.0	118	85.2	119	85.2	119
Average	94.1	129	92.9	129	92.9	129
Stdev	49.4	73.3	49.6	72.5	49.6	72.5
p (t-test)		0.0012		7.6E-4		7.6E-4
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	67	83	65	85	65	85

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	94.3	115	94.2	118	91.4	120
Average	102	134	101	134	100	135
Stdev	54.0	79.2	54.4	77.7	54.6	76.4
p (t-test)		0.0034		0.0026		0.0017
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	260	401	260	401	260	401
n (Patient)	95	54	93	56	91	58

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.60	0.64	0.62	0.61	0.65	0.63	0.61	0.65	0.64
SE	0.047	0.045	0.049	0.046	0.044	0.048	0.046	0.044	0.047
p Value	0.031	0.0020	0.016	0.020	7.6E-4	0.0091	0.020	7.6E-4	0.0039
nCohort Recovered	81	67	95	80	65	93	80	65	91
nCohort Non-recovered	69	83	54	70	85	56	70	85	58
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	81%	84%	83%	81%	85%	84%	81%	85%	84%

Specificity	31%	37%	29%	31%	38%	30%	31%	38%	31%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	57%	57%	57%	57%	58%	59%	57%	58%	60%
Specificity	56%	58%	54%	56%	60%	55%	56%	60%	56%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	33%	33%	37%	34%	33%	38%	34%	33%	38%
Specificity	81%	84%	81%	82%	85%	82%	82%	85%	82%
OR Quartile 2	1.92	3.21	2.09	1.99	3.46	2.25	1.99	3.46	2.42
p Value	0.094	0.0031	0.086	0.078	0.0017	0.058	0.078	0.0017	0.039
Lower limit of 95% CI	0.894	1.48	0.901	0.927	1.60	0.972	0.927	1.60	1.05
Upper limit of 95% CI	4.14	6.93	4.84	4.29	7.50	5.21	4.29	7.50	5.60
OR Quartile 3	1.62	1.82	1.56	1.71	2.04	1.74	1.71	2.04	1.94
p Value	0.14	0.072	0.19	0.10	0.033	0.10	0.10	0.033	0.052
Lower limit of 95% CI	0.851	0.948	0.797	0.897	1.06	0.891	0.897	1.06	0.993
Upper limit of 95% CI	3.10	3.49	3.06	3.28	3.94	3.41	3.28	3.94	3.79
OR Quartile 4	2.20	2.45	2.52	2.46	2.70	2.68	2.46	2.70	2.86
p Value	0.040	0.026	0.016	0.020	0.016	0.010	0.020	0.016	0.0064
Lower limit of 95% CI	1.04	1.11	1.18	1.15	1.20	1.26	1.15	1.20	1.34
Upper limit of 95% CI	4.66	5.42	5.35	5.25	6.08	5.70	5.25	6.08	6.11

[0175] Example 11. Use of Cathepsin B for evaluating renal status in patients admitted to the ICU: Recovery to RIFLE 0 and R from RIFLE I and F

[0176] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Cathepsin B is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0177] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output during a period starting at 12, 24, 48, or 72 hours after sample collection or at any time within 7 days after sample collection. Two cohorts are defined to represent a “recovered” and a “non-recovered” population. “Recovered” indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0) or risk of injury (R). “Non-recovered” indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is injury (I) or failure (F). If a patient dies or is placed on renal replacement therapy (RRT) within 9 days of enrollment, the patient is considered “non-recovered”.

[0178] The ability to distinguish the “recovered” and “non-recovered” cohorts is determined using receiver operating characteristic (ROC) analysis.

[0179] Table 11.1: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the “recovered” and “non-recovered” cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	2.04	5.92	2.13	5.39	2.06	4.92
Average	2.93	14.6	3.03	14.4	2.98	14.3
Stdev	3.31	22.4	3.38	22.2	3.42	22.2
p (t-test)		0.0029		0.0047		0.0054
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	14.6	111	14.6	111	14.6	111
n (Patient)	34	114	32	116	31	117

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	1.57	6.58	1.57	6.58	1.55	6.50
Average	2.86	16.0	2.86	16.0	2.82	15.9
Stdev	3.18	23.2	3.18	23.2	3.20	23.1
p (t-test)		2.0E-4		2.0E-4		2.4E-4
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	14.6	111	14.6	111	14.6	111
n (Patient)	46	102	46	102	45	103

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.05	5.36	3.29	4.83	3.17	4.85
Average	9.39	14.8	9.61	14.5	9.07	14.9
Stdev	16.2	23.9	16.3	23.6	15.8	23.8
p (t-test)		0.11		0.15		0.080
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	103	111	103	111	103	111
n (Patient)	77	70	75	72	74	73

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.69	0.72	0.57	0.68	0.72	0.56	0.68	0.72	0.57
SE	0.048	0.042	0.047	0.050	0.042	0.047	0.050	0.042	0.047
p Value	9.4E-5	2.0E-7	0.13	4.2E-4	2.0E-7	0.23	2.6E-4	1.0E-7	0.14
nCohort Recovered	34	46	77	32	46	75	31	45	74
nCohort Non-recovered	114	102	70	116	102	72	117	103	73
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	76%	80%	76%	76%	80%	75%	76%	81%	75%
Specificity	29%	37%	26%	28%	37%	25%	29%	38%	26%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	57%	60%	57%	56%	60%	56%	56%	60%	56%
Specificity	74%	72%	56%	72%	72%	55%	74%	73%	55%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	31%	34%	27%	30%	34%	26%	30%	34%	27%
Specificity	94%	96%	77%	94%	96%	76%	94%	96%	77%
OR Quartile 2	1.34	2.40	1.09	1.23	2.40	1.02	1.30	2.52	1.06
p Value	0.50	0.026	0.81	0.65	0.026	0.96	0.56	0.020	0.89
Lower limit of 95% CI	0.571	1.11	0.518	0.510	1.11	0.483	0.537	1.16	0.501
Upper limit of 95% CI	3.16	5.21	2.31	2.97	5.21	2.14	3.15	5.47	2.22
OR Quartile 3	3.68	3.78	1.69	3.26	3.78	1.51	3.72	4.16	1.59
p Value	0.0026	5.5E-4	0.12	0.0067	5.5E-4	0.22	0.0036	2.8E-4	0.16
Lower limit of 95% CI	1.58	1.78	0.878	1.39	1.78	0.787	1.54	1.93	0.830
Upper limit of 95% CI	8.60	8.03	3.24	7.65	8.03	2.89	9.00	8.98	3.05

OR Quartile 4	7.09	11.5	1.22	6.48	11.5	1.14	6.19	11.1	1.27
p Value	0.0096	0.0012	0.60	0.014	0.0012	0.74	0.016	0.0014	0.54
Lower limit of 95% CI	1.61	2.63	0.579	1.47	2.63	0.539	1.40	2.53	0.599
Upper limit of 95% CI	31.2	50.2	2.57	28.6	50.2	2.39	27.4	48.4	2.67

[0180] Table 11.2: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "recovered" and "non-recovered" cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	2.02	6.53	2.02	6.50	2.02	6.50
Average	3.19	16.0	3.21	15.7	3.21	15.7
Stdev	3.76	23.4	3.82	23.2	3.82	23.2
p (t-test)		2.8E-4		4.5E-4		4.5E-4
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	17.5	111	17.5	111	17.5	111
n (Patient)	47	101	45	103	45	103

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	1.74	7.50	1.60	7.19	1.60	7.19
Average	3.05	17.0	3.01	16.9	3.01	16.9
Stdev	3.60	23.9	3.63	23.8	3.63	23.8
p (t-test)		3.6E-5		4.4E-5		4.4E-5
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	17.5	111	17.5	111	17.5	111
n (Patient)	54	94	53	95	53	95

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.04	5.87	3.04	5.87	3.04	5.87
Average	8.93	16.0	8.51	16.3	8.51	16.3
Stdev	15.7	24.9	15.2	24.9	15.2	24.9
p (t-test)		0.039		0.023		0.023
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	103	111	103	111	103	111
n (Patient)	80	63	78	65	78	65

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.70	0.73	0.59	0.70	0.74	0.59	0.70	0.74	0.59
SE	0.044	0.041	0.048	0.044	0.041	0.048	0.044	0.041	0.048
p Value	4.0E-6	1.3E-8	0.072	8.0E-6	7.1E-9	0.061	8.0E-6	7.1E-9	0.061
nCohort Recovered	47	54	80	45	53	78	45	53	78
nCohort Non-recovered	101	94	63	103	95	65	103	95	65
Cutoff Quartile 2	1.13	1.13	1.06	1.13	1.13	1.06	1.13	1.13	1.06
Sensitivity	79%	82%	79%	79%	82%	78%	79%	82%	78%
Specificity	34%	37%	29%	33%	38%	28%	33%	38%	28%

Cutoff Quartile 3	3.63	3.63	3.80	3.63	3.63	3.80	3.63	3.63	3.80
Sensitivity	60%	63%	57%	60%	63%	57%	60%	63%	57%
Specificity	72%	72%	55%	73%	74%	55%	73%	74%	55%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	34%	36%	30%	33%	36%	31%	33%	36%	31%
Specificity	94%	94%	79%	93%	94%	79%	93%	94%	79%
OR Quartile 2	1.97	2.66	1.55	1.84	2.78	1.43	1.84	2.78	1.43
p Value	0.086	0.012	0.27	0.12	0.0087	0.36	0.12	0.0087	0.36
Lower limit of 95% CI	0.909	1.24	0.712	0.845	1.30	0.663	0.845	1.30	0.663
Upper limit of 95% CI	4.25	5.71	3.38	4.01	5.97	3.09	4.01	5.97	3.09
OR Quartile 3	3.99	4.38	1.63	4.16	4.78	1.62	4.16	4.78	1.62
p Value	3.2E-4	6.9E-5	0.15	2.8E-4	3.4E-5	0.15	2.8E-4	3.4E-5	0.15
Lower limit of 95% CI	1.88	2.12	0.838	1.93	2.28	0.836	1.93	2.28	0.836
Upper limit of 95% CI	8.47	9.07	3.17	8.98	10.0	3.15	8.98	10.0	3.15
OR Quartile 4	7.44	9.63	1.60	6.90	9.29	1.72	6.90	9.29	1.72
p Value	0.0015	3.4E-4	0.22	0.0023	4.2E-4	0.16	0.0023	4.2E-4	0.16
Lower limit of 95% CI	2.15	2.79	0.749	1.99	2.69	0.804	1.99	2.69	0.804
Upper limit of 95% CI	25.7	33.2	3.42	23.9	32.0	3.69	23.9	32.0	3.69

[0181] Table 11.3: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "recovered" and "non-recovered" cohorts where recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	2.10	6.53	2.10	6.53	2.13	6.52
Average	5.53	16.4	5.53	16.4	5.61	16.2
Stdev	10.1	24.2	10.1	24.2	10.1	24.1
p (t-test)		0.0012		0.0012		0.0017
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	57.5	111	57.5	111	57.5	111
n (Patient)	60	87	60	87	59	88

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	2.10	7.37	2.10	7.37	2.10	7.37
Average	5.35	17.3	5.35	17.3	5.35	17.3
Stdev	9.78	24.6	9.78	24.6	9.78	24.6
p (t-test)		3.7E-4		3.7E-4		3.7E-4
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	57.5	111	57.5	111	57.5	111
n (Patient)	64	82	64	82	64	82

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.61	6.53	3.61	6.53	3.61	5.87
Average	9.24	17.3	9.24	17.3	9.42	16.9
Stdev	15.8	26.0	15.8	26.0	16.0	25.7
p (t-test)		0.029		0.029		0.045
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	103	111	103	111	103	111

n (Patient)	74	57	74	57	72	59

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.67	0.69	0.60	0.67	0.69	0.60	0.67	0.69	0.59
SE	0.044	0.043	0.050	0.044	0.043	0.050	0.044	0.043	0.050
p Value	8.8E-5	6.9E-6	0.058	8.8E-5	6.9E-6	0.058	1.9E-4	6.9E-6	0.082
nCohort Recovered	60	64	74	60	64	74	59	64	72
nCohort Non-recovered	87	82	57	87	82	57	88	82	59
Cutoff Quartile 2	1.13	1.12	1.16	1.13	1.12	1.16	1.13	1.12	1.16
Sensitivity	80%	83%	79%	80%	83%	79%	80%	83%	78%
Specificity	33%	36%	28%	33%	36%	28%	32%	36%	28%
Cutoff Quartile 3	3.62	3.63	4.38	3.62	3.63	4.38	3.62	3.63	4.38
Sensitivity	63%	65%	56%	63%	65%	56%	62%	65%	56%
Specificity	68%	69%	54%	68%	69%	54%	68%	69%	54%
Cutoff Quartile 4	13.1	13.3	14.2	13.1	13.3	14.2	13.1	13.3	14.2
Sensitivity	33%	35%	30%	33%	35%	30%	33%	35%	29%
Specificity	87%	88%	78%	87%	88%	78%	86%	88%	78%
OR Quartile 2	2.06	2.72	1.49	2.06	2.72	1.49	1.85	2.72	1.36
p Value	0.061	0.011	0.34	0.061	0.011	0.34	0.11	0.011	0.45
Lower limit of 95% CI	0.968	1.26	0.659	0.968	1.26	0.659	0.870	1.26	0.610
Upper limit of 95% CI	4.38	5.88	3.35	4.38	5.88	3.35	3.92	5.88	3.04
OR Quartile 3	3.71	4.02	1.51	3.71	4.02	1.51	3.51	4.02	1.50
p Value	2.3E-4	8.9E-5	0.25	2.3E-4	8.9E-5	0.25	4.1E-4	8.9E-5	0.25
Lower limit of 95% CI	1.85	2.00	0.752	1.85	2.00	0.752	1.75	2.00	0.751
Upper limit of 95% CI	7.45	8.06	3.02	7.45	8.06	3.02	7.04	8.06	3.00
OR Quartile 4	3.25	3.83	1.54	3.25	3.83	1.54	3.13	3.83	1.42
p Value	0.0078	0.0024	0.29	0.0078	0.0024	0.29	0.0099	0.0024	0.39
Lower limit of 95% CI	1.36	1.61	0.697	1.36	1.61	0.697	1.32	1.61	0.642
Upper limit of 95% CI	7.74	9.13	3.40	7.74	9.13	3.40	7.46	9.13	3.13

[0182] Table 11.4: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "recovered" and "non-recovered" cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	2.17	7.97	2.20	6.94	2.17	7.00
Average	5.61	18.2	5.77	17.5	5.70	17.2
Stdev	9.71	25.6	9.89	25.3	10.0	24.9
p (t-test)		2.1E-4		5.6E-4		8.4E-4
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	57.5	111	57.5	111	57.5	111
n (Patient)	68	74	65	77	62	80

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	2.17	8.29	2.17	8.29	2.13	8.44
Average	5.56	18.6	5.56	18.6	5.43	18.5
Stdev	9.58	25.8	9.58	25.8	9.59	25.7
p (t-test)		1.2E-4		1.2E-4		1.1E-4
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	57.5	111	57.5	111	57.5	111
n (Patient)	70	72	70	72	69	73

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.61	7.81	3.62	6.20	3.63	6.20
Average	9.26	18.2	9.10	17.6	9.35	17.1
Stdev	15.9	26.8	15.6	26.2	15.7	25.9
p (t-test)		0.024		0.030		0.046
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	103	111	103	111	103	111
n (Patient)	70	51	65	56	64	58

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.69	0.69	0.61	0.67	0.69	0.60	0.67	0.70	0.58
SE	0.044	0.044	0.052	0.045	0.044	0.052	0.045	0.044	0.052
p Value	2.5E-5	1.3E-5	0.032	1.3E-4	1.3E-5	0.062	1.3E-4	4.9E-6	0.12
nCohort Recovered	68	70	70	65	70	65	62	69	64
nCohort Non-recovered	74	72	51	77	72	56	80	73	58
Cutoff Quartile 2	1.12	1.12	1.22	1.12	1.12	1.22	1.12	1.12	1.23
Sensitivity	82%	83%	80%	81%	83%	79%	80%	84%	76%
Specificity	34%	34%	29%	32%	34%	28%	32%	35%	27%
Cutoff Quartile 3	3.71	3.71	4.38	3.71	3.71	4.38	3.71	3.71	4.56
Sensitivity	65%	65%	59%	64%	65%	57%	64%	66%	57%
Specificity	66%	66%	56%	66%	66%	55%	68%	67%	56%
Cutoff Quartile 4	13.3	13.3	16.1	13.3	13.3	16.1	13.3	13.3	15.7
Sensitivity	36%	38%	31%	35%	38%	30%	35%	38%	29%
Specificity	87%	87%	79%	86%	87%	78%	87%	88%	78%
OR Quartile 2	2.40	2.61	1.64	1.97	2.61	1.40	1.90	2.71	1.14
p Value	0.028	0.018	0.26	0.083	0.018	0.43	0.098	0.014	0.76
Lower limit of 95% CI	1.10	1.18	0.691	0.916	1.18	0.607	0.887	1.23	0.502
Upper limit of 95% CI	5.24	5.76	3.89	4.25	5.76	3.25	4.09	5.99	2.58
OR Quartile 3	3.61	3.60	1.80	3.42	3.60	1.66	3.69	3.84	1.70
p Value	2.8E-4	2.8E-4	0.12	5.0E-4	2.8E-4	0.17	2.6E-4	1.5E-4	0.15
Lower limit of 95% CI	1.81	1.80	0.866	1.71	1.80	0.805	1.83	1.91	0.829
Upper limit of 95% CI	7.22	7.20	3.73	6.84	7.20	3.40	7.44	7.70	3.48
OR Quartile 4	3.77	4.07	1.68	3.36	4.07	1.59	3.63	4.74	1.48
p Value	0.0021	0.0012	0.22	0.0050	0.0012	0.27	0.0038	4.9E-4	0.35
Lower limit of 95% CI	1.62	1.74	0.737	1.44	1.74	0.699	1.52	1.98	0.653
Upper limit of 95% CI	8.78	9.49	3.81	7.82	9.49	3.61	8.70	11.4	3.36

[0183] Table 11.5: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	2.46	7.97	2.42	7.81	2.46	7.17
Average	8.00	18.4	8.04	18.1	8.12	17.8
Stdev	14.8	25.8	14.9	25.7	15.0	25.5
p (t-test)		0.0023		0.0030		0.0042
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126

Max	103	111	103	111	103	111
n (Patient)	92	56	91	57	90	58

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	2.22	8.53	2.22	8.53	2.22	8.53
Average	5.57	19.8	5.57	19.8	5.57	19.8
Stdev	9.15	26.7	9.15	26.7	9.15	26.7
p (t-test)		1.3E-5		1.3E-5		1.3E-5
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	57.5	111	57.5	111	57.5	111
n (Patient)	82	66	82	66	82	66

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	3.03	7.97	3.03	7.97	3.03	7.17
Average	8.64	18.9	8.64	18.9	8.76	18.2
Stdev	14.9	27.4	14.9	27.4	15.0	27.0
p (t-test)		0.0039		0.0039		0.0070
Min	0.0435	0.126	0.0435	0.126	0.0435	0.126
Max	103	111	103	111	103	111
n (Patient)	99	48	99	48	97	50

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.65	0.70	0.62	0.65	0.70	0.62	0.64	0.70	0.61
SE	0.048	0.044	0.050	0.047	0.044	0.050	0.047	0.044	0.050
p Value	0.0018	8.3E-6	0.016	0.0016	8.3E-6	0.016	0.0035	8.3E-6	0.028
nCohort Recovered	92	82	99	91	82	99	90	82	97
nCohort Non-recovered	56	66	48	57	66	48	58	66	50
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	82%	83%	79%	82%	83%	79%	81%	83%	78%
Specificity	29%	32%	27%	30%	32%	27%	29%	32%	27%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	64%	67%	62%	65%	67%	62%	64%	67%	62%
Specificity	59%	63%	56%	59%	63%	56%	59%	63%	56%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	36%	39%	33%	35%	39%	33%	34%	39%	32%
Specificity	82%	87%	79%	81%	87%	79%	81%	87%	78%
OR Quartile 2	1.91	2.32	1.42	1.98	2.32	1.42	1.74	2.32	1.30
p Value	0.12	0.038	0.40	0.10	0.038	0.40	0.18	0.038	0.53
Lower limit of 95% CI	0.843	1.05	0.624	0.876	1.05	0.624	0.781	1.05	0.580
Upper limit of 95% CI	4.33	5.15	3.25	4.49	5.15	3.25	3.86	5.15	2.91
OR Quartile 3	2.56	3.47	2.08	2.70	3.47	2.08	2.52	3.47	2.05
p Value	0.0073	3.5E-4	0.042	0.0046	3.5E-4	0.042	0.0077	3.5E-4	0.044
Lower limit of 95% CI	1.29	1.75	1.03	1.36	1.75	1.03	1.28	1.75	1.02
Upper limit of 95% CI	5.08	6.85	4.22	5.36	6.85	4.22	4.98	6.85	4.12
OR Quartile 4	2.45	4.20	1.86	2.35	4.20	1.86	2.26	4.20	1.70
p Value	0.021	4.8E-4	0.11	0.027	4.8E-4	0.11	0.035	4.8E-4	0.17
Lower limit of 95% CI	1.15	1.88	0.860	1.10	1.88	0.860	1.06	1.88	0.792
Upper limit of 95% CI	5.24	9.38	4.01	5.02	9.38	4.01	4.81	9.38	3.66

[0184] Table 11.6: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum

creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	67.7	109	67.7	109	67.1	111
Average	83.1	121	81.1	121	79.3	121
Stdev	43.4	68.6	41.1	68.5	40.7	68.2
p (t-test)		0.0032		0.0025		0.0018
Min	31.3	13.2	31.3	13.2	31.3	13.2
Max	174	401	170	401	170	401
n (Patient)	32	118	30	120	29	121

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	67.1	113	67.1	113	66.9	115
Average	83.5	124	83.5	124	82.4	125
Stdev	44.4	69.2	44.4	69.2	44.4	68.9
p (t-test)		5.8E-4		5.8E-4		4.3E-4
Min	23.6	13.2	23.6	13.2	23.6	13.2
Max	182	401	182	401	182	401
n (Patient)	41	109	41	109	40	110

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	94.2	113	94.2	113	94.2	112
Average	102	126	101	126	101	125
Stdev	53.7	75.0	53.4	74.6	53.8	74.2
p (t-test)		0.023		0.023		0.025
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	253	401	253	401	253	401
n (Patient)	76	73	74	75	73	76

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.68	0.69	0.59	0.69	0.69	0.59	0.70	0.69	0.59
SE	0.049	0.046	0.047	0.050	0.046	0.046	0.049	0.045	0.046
p Value	3.4E-4	4.2E-5	0.050	1.6E-4	4.2E-5	0.047	5.5E-5	1.7E-5	0.048
nCohort Recovered	32	41	76	30	41	74	29	40	73
nCohort Non-recovered	118	109	73	120	109	75	121	110	76
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	81%	83%	81%	80%	83%	80%	80%	83%	80%
Specificity	47%	46%	30%	47%	46%	30%	48%	48%	30%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	53%	56%	56%	53%	56%	56%	54%	56%	55%
Specificity	62%	66%	55%	63%	66%	55%	66%	68%	55%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	30%	30%	32%	30%	30%	32%	30%	30%	32%
Specificity	91%	88%	80%	93%	88%	81%	93%	88%	81%
OR Quartile 2	3.64	4.09	1.83	3.50	4.09	1.69	3.77	4.33	1.75
p Value	0.0023	4.6E-4	0.12	0.0037	4.6E-4	0.17	0.0023	2.9E-4	0.14
Lower limit of 95% CI	1.59	1.86	0.854	1.50	1.86	0.796	1.61	1.96	0.825

Upper limit of 95% CI	8.36	9.00	3.91	8.15	9.00	3.60	8.87	9.58	3.73
OR Quartile 3	1.91	2.45	1.58	1.97	2.45	1.58	2.21	2.68	1.50
p Value	0.11	0.019	0.16	0.11	0.019	0.16	0.067	0.011	0.22
Lower limit of 95% CI	0.856	1.16	0.829	0.865	1.16	0.828	0.947	1.25	0.785
Upper limit of 95% CI	4.26	5.18	3.02	4.50	5.18	3.02	5.13	5.74	2.86
OR Quartile 4	4.08	3.13	1.87	6.00	3.13	2.02	5.72	3.00	1.95
p Value	0.028	0.029	0.10	0.018	0.029	0.070	0.022	0.035	0.085
Lower limit of 95% CI	1.16	1.13	0.883	1.36	1.13	0.946	1.29	1.08	0.912
Upper limit of 95% CI	14.3	8.68	3.96	26.5	8.68	4.30	25.3	8.34	4.15

[0185] Table 11.7: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	68.2	116	67.1	118	67.1	118
Average	83.7	126	80.5	126	80.5	126
Stdev	42.8	70.0	40.8	69.5	40.8	69.5
p (t-test)		2.4E-4		7.8E-5		7.8E-5
Min	23.6	13.2	23.6	13.2	23.6	13.2
Max	174	401	171	401	171	401
n (Patient)	45	105	43	107	43	107

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	71.0	117	68.2	118	68.2	118
Average	86.0	127	85.0	127	85.0	127
Stdev	44.4	70.6	44.4	70.3	44.4	70.3
p (t-test)		2.6E-4		2.0E-4		2.0E-4
Min	23.6	13.2	23.6	13.2	23.6	13.2
Max	182	401	182	401	182	401
n (Patient)	50	100	49	101	49	101

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	88.6	120	87.0	120	87.0	120
Average	98.7	133	97.8	133	97.8	133
Stdev	54.1	74.8	54.1	73.9	54.1	73.9
p (t-test)		0.0018		0.0012		0.0012
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	253	401	253	401	253	401
n (Patient)	79	66	77	68	77	68

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only

AUC	0.69	0.68	0.64	0.71	0.69	0.65	0.71	0.69	0.65
SE	0.045	0.044	0.046	0.044	0.044	0.046	0.044	0.044	0.046
p Value	2.3E-5	5.2E-5	0.0028	1.4E-6	2.5E-5	0.0014	1.4E-6	2.5E-5	0.0014
nCohort Recovered	45	50	79	43	49	77	43	49	77
nCohort Non-recovered	105	100	66	107	101	68	107	101	68
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	83%	84%	85%	83%	84%	85%	83%	84%	85%
Specificity	44%	44%	33%	47%	45%	34%	47%	45%	34%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	57%	58%	61%	58%	58%	60%	58%	58%	60%
Specificity	67%	66%	58%	70%	67%	58%	70%	67%	58%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	31%	31%	35%	32%	31%	35%	32%	31%	35%
Specificity	89%	86%	82%	91%	86%	83%	91%	86%	83%
OR Quartile 2	3.87	4.12	2.75	4.30	4.33	2.96	4.30	4.33	2.96
p Value	6.4E-4	3.3E-4	0.016	2.7E-4	2.1E-4	0.0096	2.7E-4	2.1E-4	0.0096
Lower limit of 95% CI	1.78	1.90	1.21	1.96	1.99	1.30	1.96	1.99	1.30
Upper limit of 95% CI	8.41	8.94	6.24	9.42	9.41	6.72	9.42	9.41	6.72
OR Quartile 3	2.67	2.68	2.14	3.18	2.90	2.14	3.18	2.90	2.14
p Value	0.0085	0.0063	0.025	0.0027	0.0036	0.025	0.0027	0.0036	0.025
Lower limit of 95% CI	1.28	1.32	1.10	1.49	1.42	1.10	1.49	1.42	1.10
Upper limit of 95% CI	5.54	5.44	4.17	6.77	5.93	4.15	6.77	5.93	4.15
OR Quartile 4	3.67	2.76	2.48	4.54	2.66	2.69	4.54	2.66	2.69
p Value	0.012	0.028	0.020	0.0074	0.034	0.013	0.0074	0.034	0.013
Lower limit of 95% CI	1.33	1.12	1.15	1.50	1.07	1.24	1.50	1.07	1.24
Upper limit of 95% CI	10.1	6.82	5.35	13.7	6.57	5.84	13.7	6.57	5.84

[0186] Table 11.8: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	80.0	120	80.0	120	80.3	119
Average	90.7	128	90.7	128	91.3	128
Stdev	49.3	71.0	49.3	71.0	49.5	71.0
p (t-test)		5.5E-4		5.5E-4		9.3E-4
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	58	91	58	91	57	92

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	85.2	119	85.2	119	85.2	119
Average	95.4	127	95.4	127	95.4	127
Stdev	50.6	72.1	50.6	72.1	50.6	72.1
p (t-test)		0.0034		0.0034		0.0034
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	61	87	61	87	61	87

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	94.2	129	94.2	129	94.2	122
Average	103	136	103	136	104	134
Stdev	56.0	74.2	56.0	74.2	56.5	73.8
p (t-test)		0.0049		0.0049		0.0082
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	260	401	260	401	260	401
n (Patient)	72	61	72	61	70	63

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.67	0.63	0.64	0.67	0.63	0.64	0.66	0.63	0.63
SE	0.044	0.046	0.049	0.044	0.046	0.049	0.045	0.046	0.049
p Value	1.6E-4	0.0037	0.0051	1.6E-4	0.0037	0.0051	3.5E-4	0.0037	0.0086
nCohort Recovered	58	61	72	58	61	72	57	61	70
nCohort Non-recovered	91	87	61	91	87	61	92	87	63
Cutoff Quartile 2	66.7	66.8	69.2	66.7	66.8	69.2	66.7	66.8	69.2
Sensitivity	84%	83%	87%	84%	83%	87%	83%	83%	86%
Specificity	38%	36%	35%	38%	36%	35%	37%	36%	34%
Cutoff Quartile 3	101	101	106	101	101	106	101	101	106
Sensitivity	57%	56%	57%	57%	56%	57%	57%	56%	57%
Specificity	60%	59%	56%	60%	59%	56%	60%	59%	56%
Cutoff Quartile 4	142	143	148	142	143	148	142	143	148
Sensitivity	33%	30%	36%	33%	30%	36%	33%	30%	35%
Specificity	86%	82%	83%	86%	82%	83%	86%	82%	83%
OR Quartile 2	3.10	2.71	3.52	3.10	2.71	3.52	2.77	2.71	3.13
p Value	0.0039	0.011	0.0054	0.0039	0.011	0.0054	0.0087	0.011	0.0094
Lower limit of 95% CI	1.44	1.26	1.45	1.44	1.26	1.45	1.29	1.26	1.32
Upper limit of 95% CI	6.67	5.81	8.56	6.67	5.81	8.56	5.94	5.81	7.41
OR Quartile 3	2.03	1.86	1.68	2.03	1.86	1.68	1.92	1.86	1.68
p Value	0.039	0.067	0.14	0.039	0.067	0.14	0.056	0.067	0.14
Lower limit of 95% CI	1.04	0.957	0.846	1.04	0.957	0.846	0.983	0.957	0.844
Upper limit of 95% CI	3.97	3.60	3.35	3.97	3.60	3.35	3.76	3.60	3.33
OR Quartile 4	3.07	1.94	2.82	3.07	1.94	2.82	2.96	1.94	2.59
p Value	0.011	0.10	0.012	0.011	0.10	0.012	0.014	0.10	0.021
Lower limit of 95% CI	1.29	0.872	1.25	1.29	0.872	1.25	1.25	0.872	1.15
Upper limit of 95% CI	7.30	4.30	6.34	7.30	4.30	6.34	7.04	4.30	5.82

[0187] Table 11.9: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	88.6	122	87.8	120	88.6	119
Average	96.6	131	96.1	130	96.1	129
Stdev	49.0	74.1	49.3	73.2	50.4	72.3
p (t-test)		0.0016		0.0019		0.0030
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	65	79	62	82	59	85

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	91.4	122	91.4	122	92.9	120
Average	97.8	131	97.8	131	98.0	130
Stdev	49.1	74.8	49.1	74.8	49.5	74.5
p (t-test)		0.0024		0.0024		0.0032
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	67	77	67	77	66	78

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	103	122	106	118	103	118
Average	110	136	111	133	111	132
Stdev	55.0	77.5	56.3	75.3	56.8	74.4
p (t-test)		0.034		0.069		0.077
Min	24.0	13.2	24.0	13.2	24.0	13.2
Max	260	401	260	401	260	401
n (Patient)	70	55	65	60	64	62

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.64	0.63	0.59	0.64	0.63	0.58	0.63	0.62	0.58
SE	0.046	0.046	0.052	0.046	0.046	0.051	0.046	0.046	0.051
p Value	0.0031	0.0063	0.078	0.0027	0.0063	0.13	0.0036	0.0086	0.12
nCohort Recovered	65	67	70	62	67	65	59	66	64
nCohort Non-recovered	79	77	55	82	77	60	85	78	62
Cutoff Quartile 2	67.0	67.0	75.7	67.0	67.0	75.7	67.0	67.0	75.8
Sensitivity	82%	82%	84%	82%	82%	83%	82%	82%	82%
Specificity	34%	33%	31%	34%	33%	32%	36%	33%	33%
Cutoff Quartile 3	103	103	113	103	103	113	103	103	112
Sensitivity	56%	56%	55%	56%	56%	53%	55%	55%	53%
Specificity	57%	57%	53%	58%	57%	52%	58%	56%	53%
Cutoff Quartile 4	146	146	152	146	146	152	146	146	152
Sensitivity	33%	32%	36%	33%	32%	33%	32%	32%	32%
Specificity	85%	84%	83%	85%	84%	82%	85%	83%	81%
OR Quartile 2	2.38	2.20	2.34	2.29	2.20	2.39	2.58	2.29	2.26
p Value	0.028	0.045	0.056	0.035	0.045	0.046	0.016	0.036	0.055
Lower limit of 95% CI	1.10	1.02	0.977	1.06	1.02	1.01	1.19	1.06	0.983
Upper limit of 95% CI	5.15	4.76	5.62	4.93	4.76	5.61	5.58	4.95	5.22
OR Quartile 3	1.66	1.66	1.35	1.77	1.66	1.25	1.68	1.57	1.29
p Value	0.13	0.13	0.41	0.094	0.13	0.53	0.13	0.18	0.48
Lower limit of 95% CI	0.857	0.856	0.662	0.908	0.856	0.621	0.860	0.810	0.640
Upper limit of 95% CI	3.22	3.21	2.73	3.45	3.21	2.53	3.29	3.03	2.60
OR Quartile 4	2.70	2.45	2.76	2.89	2.45	2.21	2.59	2.36	2.06
p Value	0.018	0.029	0.016	0.014	0.029	0.060	0.027	0.036	0.085
Lower limit of 95% CI	1.19	1.10	1.20	1.24	1.10	0.968	1.11	1.06	0.906
Upper limit of 95% CI	6.13	5.47	6.33	6.72	5.47	5.04	6.01	5.27	4.70

[0188] Table 11.10: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	94.2	113	92.8	115	91.4	118
Average	101	131	101	130	101	131
Stdev	52.5	78.8	52.8	78.2	52.8	77.6
p (t-test)		0.0070		0.0068		0.0053
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	253	401	253	401	253	401
n (Patient)	89	61	88	62	87	63

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	91.4	118	91.4	118	91.4	118
Average	96.8	132	96.8	132	96.8	132
Stdev	48.9	76.9	48.9	76.9	48.9	76.9
p (t-test)		0.0010		0.0010		0.0010
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	246	401
n (Patient)	79	71	79	71	79	71

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	95.2	113	95.2	113	94.2	118
Average	103	134	103	134	102	134
Stdev	54.5	80.1	54.5	80.1	54.9	78.6
p (t-test)		0.0051		0.0051		0.0040
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	260	401	260	401	260	401
n (Patient)	98	51	98	51	96	53

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.60	0.63	0.61	0.60	0.63	0.61	0.61	0.63	0.62
SE	0.048	0.046	0.050	0.047	0.046	0.050	0.047	0.046	0.049
p Value	0.033	0.0045	0.028	0.029	0.0045	0.028	0.019	0.0045	0.016
nCohort Recovered	89	79	98	88	79	98	87	79	96
nCohort Non-recovered	61	71	51	62	71	51	63	71	53
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	82%	85%	84%	82%	85%	84%	83%	85%	85%
Specificity	30%	34%	30%	31%	34%	30%	31%	34%	30%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	56%	56%	57%	56%	56%	57%	57%	56%	58%
Specificity	54%	56%	53%	55%	56%	53%	55%	56%	54%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	34%	35%	35%	34%	35%	35%	35%	35%	36%
Specificity	81%	84%	80%	81%	84%	80%	82%	84%	80%
OR Quartile 2	1.98	2.83	2.26	2.05	2.83	2.26	2.13	2.83	2.43
p Value	0.092	0.010	0.067	0.076	0.010	0.067	0.062	0.010	0.045
Lower limit of 95% CI	0.895	1.28	0.946	0.928	1.28	0.946	0.962	1.28	1.02
Upper limit of 95% CI	4.38	6.26	5.39	4.54	6.26	5.39	4.70	6.26	5.81
OR Quartile 3	1.47	1.62	1.49	1.56	1.62	1.49	1.64	1.62	1.67
p Value	0.25	0.14	0.25	0.19	0.14	0.25	0.14	0.14	0.14
Lower limit of 95% CI	0.766	0.850	0.754	0.809	0.850	0.754	0.853	0.850	0.845
Upper limit of 95% CI	2.84	3.09	2.95	2.99	3.09	2.95	3.16	3.09	3.28

OR Quartile 4	2.22	2.76	2.13	2.14	2.76	2.13	2.38	2.76	2.26
p Value	0.036	0.0097	0.050	0.046	0.0097	0.050	0.023	0.0097	0.033
Lower limit of 95% CI	1.05	1.28	0.999	1.01	1.28	0.999	1.12	1.28	1.07
Upper limit of 95% CI	4.69	5.95	4.53	4.51	5.95	4.53	5.04	5.95	4.81

[0189] Example 12. Use of Tenascin for evaluating renal status in patients admitted to the ICU: Recovery to RIFLE 0 from RIFLE I and F

[0190] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Tenascin is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0191] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output during a period starting at 12, 24, 48, or 72 hours after sample collection or at any time within 7 days after sample collection. Two cohorts are defined to represent a “recovered” and a “non-recovered” population. “Recovered” indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0). “Non-recovered” indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is risk of injury (R), injury (I) or failure (F). If a patient dies or is placed on renal replacement therapy (RRT) within 9 days of enrollment, the patient is considered “non-recovered”.

[0192] The ability to distinguish the “recovered” and “non-recovered” cohorts is determined using receiver operating characteristic (ROC) analysis.

[0193] Table 12.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	24200	53600	23000	53700	23000	53700
Average	30200	56900	26300	56900	26300	56900
Stdev	14500	26100	9010	26000	9010	26000
p (t-test)		0.0028		0.0011		0.0011
Min	20500	15600	20500	15600	20500	15600

Max	61600	141000	47900	141000	47900	141000
n (Patient)	9	141	8	142	8	142

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	36100	53700	35600	53800	35600	53800
Average	44200	56800	43200	56800	43200	56800
Stdev	27100	25900	27600	25800	27600	25800
p (t-test)		0.057		0.044		0.044
Min	20500	15600	20500	15600	20500	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	18	132	17	133	17	133

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	46800	57200	45600	58200	46800	55700
Average	46100	61700	45900	61400	46100	60700
Stdev	20600	28200	20300	28100	20700	27900
p (t-test)		2.8E-4		3.3E-4		8.3E-4
Min	17100	15600	17100	15600	17100	15600
Max	97900	141000	97900	141000	97900	141000
n (Patient)	63	86	60	89	57	92

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.85	0.67	0.67	0.91	0.69	0.67	0.91	0.69	0.66
SE	0.048	0.061	0.044	0.034	0.060	0.044	0.034	0.060	0.044
p Value	3.8E-13	0.0047	1.2E-4	0	0.0014	9.6E-5	0	0.0014	2.8E-4
nCohort Recovered	9	18	63	8	17	60	8	17	57
nCohort Non-recovered	141	132	86	142	133	89	142	133	92
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	78%	77%	83%	78%	77%	82%	78%	77%	82%
Specificity	78%	44%	35%	88%	47%	35%	88%	47%	35%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	52%	53%	59%	53%	53%	60%	53%	53%	59%
Specificity	89%	72%	62%	100%	76%	63%	100%	76%	63%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	27%	27%	33%	27%	27%	33%	27%	27%	32%
Specificity	100%	89%	84%	100%	88%	85%	100%	88%	84%
OR Quartile 2	12.4	2.72	2.54	25.1	3.05	2.46	25.1	3.05	2.38
p Value	0.0023	0.053	0.016	0.0031	0.035	0.020	0.0031	0.035	0.024
Lower limit of 95% CI	2.45	0.986	1.19	2.97	1.08	1.15	2.97	1.08	1.12
Upper limit of 95% CI	62.8	7.50	5.43	212	8.60	5.24	212	8.60	5.08
OR Quartile 3	8.84	2.94	2.37	19.0	3.72	2.54	19.0	3.72	2.44
p Value	0.042	0.052	0.011	0.044	0.028	0.0067	0.044	0.028	0.010
Lower limit of 95% CI	1.08	0.990	1.22	1.08	1.15	1.30	1.08	1.15	1.23
Upper limit of 95% CI	72.5	8.70	4.61	336	12.0	4.99	336	12.0	4.81
OR Quartile 4	7.07	3.00	2.56	6.26	2.78	2.74	6.26	2.78	2.46
p Value	0.18	0.16	0.023	0.21	0.19	0.018	0.21	0.19	0.035
Lower limit of 95% CI	0.402	0.657	1.14	0.353	0.606	1.19	0.353	0.606	1.06
Upper limit of 95% CI	124	13.7	5.77	111	12.8	6.32	111	12.8	5.67

[0194] Table 12.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum

creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	29900	55100	26200	55100	25200	55100
Average	33900	58800	31900	58500	30300	58500
Stdev	13200	26200	12400	26100	10700	26000
p (t-test)		3.7E-5		3.9E-5		2.0E-5
Min	20500	15600	20500	15600	20500	15600
Max	61600	141000	59100	141000	51700	141000
n (Patient)	21	129	18	132	17	133

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	36100	55100	35300	55100	35000	55100
Average	40900	58600	40300	58400	39500	58400
Stdev	23100	25900	23600	25800	23700	25700
p (t-test)		0.0012		0.0012		8.6E-4
Min	20500	15600	20500	15600	20500	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	28	122	26	124	25	125

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	44700	62700	44500	62000	44500	61600
Average	46300	64800	46100	63900	46100	63400
Stdev	19100	28900	19000	28700	19100	28500
p (t-test)		1.2E-5		3.1E-5		5.1E-5
Min	18800	15600	20500	15600	20500	15600
Max	97900	141000	97900	141000	97900	141000
n (Patient)	71	74	66	79	64	81

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.81	0.73	0.70	0.84	0.74	0.69	0.86	0.75	0.69
SE	0.041	0.047	0.043	0.039	0.047	0.043	0.036	0.046	0.043
p Value	5.1E-14	1.3E-6	4.2E-6	0	3.1E-7	7.0E-6	0	4.4E-8	1.0E-5
nCohort Recovered	21	28	71	18	26	66	17	25	64
nCohort Non-recovered	129	122	74	132	124	79	133	125	81
Cutoff Quartile 2	34800	34800	35000	34800	34800	35000	34800	34800	35000
Sensitivity	79%	79%	84%	80%	79%	84%	80%	79%	83%
Specificity	52%	43%	34%	61%	46%	35%	65%	48%	34%
Cutoff Quartile 3	52000	52000	52200	52000	52000	52200	52000	52000	52200
Sensitivity	57%	57%	65%	56%	56%	65%	56%	57%	64%
Specificity	90%	79%	65%	94%	81%	67%	100%	84%	67%
Cutoff Quartile 4	70700	70700	70800	70700	70700	70800	70700	70700	70800
Sensitivity	29%	30%	38%	29%	29%	37%	29%	29%	36%
Specificity	100%	93%	87%	100%	92%	88%	100%	92%	88%
OR Quartile 2	4.16	2.77	2.64	6.11	3.23	2.72	7.20	3.51	2.51
p Value	0.0035	0.021	0.016	6.3E-4	0.0093	0.012	3.4E-4	0.0059	0.020
Lower limit of 95% CI	1.60	1.17	1.20	2.16	1.33	1.24	2.44	1.44	1.16

Upper limit of 95% CI	10.8	6.58	5.81	17.3	7.82	5.93	21.2	8.61	5.43
OR Quartile 3	12.4	4.77	3.40	21.7	5.44	3.64	45.2	6.90	3.67
p Value	9.9E-4	0.0016	4.4E-4	0.0032	0.0014	2.3E-4	0.0084	7.7E-4	2.3E-4
Lower limit of 95% CI	2.77	1.81	1.72	2.80	1.93	1.83	2.66	2.24	1.84
Upper limit of 95% CI	55.4	12.6	6.72	168	15.4	7.25	767	21.3	7.33
OR Quartile 4	18.1	5.44	4.19	15.1	4.91	4.20	14.1	4.65	3.90
p Value	0.045	0.026	8.5E-4	0.061	0.037	0.0012	0.067	0.044	0.0021
Lower limit of 95% CI	1.07	1.23	1.81	0.886	1.10	1.76	0.828	1.04	1.64
Upper limit of 95% CI	306	24.1	9.74	256	21.9	10.0	241	20.8	9.31

[0195] Table 12.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	35000	55200	34900	55800	34700	56000
Average	41700	59200	38500	59800	36800	59600
Stdev	23300	25800	18300	26300	17100	26200
p (t-test)		7.0E-4		4.8E-5		2.9E-5
Min	20500	15600	20500	15600	20500	15600
Max	123000	141000	90400	141000	90400	141000
n (Patient)	32	117	30	119	27	122

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	36900	55500	36600	55800	36600	55800
Average	43500	59800	43100	59800	43100	59800
Stdev	23000	26100	23200	26000	23200	26000
p (t-test)		8.7E-4		7.1E-4		7.1E-4
Min	20500	15600	20500	15600	20500	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	38	110	37	111	37	111

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	47800	61600	47700	61200	47700	59500
Average	51200	63500	50200	63900	50500	62600
Stdev	20900	29200	19100	29700	19200	29300
p (t-test)		0.0063		0.0024		0.0079
Min	20500	15600	20500	15600	20500	15600
Max	123000	141000	97900	141000	97900	141000
n (Patient)	64	69	61	72	55	78

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only

AUC	0.73	0.70	0.63	0.76	0.71	0.63	0.79	0.71	0.62
SE	0.045	0.045	0.048	0.043	0.045	0.048	0.042	0.045	0.049
p Value	4.4E-7	7.4E-6	0.0095	6.9E-10	3.1E-6	0.0053	6.3E-12	3.1E-6	0.015
nCohort Recovered	32	38	64	30	37	61	27	37	55
nCohort Non-recovered	117	110	69	119	111	72	122	111	78
Cutoff Quartile 2	35000	35000	37100	35000	35000	37100	35000	35000	37100
Sensitivity	81%	81%	78%	82%	81%	78%	81%	81%	77%
Specificity	47%	42%	28%	50%	43%	28%	52%	43%	27%
Cutoff Quartile 3	52200	52300	54300	52200	52300	54300	52200	52300	54300
Sensitivity	58%	58%	58%	59%	59%	58%	59%	59%	58%
Specificity	78%	74%	58%	83%	76%	59%	89%	76%	60%
Cutoff Quartile 4	70800	70900	71600	70800	70900	71600	70800	70900	71600
Sensitivity	29%	29%	35%	29%	29%	35%	30%	29%	33%
Specificity	88%	87%	84%	90%	86%	85%	93%	86%	85%
OR Quartile 2	3.81	3.08	1.41	4.41	3.27	1.35	4.64	3.27	1.25
p Value	0.0017	0.0058	0.40	6.5E-4	0.0040	0.45	6.4E-4	0.0040	0.58
Lower limit of 95% CI	1.65	1.38	0.639	1.88	1.46	0.615	1.92	1.46	0.565
Upper limit of 95% CI	8.78	6.86	3.10	10.3	7.31	2.98	11.2	7.31	2.76
OR Quartile 3	4.96	3.90	1.89	7.14	4.40	2.02	11.5	4.40	2.05
p Value	6.1E-4	0.0011	0.070	1.8E-4	5.6E-4	0.047	1.3E-4	5.6E-4	0.046
Lower limit of 95% CI	1.98	1.72	0.949	2.56	1.90	1.01	3.29	1.90	1.01
Upper limit of 95% CI	12.4	8.80	3.76	20.0	10.2	4.03	40.3	10.2	4.13
OR Quartile 4	2.87	2.71	2.88	3.75	2.59	3.07	5.23	2.59	2.94
p Value	0.066	0.057	0.013	0.039	0.069	0.010	0.030	0.069	0.017
Lower limit of 95% CI	0.935	0.970	1.25	1.07	0.927	1.30	1.18	0.927	1.21
Upper limit of 95% CI	8.80	7.56	6.65	13.2	7.25	7.25	23.3	7.25	7.12

[0196] Table 12.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	37700	57200	37400	58200	37400	58200
Average	42400	61000	41100	60600	40300	60400
Stdev	18900	26900	18500	26600	17100	26700
p (t-test)		1.3E-4		1.4E-4		1.2E-4
Min	20500	15600	20500	15600	20500	15600
Max	90400	141000	90400	141000	90400	141000
n (Patient)	38	106	33	111	31	113

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	38000	58200	38000	58200	38000	58200
Average	44600	61300	44600	61300	44200	61200
Stdev	22600	26300	22600	26300	22000	26400
p (t-test)		3.1E-4		3.1E-4		3.2E-4
Min	18800	15600	18800	15600	18800	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	45	99	45	99	43	101

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	51300	59900	51300	58900	48300	59100
Average	52900	64300	53600	62500	51800	62900
Stdev	19000	30800	19300	30000	18700	29100
p (t-test)		0.015		0.062		0.021
Min	20500	15600	20500	15600	20500	15600
Max	97900	141000	97900	141000	97900	141000
n (Patient)	60	65	52	73	47	79

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.72	0.70	0.60	0.73	0.70	0.57	0.74	0.71	0.61
SE	0.045	0.044	0.051	0.045	0.044	0.052	0.045	0.044	0.051
p Value	8.7E-7	3.6E-6	0.058	1.6E-7	3.6E-6	0.17	6.1E-8	2.9E-6	0.039
nCohort Recovered	38	45	60	33	45	52	31	43	47
nCohort Non-recovered	106	99	65	111	99	73	113	101	79
Cutoff Quartile 2	36300	36300	37600	36300	36300	37600	36300	36300	37700
Sensitivity	81%	83%	77%	80%	83%	75%	80%	82%	76%
Specificity	42%	42%	27%	42%	42%	25%	42%	42%	28%
Cutoff Quartile 3	52700	52700	55100	52700	52700	55100	52700	52700	55100
Sensitivity	59%	61%	57%	59%	61%	55%	59%	60%	56%
Specificity	76%	73%	57%	82%	73%	56%	84%	74%	60%
Cutoff Quartile 4	70900	70900	74700	70900	70900	74700	70900	70900	74300
Sensitivity	30%	30%	32%	30%	30%	30%	30%	31%	32%
Specificity	89%	87%	82%	91%	87%	81%	94%	88%	85%
OR Quartile 2	3.13	3.52	1.21	2.98	3.52	1.02	2.83	3.32	1.21
p Value	0.0056	0.0018	0.64	0.010	0.0018	0.97	0.016	0.0030	0.65
Lower limit of 95% CI	1.40	1.60	0.538	1.30	1.60	0.447	1.21	1.50	0.531
Upper limit of 95% CI	7.01	7.76	2.73	6.86	7.76	2.32	6.60	7.33	2.75
OR Quartile 3	4.72	4.23	1.73	6.60	4.23	1.53	7.57	4.44	1.85
p Value	3.0E-4	2.6E-4	0.13	1.2E-4	2.6E-4	0.25	1.1E-4	2.3E-4	0.099
Lower limit of 95% CI	2.03	1.95	0.851	2.52	1.95	0.747	2.71	2.01	0.891
Upper limit of 95% CI	11.0	9.17	3.51	17.3	9.17	3.13	21.2	9.80	3.85
OR Quartile 4	3.68	2.83	2.13	4.23	2.83	1.81	6.24	3.37	2.65
p Value	0.022	0.034	0.077	0.024	0.034	0.17	0.016	0.020	0.041
Lower limit of 95% CI	1.20	1.08	0.922	1.21	1.08	0.773	1.41	1.21	1.04
Upper limit of 95% CI	11.2	7.38	4.90	14.8	7.38	4.25	27.6	9.37	6.72

[0197] Table 12.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	44300	62000	44100	62800	44100	62800
Average	47600	64300	47200	64500	47200	64500
Stdev	20900	29100	20600	29000	20600	29000
p (t-test)		7.7E-5		3.5E-5		3.5E-5
Min	18800	15600	18800	15600	18800	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	81	69	80	70	80	70

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	42800	59300	41000	59300	41000	59300
Average	46100	62700	45600	62700	45600	62700
Stdev	20900	27900	20800	27700	20800	27700
p (t-test)		9.3E-5		5.1E-5		5.1E-5
Min	18800	15600	18800	15600	18800	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	67	83	65	85	65	85

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	47500	63200	47400	64500	47000	64500
Average	49000	65900	48500	66200	47900	66400
Stdev	20700	31400	20600	30900	20400	30500
p (t-test)		1.3E-4		4.8E-5		1.7E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	95	54	93	56	91	58

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.68	0.68	0.66	0.69	0.69	0.67	0.69	0.69	0.69
SE	0.044	0.043	0.048	0.044	0.043	0.047	0.044	0.043	0.046
p Value	6.3E-5	2.2E-5	8.7E-4	1.9E-5	6.0E-6	2.1E-4	1.9E-5	6.0E-6	4.4E-5
nCohort Recovered	81	67	95	80	65	93	80	65	91
nCohort Non-recovered	69	83	54	70	85	56	70	85	58
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	80%	81%	78%	80%	81%	79%	80%	81%	79%
Specificity	30%	33%	26%	30%	34%	27%	30%	34%	27%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	65%	63%	65%	66%	62%	66%	66%	62%	67%
Specificity	63%	66%	58%	64%	66%	59%	64%	66%	60%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	38%	36%	41%	39%	36%	41%	39%	36%	41%
Specificity	85%	88%	83%	86%	89%	84%	86%	89%	85%
OR Quartile 2	1.65	2.05	1.25	1.71	2.21	1.35	1.71	2.21	1.45
p Value	0.19	0.060	0.58	0.16	0.038	0.46	0.16	0.038	0.35
Lower limit of 95% CI	0.777	0.970	0.569	0.805	1.04	0.614	0.805	1.04	0.663
Upper limit of 95% CI	3.52	4.32	2.75	3.65	4.66	2.96	3.65	4.66	3.18
OR Quartile 3	3.19	3.21	2.53	3.37	3.24	2.82	3.37	3.24	3.14
p Value	7.0E-4	6.8E-4	0.0084	3.9E-4	6.5E-4	0.0033	3.9E-4	6.5E-4	0.0012
Lower limit of 95% CI	1.63	1.64	1.27	1.72	1.65	1.41	1.72	1.65	1.57
Upper limit of 95% CI	6.23	6.29	5.06	6.60	6.36	5.62	6.60	6.36	6.26
OR Quartile 4	3.48	4.17	3.39	3.94	4.76	3.62	3.94	4.76	3.88
p Value	0.0018	0.0012	0.0017	7.6E-4	6.8E-4	0.0010	7.6E-4	6.8E-4	5.8E-4
Lower limit of 95% CI	1.59	1.76	1.58	1.77	1.93	1.68	1.77	1.93	1.79
Upper limit of 95% CI	7.61	9.90	7.29	8.75	11.7	7.81	8.75	11.7	8.41

[0198] Example 13. Use of Tenascin for evaluating renal status in patients admitted to the ICU: Recovery to RIFLE 0 and R from RIFLE I and F

[0199] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10

mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Tenascin is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0200] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output during a period starting at 12, 24, 48, or 72 hours after sample collection or at any time within 7 days after sample collection. Two cohorts are defined to represent a "recovered" and a "non-recovered" population. "Recovered" indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0) or risk of injury (R). "Non-recovered" indicates those patients whose maximum RIFLE stage during a period of 24, 48 or 72 hours is injury (I) or failure (F). If a patient dies or is placed on renal replacement therapy (RRT) within 9 days of enrollment, the patient is considered "non-recovered".

[0201] The ability to distinguish the "recovered" and "non-recovered" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0202] Table 13.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 12 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	36100	55200	35800	55200	36600	55100
Average	41800	58900	41400	58800	41800	58500
Stdev	22000	26200	22400	26100	22700	26100
p (t-test)		9.4E-4		0.0010		0.0018
Min	20500	15600	20500	15600	20500	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	32	118	30	120	29	121

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	37100	55800	37100	55800	37400	55500
Average	43400	59700	43400	59700	43800	59400
Stdev	21400	26600	21400	26600	21600	26700
p (t-test)		6.0E-4		6.0E-4		0.0011
Min	20500	15600	20500	15600	20500	15600

Max	123000	141000	123000	141000	123000	141000
n (Patient)	41	109	41	109	40	110

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	45700	58900	45700	58900	44700	58600
Average	47900	62700	47900	62300	47800	62200
Stdev	21700	28600	21900	28400	22100	28200
p (t-test)		5.1E-4		6.9E-4		7.1E-4
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	76	73	74	75	73	76

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.70	0.66	0.72	0.70	0.66	0.71	0.69	0.66
SE	0.046	0.045	0.045	0.047	0.045	0.045	0.048	0.046	0.044
p Value	3.8E-6	1.4E-5	4.3E-4	1.9E-6	1.4E-5	4.8E-4	7.9E-6	4.3E-5	4.3E-4
nCohort Recovered	32	41	76	30	41	74	29	40	73
nCohort Non-recovered	118	109	73	120	109	75	121	110	76
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	80%	81%	81%	80%	81%	81%	79%	80%	82%
Specificity	44%	41%	30%	47%	41%	31%	45%	40%	32%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	56%	57%	62%	56%	57%	61%	55%	56%	62%
Specificity	72%	68%	61%	73%	68%	61%	72%	68%	62%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	30%	31%	33%	29%	31%	32%	29%	31%	32%
Specificity	91%	90%	82%	90%	90%	81%	90%	90%	81%
OR Quartile 2	3.05	2.97	1.83	3.50	2.97	1.96	3.12	2.67	2.04
p Value	0.0085	0.0064	0.12	0.0037	0.0064	0.082	0.0090	0.015	0.067
Lower limit of 95% CI	1.33	1.36	0.854	1.50	1.36	0.918	1.33	1.21	0.951
Upper limit of 95% CI	6.99	6.49	3.91	8.15	6.49	4.21	7.33	5.85	4.36
OR Quartile 3	3.24	2.84	2.46	3.48	2.84	2.46	3.26	2.68	2.60
p Value	0.0068	0.0070	0.0073	0.0058	0.0070	0.0074	0.0093	0.011	0.0045
Lower limit of 95% CI	1.38	1.33	1.28	1.43	1.33	1.27	1.34	1.25	1.35
Upper limit of 95% CI	7.60	6.07	4.76	8.43	6.07	4.76	7.93	5.74	5.04
OR Quartile 4	4.08	4.19	2.17	3.71	4.19	2.02	3.53	4.03	1.95
p Value	0.028	0.011	0.045	0.041	0.011	0.070	0.050	0.014	0.085
Lower limit of 95% CI	1.16	1.38	1.02	1.06	1.38	0.946	1.00	1.33	0.912
Upper limit of 95% CI	14.3	12.7	4.63	13.0	12.7	4.30	12.4	12.2	4.15

[0203] Table 13.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	37100	58200	37400	56200	37400	56200
Average	42900	60600	43400	60000	43400	60000
Stdev	21400	26500	21800	26500	21800	26500

p (t-test)		1.2E-4		3.7E-4		3.7E-4
Min	18800	15600	18800	15600	18800	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	45	105	43	107	43	107

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	37300	57200	37400	56200	37400	56200
Average	43900	61000	44200	60700	44200	60700
Stdev	21800	26600	21900	26600	21900	26600
p (t-test)		1.3E-4		2.5E-4		2.5E-4
Min	18800	15600	18800	15600	18800	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	50	100	49	101	49	101

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	47000	62700	47000	62000	47000	62000
Average	48500	64500	48600	64000	48600	64000
Stdev	20800	29300	21000	29100	21000	29100
p (t-test)		1.7E-4		3.3E-4		3.3E-4
Min	18800	15600	18800	15600	18800	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	79	66	77	68	77	68

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.72	0.70	0.67	0.70	0.70	0.66	0.70	0.70	0.66
SE	0.043	0.043	0.045	0.044	0.043	0.045	0.044	0.043	0.045
p Value	4.2E-7	1.7E-6	1.8E-4	3.6E-6	5.8E-6	3.2E-4	3.6E-6	5.8E-6	3.2E-4
nCohort Recovered	45	50	79	43	49	77	43	49	77
nCohort Non-recovered	105	100	66	107	101	68	107	101	68
Cutoff Quartile 2	34800	34800	35000	34800	34800	35000	34800	34800	35000
Sensitivity	81%	82%	82%	80%	81%	82%	80%	81%	82%
Specificity	40%	40%	30%	40%	39%	31%	40%	39%	31%
Cutoff Quartile 3	52000	52000	52200	52000	52000	52200	52000	52000	52200
Sensitivity	59%	59%	64%	58%	58%	63%	58%	58%	63%
Specificity	71%	68%	61%	70%	67%	61%	70%	67%	61%
Cutoff Quartile 4	70700	70700	70800	70700	70700	70800	70700	70700	70800
Sensitivity	31%	32%	36%	31%	32%	35%	31%	32%	35%
Specificity	89%	88%	84%	88%	88%	83%	88%	88%	83%
OR Quartile 2	2.83	3.04	1.96	2.68	2.73	2.11	2.68	2.73	2.11
p Value	0.0080	0.0043	0.093	0.013	0.0096	0.063	0.013	0.0096	0.063
Lower limit of 95% CI	1.31	1.42	0.893	1.23	1.28	0.961	1.23	1.28	0.961
Upper limit of 95% CI	6.12	6.51	4.32	5.81	5.85	4.65	5.81	5.85	4.65
OR Quartile 3	3.55	3.06	2.71	3.18	2.90	2.69	3.18	2.90	2.69
p Value	9.8E-4	0.0022	0.0038	0.0027	0.0036	0.0039	0.0027	0.0036	0.0039
Lower limit of 95% CI	1.67	1.50	1.38	1.49	1.42	1.37	1.49	1.42	1.37
Upper limit of 95% CI	7.54	6.25	5.32	6.77	5.93	5.28	6.77	5.93	5.28
OR Quartile 4	3.67	3.45	2.90	3.39	3.32	2.69	3.39	3.32	2.69
p Value	0.012	0.011	0.0073	0.019	0.013	0.013	0.019	0.013	0.013
Lower limit of 95% CI	1.33	1.33	1.33	1.22	1.28	1.24	1.22	1.28	1.24
Upper limit of 95% CI	10.1	8.93	6.32	9.39	8.61	5.84	9.39	8.61	5.84

[0204] Table 13.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “recovered” and “non-recovered” cohorts where

recovery starts at 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	41900	58900	41900	58900	41000	58600
Average	45400	61900	45400	61900	45300	61800
Stdev	21400	27100	21400	27100	21600	27000
p (t-test)		1.5E-4		1.5E-4		1.4E-4
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	58	91	58	91	57	92

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	42800	58900	42800	58900	42800	58900
Average	46100	62300	46100	62300	46100	62300
Stdev	21700	27300	21700	27300	21700	27300
p (t-test)		1.8E-4		1.8E-4		1.8E-4
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	61	87	61	87	61	87

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	47800	62000	47800	62000	47600	62000
Average	51100	65300	51100	65300	50800	65100
Stdev	20500	30000	20500	30000	20800	29500
p (t-test)		0.0016		0.0016		0.0014
Min	18800	15600	18800	15600	18800	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	72	61	72	61	70	63

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.69	0.68	0.64	0.69	0.68	0.64	0.69	0.68	0.64
SE	0.043	0.043	0.048	0.043	0.043	0.048	0.043	0.043	0.048
p Value	1.2E-5	2.7E-5	0.0041	1.2E-5	2.7E-5	0.0041	8.5E-6	2.7E-5	0.0027
nCohort Recovered	58	61	72	58	61	72	57	61	70
nCohort Non-recovered	91	87	61	91	87	61	92	87	63
Cutoff Quartile 2	35000	35000	37100	35000	35000	37100	35000	35000	37100
Sensitivity	81%	82%	79%	81%	82%	79%	82%	82%	79%
Specificity	34%	34%	28%	34%	34%	28%	35%	34%	29%
Cutoff Quartile 3	52200	52300	54300	52200	52300	54300	52200	52300	54300
Sensitivity	60%	60%	59%	60%	60%	59%	61%	60%	60%
Specificity	66%	64%	57%	66%	64%	57%	67%	64%	59%
Cutoff Quartile 4	70800	70900	71600	70800	70900	71600	70800	70900	71600
Sensitivity	34%	33%	38%	34%	33%	38%	34%	33%	37%
Specificity	88%	87%	85%	88%	87%	85%	88%	87%	84%
OR Quartile 2	2.29	2.33	1.42	2.29	2.33	1.42	2.38	2.33	1.54

p Value	0.032	0.029	0.39	0.032	0.029	0.39	0.024	0.029	0.29
Lower limit of 95% CI	1.08	1.09	0.638	1.08	1.09	0.638	1.12	1.09	0.691
Upper limit of 95% CI	4.88	4.97	3.16	4.88	4.97	3.16	5.08	4.97	3.43
OR Quartile 3	2.90	2.63	1.90	2.90	2.63	1.90	3.11	2.63	2.15
p Value	0.0023	0.0050	0.068	0.0023	0.0050	0.068	0.0013	0.0050	0.031
Lower limit of 95% CI	1.46	1.34	0.954	1.46	1.34	0.954	1.56	1.34	1.07
Upper limit of 95% CI	5.76	5.18	3.80	5.76	5.18	3.80	6.21	5.18	4.30
OR Quartile 4	3.76	3.31	3.36	3.76	3.31	3.36	3.63	3.31	3.08
p Value	0.0039	0.0068	0.0040	0.0039	0.0068	0.0040	0.0051	0.0068	0.0073
Lower limit of 95% CI	1.53	1.39	1.47	1.53	1.39	1.47	1.47	1.39	1.35
Upper limit of 95% CI	9.27	7.88	7.66	9.27	7.88	7.66	8.94	7.88	7.02

[0205] Table 13.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts at 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	44300	58900	43700	59100	43500	58200
Average	47700	63000	46700	63200	46600	62700
Stdev	21600	27800	21500	27400	22000	27100
p (t-test)		3.9E-4		1.4E-4		2.3E-4
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	65	79	62	82	59	85

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	44300	58900	44300	58900	44100	58600
Average	47800	63400	47800	63400	47700	63200
Stdev	21500	28000	21500	28000	21600	27800
p (t-test)		3.0E-4		3.0E-4		3.2E-4
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	67	77	67	77	66	78

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	51300	62000	48300	61000	50000	59400
Average	53100	66100	52700	65500	52900	64900
Stdev	20800	30700	21100	29800	21200	29500
p (t-test)		0.0057		0.0062		0.0097
Min	18800	15600	18800	15600	18800	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	70	55	65	60	64	62

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.67	0.67	0.62	0.68	0.67	0.62	0.68	0.67	0.61
SE	0.045	0.045	0.051	0.044	0.045	0.050	0.044	0.045	0.050
p Value	2.1E-4	2.1E-4	0.020	2.6E-5	2.1E-4	0.014	3.7E-5	2.0E-4	0.022
nCohort Recovered	65	67	70	62	67	65	59	66	64
nCohort Non-recovered	79	77	55	82	77	60	85	78	62
Cutoff Quartile 2	36300	36300	37600	36300	36300	37600	36300	36300	37700
Sensitivity	82%	83%	80%	83%	83%	80%	84%	83%	81%
Specificity	34%	34%	29%	35%	34%	29%	37%	35%	31%
Cutoff Quartile 3	52700	52700	55100	52700	52700	55100	52700	52700	55100
Sensitivity	59%	60%	60%	61%	60%	58%	60%	60%	56%
Specificity	62%	61%	57%	65%	61%	57%	64%	62%	56%
Cutoff Quartile 4	70900	70900	74700	70900	70900	74700	70900	70900	74300
Sensitivity	34%	35%	35%	34%	35%	33%	33%	35%	32%
Specificity	86%	87%	81%	87%	87%	82%	86%	86%	81%
OR Quartile 2	2.38	2.57	1.60	2.67	2.57	1.65	3.02	2.67	1.89
p Value	0.028	0.018	0.27	0.013	0.018	0.23	0.0055	0.014	0.13
Lower limit of 95% CI	1.10	1.18	0.691	1.23	1.18	0.722	1.38	1.22	0.832
Upper limit of 95% CI	5.15	5.62	3.71	5.80	5.62	3.78	6.57	5.84	4.31
OR Quartile 3	2.35	2.34	2.00	2.84	2.34	1.85	2.71	2.49	1.67
p Value	0.013	0.013	0.058	0.0028	0.013	0.090	0.0044	0.0080	0.16
Lower limit of 95% CI	1.20	1.20	0.976	1.43	1.20	0.909	1.37	1.27	0.824
Upper limit of 95% CI	4.60	4.57	4.10	5.63	4.57	3.76	5.40	4.87	3.37
OR Quartile 4	3.23	3.48	2.31	3.50	3.48	2.21	3.13	3.35	2.06
p Value	0.0064	0.0038	0.045	0.0048	0.0038	0.060	0.010	0.0049	0.085
Lower limit of 95% CI	1.39	1.50	1.02	1.46	1.50	0.968	1.31	1.44	0.906
Upper limit of 95% CI	7.51	8.09	5.25	8.37	8.09	5.04	7.49	7.80	4.70

[0206] Table 13.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "recovered" and "non-recovered" cohorts where recovery starts within 7 days after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	46800	64300	45700	64500	44700	64600
Average	48100	65800	47900	65700	47500	66000
Stdev	20900	29800	20900	29500	20700	29400
p (t-test)		3.5E-5		2.7E-5		1.2E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	89	61	88	62	87	63

sCr only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	44300	62000	44300	62000	44300	62000
Average	46700	64800	46700	64800	46700	64800
Stdev	20400	28800	20400	28800	20400	28800
p (t-test)		1.6E-5		1.6E-5		1.6E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	79	71	79	71	79	71

UO only

Recovery Period Duration (hr)	24		48		72	
	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort	Recovered Cohort	Non-recovered Cohort
Median	47400	64300	47400	64300	47200	64600
Average	48800	67300	48800	67300	48300	67500
Stdev	20800	31300	20800	31300	20700	30800
p (t-test)		3.2E-5		3.2E-5		1.1E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	98	51	98	51	96	53

Recovery Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.68	0.69	0.68	0.68	0.69	0.68	0.69	0.69	0.69
SE	0.045	0.043	0.048	0.045	0.043	0.048	0.044	0.043	0.047
p Value	6.9E-5	1.0E-5	2.2E-4	3.8E-5	1.0E-5	2.2E-4	1.2E-5	1.0E-5	4.4E-5
nCohort Recovered	89	79	98	88	79	98	87	79	96
nCohort Non-recovered	61	71	51	62	71	51	63	71	53
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	80%	82%	80%	81%	82%	80%	81%	82%	81%
Specificity	29%	32%	28%	30%	32%	28%	30%	32%	28%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	64%	63%	67%	65%	63%	67%	65%	63%	68%
Specificity	60%	62%	58%	60%	62%	58%	61%	62%	59%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	41%	41%	41%	40%	41%	41%	41%	41%	42%
Specificity	85%	89%	83%	85%	89%	83%	86%	89%	83%
OR Quartile 2	1.69	2.07	1.56	1.75	2.07	1.56	1.81	2.07	1.68
p Value	0.19	0.063	0.29	0.16	0.063	0.29	0.13	0.063	0.21
Lower limit of 95% CI	0.773	0.960	0.686	0.802	0.960	0.686	0.832	0.960	0.742
Upper limit of 95% CI	3.67	4.44	3.54	3.81	4.44	3.54	3.95	4.44	3.82
OR Quartile 3	2.61	2.83	2.78	2.75	2.83	2.78	2.91	2.83	3.10
p Value	0.0052	0.0021	0.0046	0.0032	0.0021	0.0046	0.0019	0.0021	0.0017
Lower limit of 95% CI	1.33	1.46	1.37	1.40	1.46	1.37	1.48	1.46	1.53
Upper limit of 95% CI	5.11	5.49	5.64	5.40	5.49	5.64	5.70	5.49	6.27
OR Quartile 4	4.06	5.37	3.34	3.90	5.37	3.34	4.39	5.37	3.55
p Value	4.2E-4	8.8E-5	0.0020	6.0E-4	8.8E-5	0.0020	2.4E-4	8.8E-5	0.0012
Lower limit of 95% CI	1.86	2.32	1.55	1.79	2.32	1.55	1.99	2.32	1.65
Upper limit of 95% CI	8.85	12.4	7.16	8.48	12.4	7.16	9.67	12.4	7.63

[0207] Example 14. Use of Follistatin-related protein 3 for evaluating renal status in patients admitted to the ICU: Persistent at RIFLE F

[0208] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Follistatin-related protein 3 is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0209] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output. Two cohorts are defined to represent a

"persistent" and a "non-persistent" population. "Persistent" indicates those patients whose minimum RIFLE stage during a period of 24, 48 or 72 hours is failure (F) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. "Non-persistent" indicates those patients who are not persistent at failure (F) and whose minimum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0), risk of injury (R), or injury (I) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. If a patient dies after failure (F) or is placed on renal replacement therapy (RRT) at any time from sample collection to 24, 48, 72, 96 or 168 hours after sample collection, the patient is considered "persistent".

[0210] The ability to distinguish the "persistent" and "non-persistent" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0211] Table 14.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	49500	81000	50300	81000	52000	77400
Average	81100	87400	82200	86200	81800	88000
Stdev	141000	43300	136000	42000	132000	43500
p (t-test)		0.75		0.84		0.77
Min	10500	20700	10500	20700	10500	20700
Max	1230000	204000	1230000	204000	1230000	204000
n (Patient)	95	55	103	47	110	40

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	49300	81400	50300	81000	50500	80900
Average	80700	88100	82800	84800	82300	86300
Stdev	142000	43200	137000	38700	134000	38800
p (t-test)		0.70		0.92		0.85
Min	10500	20700	10500	20700	10500	20700
Max	1230000	204000	1230000	162000	1230000	162000
n (Patient)	94	56	103	47	108	42

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	60000	80700	60000	80700	60400	74700
Average	82700	90800	82700	90800	82900	89400
Stdev	123000	44800	123000	44800	122000	45600
p (t-test)		0.77		0.77		0.82
Min	10500	34800	10500	34800	10500	34800
Max	1230000	204000	1230000	204000	1230000	204000
n (Patient)	130	19	130	19	131	18

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.67	0.68	0.65	0.66	0.65	0.65	0.65	0.66	0.63
SE	0.047	0.046	0.072	0.050	0.050	0.072	0.053	0.052	0.074
p Value	2.1E-4	7.8E-5	0.044	0.0017	0.0021	0.044	0.0033	0.0018	0.074
nCohort Non-persistent	95	94	130	103	103	130	110	108	131
nCohort Persistent	55	56	19	47	47	19	40	42	18
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	85%	86%	89%	85%	85%	89%	88%	88%	89%
Specificity	32%	32%	27%	30%	30%	27%	30%	31%	27%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	69%	70%	68%	70%	70%	68%	70%	71%	67%
Specificity	61%	62%	52%	59%	59%	52%	57%	58%	52%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	40%	41%	37%	38%	38%	37%	38%	38%	33%
Specificity	83%	84%	76%	81%	81%	76%	79%	80%	76%
OR Quartile 2	2.71	2.81	3.13	2.46	2.46	3.13	3.00	3.26	2.92
p Value	0.024	0.019	0.14	0.052	0.052	0.14	0.035	0.023	0.17
Lower limit of 95% CI	1.14	1.18	0.688	0.994	0.994	0.688	1.08	1.17	0.638
Upper limit of 95% CI	6.44	6.68	14.3	6.09	6.09	14.3	8.34	9.03	13.3
OR Quartile 3	3.50	3.70	2.38	3.42	3.42	2.38	3.13	3.50	2.16
p Value	4.9E-4	2.8E-4	0.098	0.0011	0.0011	0.098	0.0039	0.0015	0.15
Lower limit of 95% CI	1.73	1.83	0.851	1.64	1.64	0.851	1.44	1.62	0.764
Upper limit of 95% CI	7.09	7.48	6.63	7.16	7.16	6.63	6.79	7.57	6.10
OR Quartile 4	3.29	3.67	1.86	2.58	2.58	1.86	2.27	2.41	1.55
p Value	0.0022	8.9E-4	0.23	0.015	0.015	0.23	0.041	0.027	0.42
Lower limit of 95% CI	1.54	1.70	0.675	1.20	1.20	0.675	1.03	1.10	0.537
Upper limit of 95% CI	7.05	7.90	5.14	5.53	5.53	5.14	4.99	5.24	4.46

[0212] Table 14.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	48000	80900	48800	80900	49500	80700
Average	68600	104000	70400	105000	70400	110000
Stdev	77500	152000	76700	159000	74400	169000
p (t-test)		0.060		0.072		0.046
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	88	62	94	56	101	49

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	48000	80900	48400	80700	49100	80700
Average	81200	86600	82500	84900	81700	86900
Stdev	146000	42900	143000	40800	139000	41200
p (t-test)		0.78		0.90		0.80
Min	10500	20700	10500	20700	10500	20700
Max	1230000	204000	1230000	204000	1230000	204000
n (Patient)	88	62	93	57	99	51

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	55100	81600	55100	81600	55200	80700
Average	72800	136000	72800	136000	73100	136000
Stdev	69600	228000	69600	228000	69400	233000
p (t-test)		0.011		0.011		0.012
Min	10500	34800	10500	34800	10500	34800
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	123	26	123	26	124	25

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.68	0.68	0.68	0.67	0.67	0.68	0.68	0.67	0.67
SE	0.045	0.045	0.062	0.047	0.047	0.062	0.048	0.048	0.063
p Value	3.9E-5	5.8E-5	0.0029	1.9E-4	3.8E-4	0.0029	2.0E-4	2.9E-4	0.0058
nCohort Non-persistent	88	88	123	94	93	123	101	99	124
nCohort Persistent	62	62	26	56	57	26	49	51	25
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	85%	85%	92%	86%	86%	92%	88%	88%	92%
Specificity	33%	33%	28%	32%	32%	28%	32%	32%	28%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	66%	66%	69%	68%	67%	69%	69%	69%	68%
Specificity	61%	61%	54%	61%	60%	54%	59%	60%	53%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	39%	39%	42%	38%	37%	42%	39%	37%	40%
Specificity	84%	84%	78%	82%	82%	78%	81%	81%	77%
OR Quartile 2	2.89	2.89	4.77	2.81	2.92	4.77	3.32	3.58	4.52
p Value	0.013	0.013	0.040	0.019	0.015	0.040	0.013	0.0085	0.048
Lower limit of 95% CI	1.26	1.26	1.07	1.18	1.23	1.07	1.28	1.38	1.01
Upper limit of 95% CI	6.67	6.67	21.3	6.68	6.92	21.3	8.61	9.26	20.2
OR Quartile 3	3.10	3.10	2.61	3.25	3.03	2.61	3.32	3.23	2.42
p Value	0.0011	0.0011	0.038	9.1E-4	0.0016	0.038	0.0012	0.0013	0.058
Lower limit of 95% CI	1.57	1.57	1.05	1.62	1.52	1.05	1.61	1.58	0.972
Upper limit of 95% CI	6.11	6.11	6.44	6.53	6.03	6.44	6.85	6.59	6.02
OR Quartile 4	3.34	3.34	2.61	2.72	2.61	2.61	2.73	2.50	2.29
p Value	0.0021	0.0021	0.034	0.0094	0.013	0.034	0.0096	0.018	0.073
Lower limit of 95% CI	1.55	1.55	1.07	1.28	1.23	1.07	1.28	1.17	0.925
Upper limit of 95% CI	7.18	7.18	6.33	5.78	5.53	6.33	5.85	5.33	5.65

[0213] Table 14.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47100	74000	47300	77400	48200	73900
Average	68100	102000	68200	104000	69800	106000
Stdev	79600	146000	78800	149000	76600	159000
p (t-test)		0.069		0.060		0.060
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	83	67	86	64	94	56

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	46500	77400	47300	80900	47900	80700
Average	67400	103000	67600	105000	69100	107000
Stdev	79800	145000	78500	149000	76800	157000
p (t-test)		0.061		0.051		0.051
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	82	68	86	64	93	57

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	53300	77200	53300	77200	53900	73800
Average	72300	122000	72300	122000	72700	123000
Stdev	71600	200000	71600	200000	71400	204000
p (t-test)		0.026		0.026		0.028
Min	10500	34800	10500	34800	10500	34800
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	115	34	115	34	116	33

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.70	0.70	0.68	0.70	0.71	0.68	0.69	0.70	0.68
SE	0.044	0.043	0.055	0.044	0.044	0.055	0.046	0.045	0.056
p Value	7.5E-6	2.0E-6	8.3E-4	4.0E-6	1.6E-6	8.3E-4	3.6E-5	1.0E-5	0.0017
nCohort Non-persistent	83	82	115	86	86	115	94	93	116
nCohort Persistent	67	68	34	64	64	34	56	57	33
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	87%	87%	94%	88%	88%	94%	89%	89%	94%
Specificity	35%	35%	30%	35%	35%	30%	34%	34%	30%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	67%	68%	71%	69%	69%	71%	70%	70%	70%
Specificity	64%	65%	56%	64%	64%	56%	62%	62%	55%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	37%	38%	35%	38%	39%	35%	36%	37%	33%
Specificity	84%	85%	77%	84%	85%	77%	81%	82%	77%
OR Quartile 2	3.46	3.59	7.00	3.75	3.75	7.00	4.30	4.46	6.70
p Value	0.0036	0.0027	0.010	0.0027	0.0027	0.010	0.0026	0.0020	0.012
Lower limit of 95% CI	1.50	1.56	1.59	1.58	1.58	1.59	1.67	1.73	1.52
Upper limit of 95% CI	7.97	8.27	30.8	8.89	8.89	30.8	11.1	11.5	29.5
OR Quartile 3	3.61	3.82	3.01	3.90	3.90	3.01	3.70	3.90	2.83
p Value	2.1E-4	1.1E-4	0.0088	1.0E-4	1.0E-4	0.0088	2.8E-4	1.6E-4	0.014
Lower limit of 95% CI	1.83	1.93	1.32	1.96	1.96	1.32	1.83	1.93	1.24
Upper limit of 95% CI	7.12	7.55	6.87	7.77	7.77	6.87	7.48	7.90	6.48

OR Quartile 4	3.21	3.61	1.87	3.09	3.60	1.87	2.35	2.61	1.65
p Value	0.0031	0.0013	0.14	0.0038	0.0012	0.14	0.026	0.013	0.24
Lower limit of 95% CI	1.48	1.65	0.816	1.44	1.66	0.816	1.11	1.23	0.710
Upper limit of 95% CI	6.93	7.91	4.27	6.63	7.81	4.27	4.97	5.53	3.83

[0214] Table 14.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47100	74000	47500	74000	48400	73800
Average	67800	102000	68500	103000	70300	104000
Stdev	80400	144000	79200	148000	77700	155000
p (t-test)		0.072		0.069		0.083
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	81	69	85	65	91	59

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47100	74000	47300	77400	48200	73900
Average	67700	102000	67800	103000	69700	104000
Stdev	80300	144000	79400	147000	78000	154000
p (t-test)		0.069		0.061		0.073
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	81	69	84	66	90	60

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	52900	77200	53100	73800	53300	72700
Average	71300	118000	71700	118000	72100	118000
Stdev	72600	186000	72400	188000	72200	190000
p (t-test)		0.029		0.032		0.035
Min	10500	34800	10500	34800	10500	34800
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	109	40	110	39	111	38

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.70	0.70	0.69	0.70	0.70	0.68	0.68	0.69	0.67
SE	0.043	0.043	0.052	0.044	0.043	0.053	0.046	0.045	0.053
p Value	5.2E-6	4.3E-6	2.9E-4	8.5E-6	2.3E-6	6.2E-4	1.1E-4	3.9E-5	0.0013
nCohort Non-persistent	81	81	109	85	84	110	91	90	111
nCohort Persistent	69	69	40	65	66	39	59	60	38

Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	87%	87%	92%	88%	88%	92%	88%	88%	92%
Specificity	36%	36%	31%	35%	36%	31%	34%	34%	31%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	67%	67%	70%	68%	68%	69%	68%	68%	68%
Specificity	64%	64%	57%	64%	64%	56%	62%	62%	56%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	38%	38%	38%	37%	38%	36%	34%	35%	34%
Specificity	85%	85%	79%	84%	85%	78%	80%	81%	77%
OR Quartile 2	3.72	3.72	5.59	3.89	4.03	5.37	3.84	3.98	5.15
p Value	0.0021	0.0021	0.0067	0.0021	0.0016	0.0082	0.0034	0.0026	0.0099
Lower limit of 95% CI	1.61	1.61	1.61	1.64	1.70	1.55	1.56	1.62	1.48
Upper limit of 95% CI	8.57	8.57	19.4	9.22	9.55	18.6	9.44	9.79	17.9
OR Quartile 3	3.59	3.59	3.08	3.65	3.86	2.91	3.37	3.55	2.74
p Value	2.1E-4	2.1E-4	0.0045	2.0E-4	1.1E-4	0.0072	5.6E-4	3.2E-4	0.011
Lower limit of 95% CI	1.82	1.82	1.42	1.85	1.95	1.34	1.69	1.78	1.26
Upper limit of 95% CI	7.05	7.05	6.68	7.22	7.64	6.32	6.72	7.09	5.98
OR Quartile 4	3.48	3.48	2.24	2.97	3.33	2.01	2.08	2.31	1.79
p Value	0.0018	0.0018	0.045	0.0052	0.0023	0.086	0.054	0.028	0.16
Lower limit of 95% CI	1.59	1.59	1.02	1.38	1.54	0.906	0.986	1.09	0.800
Upper limit of 95% CI	7.61	7.61	4.94	6.37	7.21	4.45	4.39	4.89	4.00

[0215] Table 14.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	45600	73900	45900	74000	47700	73900
Average	67300	101000	67400	102000	69300	103000
Stdev	81600	141000	80700	144000	78700	151000
p (t-test)		0.073		0.065		0.074
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	78	72	81	69	88	62

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	45900	73800	46500	73900	47700	72700
Average	67900	101000	68000	102000	69900	103000
Stdev	81300	142000	80400	145000	78800	151000
p (t-test)		0.081		0.072		0.086
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	79	71	82	68	88	62

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	51800	80700	51800	80700	52900	77200

Average	70400	119000	70400	119000	70900	119000
Stdev	72400	183000	72400	183000	72200	186000
p (t-test)		0.022		0.022		0.024
Min	10500	34800	10500	34800	10500	34800
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	108	41	108	41	109	40

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.70	0.70	0.70	0.71	0.70	0.70	0.69	0.68	0.69
SE	0.043	0.043	0.051	0.043	0.043	0.051	0.045	0.045	0.052
p Value	1.5E-6	5.0E-6	8.2E-5	8.5E-7	2.8E-6	8.2E-5	1.9E-5	4.8E-5	1.9E-4
nCohort Non-persistent	78	79	108	81	82	108	88	88	109
nCohort Persistent	72	71	41	69	68	41	62	62	40
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	88%	87%	93%	88%	88%	93%	89%	89%	92%
Specificity	37%	37%	31%	37%	37%	31%	35%	35%	31%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	67%	66%	71%	68%	68%	71%	68%	68%	70%
Specificity	65%	65%	57%	65%	65%	57%	62%	62%	57%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	38%	37%	39%	38%	37%	39%	35%	34%	38%
Specificity	86%	85%	80%	85%	84%	80%	82%	81%	79%
OR Quartile 2	4.14	4.00	5.82	4.49	4.33	5.82	4.27	4.27	5.59
p Value	8.6E-4	0.0012	0.0055	6.6E-4	8.9E-4	0.0055	0.0016	0.0016	0.0067
Lower limit of 95% CI	1.80	1.73	1.68	1.89	1.82	1.68	1.74	1.74	1.61
Upper limit of 95% CI	9.56	9.21	20.2	10.6	10.3	20.2	10.5	10.5	19.4
OR Quartile 3	3.78	3.57	3.26	4.04	3.82	3.26	3.50	3.50	3.08
p Value	1.2E-4	2.2E-4	0.0028	6.0E-5	1.1E-4	0.0028	3.4E-4	3.4E-4	0.0045
Lower limit of 95% CI	1.92	1.82	1.50	2.04	1.93	1.50	1.76	1.76	1.42
Upper limit of 95% CI	7.43	7.00	7.06	8.00	7.55	7.06	6.95	6.95	6.68
OR Quartile 4	3.65	3.23	2.50	3.48	3.09	2.50	2.48	2.14	2.24
p Value	0.0014	0.0033	0.022	0.0018	0.0042	0.022	0.018	0.046	0.045
Lower limit of 95% CI	1.65	1.48	1.14	1.59	1.43	1.14	1.17	1.01	1.02
Upper limit of 95% CI	8.10	7.05	5.47	7.61	6.67	5.47	5.25	4.51	4.94

[0216] Example 15. Use of Follistatin-related protein 3 for evaluating renal status in patients admitted to the ICU: Persistent at RIFLE I or F

[0217] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Follistatin-related protein 3 is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0218] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output. Two cohorts are defined to represent a "persistent" and a "non-persistent" population. "Persistent" indicates those patients whose minimum RIFLE stage during a period of 24, 48 or 72 hours is injury (I) or failure (F) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. "Non-persistent" indicates those patients who are not persistent at injury (I) or failure (F) and whose minimum RIFLE stage during a period

of 24, 48 or 72 hours is non-injury (RIFLE 0) or risk of injury (R) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. If a patient dies after injury (I) or failure (F) or is placed on renal replacement therapy (RRT) at any time from sample collection to 24, 48, 72, 96 or 168 hours after sample collection, the patient is considered "persistent".

[0219] The ability to distinguish the "persistent" and "non-persistent" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0220] Table 15.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	41100	71900	45900	71700	47900	74000
Average	52000	99200	84100	82800	82300	84900
Stdev	40900	136000	158000	41000	149000	41400
p (t-test)		0.018		0.95		0.89
Min	10500	20700	10500	20700	10500	20700
Max	265000	1230000	1230000	204000	1230000	204000
n (Patient)	50	100	75	75	85	65

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	41800	71900	45400	74000	48500	80900
Average	64000	93800	66800	99300	69700	102000
Stdev	96900	123000	83700	137000	79800	149000
p (t-test)		0.13		0.084		0.089
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	52	98	73	77	86	64

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	54800	82000	55600	80700	55800	77200
Average	77300	103000	83200	85900	82700	89000
Stdev	118000	107000	127000	41900	125000	43000
p (t-test)		0.24		0.91		0.81
Min	10500	24400	10500	24400	10500	34000
Max	1230000	689000	1230000	204000	1230000	204000
n (Patient)	112	37	120	29	125	24

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.77	0.76	0.66	0.67	0.71	0.63	0.68	0.68	0.64
SE	0.038	0.039	0.054	0.044	0.042	0.061	0.045	0.045	0.065
p Value	9.5E-13	3.3E-11	0.0029	7.4E-5	7.4E-7	0.036	8.9E-5	3.8E-5	0.027
nCohort Non-persistent	50	52	112	75	73	120	85	86	125
nCohort Persistent	100	98	37	75	77	29	65	64	24
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	87%	87%	89%	85%	86%	86%	86%	86%	88%
Specificity	50%	48%	29%	36%	37%	28%	34%	34%	27%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	65%	65%	70%	65%	68%	69%	68%	69%	71%
Specificity	80%	79%	56%	65%	68%	54%	64%	64%	54%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	33%	33%	38%	35%	38%	31%	35%	38%	33%
Specificity	90%	88%	79%	84%	88%	76%	82%	84%	76%
OR Quartile 2	6.69	6.05	3.45	3.27	3.52	2.37	3.22	3.11	2.62
p Value	3.6E-6	9.7E-6	0.030	0.0035	0.0019	0.13	0.0060	0.0077	0.14
Lower limit of 95% CI	2.99	2.73	1.13	1.48	1.59	0.767	1.40	1.35	0.733
Upper limit of 95% CI	15.0	13.4	10.5	7.25	7.80	7.33	7.42	7.16	9.33
OR Quartile 3	7.43	7.02	3.04	3.55	4.52	2.63	3.65	3.90	2.81
p Value	1.1E-6	1.1E-6	0.0063	2.2E-4	1.7E-5	0.029	2.0E-4	1.0E-4	0.033
Lower limit of 95% CI	3.32	3.20	1.37	1.81	2.28	1.11	1.85	1.96	1.09
Upper limit of 95% CI	16.6	15.4	6.75	6.96	8.98	6.24	7.22	7.77	7.24
OR Quartile 4	4.43	3.72	2.23	2.79	4.30	1.41	2.56	3.09	1.58
p Value	0.0040	0.0067	0.050	0.0100	6.3E-4	0.45	0.015	0.0038	0.34
Lower limit of 95% CI	1.61	1.44	1.000	1.28	1.86	0.579	1.20	1.44	0.617
Upper limit of 95% CI	12.2	9.61	4.98	6.07	9.91	3.44	5.44	6.63	4.06

[0221] Table 15.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	40400	72000	45000	73900	45900	81000
Average	50500	99400	66400	98400	66400	102000
Stdev	39900	135000	85200	135000	81100	142000
p (t-test)		0.014		0.090		0.056
Min	10500	20700	10500	20700	10500	20700
Max	265000	1230000	689000	1230000	689000	1230000
n (Patient)	49	101	70	80	79	71

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	41800	72000	45000	73900	45900	80700
Average	62700	94100	66200	98500	67500	101000
Stdev	97500	122000	85100	135000	81500	142000
p (t-test)		0.11		0.087		0.074
Min	10500	20700	10500	20700	10500	20700

Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	51	99	70	80	79	71

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	50300	85100	52900	82200	53100	82400
Average	64600	127000	71900	118000	71800	125000
Stdev	41700	193000	72400	190000	71100	203000
p (t-test)		0.0022		0.032		0.018
Min	10500	24400	10500	24400	10500	34000
Max	265000	1230000	689000	1230000	689000	1230000
n (Patient)	103	46	111	38	116	33

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.79	0.77	0.71	0.71	0.72	0.68	0.72	0.71	0.69
SE	0.037	0.038	0.048	0.042	0.041	0.053	0.042	0.043	0.056
p Value	1.0E-14	7.6E-13	1.9E-5	2.5E-7	1.9E-7	7.7E-4	1.7E-7	1.2E-6	4.7E-4
nCohort Non-persistent	49	51	103	70	70	111	79	79	116
nCohort Persistent	101	99	46	80	80	38	71	71	33
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	87%	87%	91%	86%	86%	89%	87%	87%	91%
Specificity	51%	49%	32%	39%	39%	30%	37%	37%	29%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	65%	66%	72%	66%	66%	71%	69%	68%	73%
Specificity	82%	80%	59%	69%	69%	57%	67%	66%	56%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	34%	33%	41%	38%	38%	37%	39%	38%	39%
Specificity	92%	90%	82%	89%	89%	78%	87%	86%	78%
OR Quartile 2	7.05	6.36	4.95	3.94	3.94	3.60	4.00	4.00	4.15
p Value	2.2E-6	6.0E-6	0.0046	7.6E-4	7.6E-4	0.024	0.0012	0.0012	0.026
Lower limit of 95% CI	3.14	2.86	1.64	1.77	1.77	1.18	1.73	1.73	1.19
Upper limit of 95% CI	15.8	14.2	15.0	8.75	8.75	10.9	9.21	9.21	14.5
OR Quartile 3	8.38	7.84	3.69	4.28	4.28	3.22	4.54	4.02	3.40
p Value	5.4E-7	5.6E-7	6.8E-4	3.2E-5	3.2E-5	0.0039	1.6E-5	6.2E-5	0.0048
Lower limit of 95% CI	3.65	3.50	1.74	2.16	2.16	1.45	2.28	2.04	1.45
Upper limit of 95% CI	19.2	17.6	7.83	8.50	8.50	7.14	9.03	7.94	7.95
OR Quartile 4	5.71	4.60	3.11	4.65	4.65	2.11	4.49	3.79	2.37
p Value	0.0020	0.0032	0.0038	4.9E-4	4.9E-4	0.066	3.1E-4	0.0010	0.041
Lower limit of 95% CI	1.90	1.67	1.44	1.96	1.96	0.951	1.99	1.71	1.04
Upper limit of 95% CI	17.2	12.7	6.72	11.0	11.0	4.70	10.2	8.42	5.41

[0222] Table 15.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “persistent” and “non-persistent” cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	40400	72000	44700	73800	45200	74000
Average	50500	99400	66500	97800	66600	100000
Stdev	39900	135000	85900	134000	83200	139000

p (t-test)		0.014		0.097		0.074
Min	10500	20700	10500	20700	10500	20700
Max	265000	1230000	689000	1230000	689000	1230000
n (Patient)	49	101	69	81	75	75

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	41800	72000	44700	73800	45200	74000
Average	62700	94100	66400	98000	66500	100000
Stdev	97500	122000	85800	134000	83100	139000
p (t-test)		0.11		0.094		0.072
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	51	99	69	81	75	75

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	50100	82000	52900	77200	53100	73800
Average	63900	122000	71900	112000	71800	117000
Stdev	41800	184000	73900	178000	72600	188000
p (t-test)		0.0034		0.053		0.034
Min	10500	24400	10500	24400	10500	34000
Max	265000	1230000	689000	1230000	689000	1230000
n (Patient)	98	51	105	44	110	39

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.79	0.77	0.71	0.71	0.71	0.67	0.72	0.72	0.68
SE	0.037	0.038	0.047	0.042	0.041	0.051	0.042	0.041	0.052
p Value	1.0E-14	7.6E-13	9.0E-6	2.9E-7	2.3E-7	7.8E-4	1.2E-7	9.1E-8	5.7E-4
nCohort Non-persistent	49	51	98	69	69	105	75	75	110
nCohort Persistent	101	99	51	81	81	44	75	75	39
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	87%	87%	92%	86%	86%	91%	88%	88%	92%
Specificity	51%	49%	34%	39%	39%	31%	39%	39%	31%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	65%	66%	71%	65%	65%	68%	68%	68%	69%
Specificity	82%	80%	60%	68%	68%	57%	68%	68%	56%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	34%	33%	39%	37%	37%	34%	37%	37%	36%
Specificity	92%	90%	82%	88%	88%	78%	87%	87%	78%
OR Quartile 2	7.05	6.36	5.97	4.09	4.09	4.58	4.62	4.62	5.37
p Value	2.2E-6	6.0E-6	0.0015	5.5E-4	5.5E-4	0.0070	3.4E-4	3.4E-4	0.0082
Lower limit of 95% CI	3.14	2.86	1.98	1.84	1.84	1.51	2.00	2.00	1.55
Upper limit of 95% CI	15.8	14.2	18.0	9.09	9.09	13.9	10.7	10.7	18.6
OR Quartile 3	8.38	7.84	3.63	4.04	4.04	2.86	4.52	4.52	2.91
p Value	5.4E-7	5.6E-7	5.0E-4	6.0E-5	6.0E-5	0.0056	1.7E-5	1.7E-5	0.0072
Lower limit of 95% CI	3.65	3.50	1.76	2.04	2.04	1.36	2.27	2.27	1.34
Upper limit of 95% CI	19.2	17.6	7.50	8.00	8.00	6.01	8.97	8.97	6.32
OR Quartile 4	5.71	4.60	2.87	4.49	4.49	1.84	3.87	3.87	2.01
p Value	0.0020	0.0032	0.0066	6.6E-4	6.6E-4	0.12	0.0011	0.0011	0.086
Lower limit of 95% CI	1.90	1.67	1.34	1.89	1.89	0.849	1.72	1.72	0.906
Upper limit of 95% CI	17.2	12.7	6.13	10.6	10.6	4.01	8.74	8.74	4.45

[0223] Table 15.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “persistent” and “non-persistent” cohorts where

persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	40400	72000	45000	72700	45300	73900
Average	50500	99400	66900	97200	66900	99500
Stdev	39900	135000	86400	133000	83700	138000
p (t-test)		0.014		0.11		0.083
Min	10500	20700	10500	20700	10500	20700
Max	265000	1230000	689000	1230000	689000	1230000
n (Patient)	49	101	68	82	74	76

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	41800	72000	45000	72700	45300	73900
Average	62700	94100	66700	97300	66800	99600
Stdev	97500	122000	86400	133000	83700	138000
p (t-test)		0.11		0.11		0.081
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	51	99	68	82	74	76

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	50300	81200	51800	73800	52900	72700
Average	64200	118000	71900	108000	71900	112000
Stdev	42300	179000	75500	169000	74000	178000
p (t-test)		0.0059		0.075		0.053
Min	10500	24400	10500	24400	10500	34000
Max	265000	1230000	689000	1230000	689000	1230000
n (Patient)	95	54	100	49	105	44

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.79	0.77	0.69	0.71	0.71	0.66	0.71	0.72	0.67
SE	0.037	0.038	0.046	0.042	0.042	0.049	0.042	0.042	0.051
p Value	1.0E-14	7.6E-13	3.3E-5	6.3E-7	5.0E-7	0.0010	2.7E-7	2.1E-7	8.3E-4
nCohort Non-persistent	49	51	95	68	68	100	74	74	105
nCohort Persistent	101	99	54	82	82	49	76	76	44
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	87%	87%	91%	87%	87%	90%	88%	88%	91%
Specificity	51%	49%	34%	40%	40%	32%	39%	39%	31%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	65%	66%	69%	65%	65%	67%	67%	67%	68%
Specificity	82%	80%	60%	68%	68%	58%	68%	68%	57%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	34%	33%	37%	37%	37%	33%	37%	37%	34%
Specificity	92%	90%	81%	88%	88%	78%	86%	86%	78%
OR Quartile 2	7.05	6.36	4.98	4.25	4.25	4.14	4.80	4.80	4.58

p Value	2.2E-6	6.0E-6	0.0019	3.9E-4	3.9E-4	0.0061	2.4E-4	2.4E-4	0.0070
Lower limit of 95% CI	3.14	2.86	1.81	1.91	1.91	1.50	2.08	2.08	1.51
Upper limit of 95% CI	15.8	14.2	13.7	9.46	9.46	11.4	11.1	11.1	13.9
OR Quartile 3	8.38	7.84	3.26	3.82	3.82	2.85	4.25	4.25	2.86
p Value	5.4E-7	5.6E-7	0.0010	1.1E-4	1.1E-4	0.0042	3.3E-5	3.3E-5	0.0056
Lower limit of 95% CI	3.65	3.50	1.61	1.93	1.93	1.39	2.15	2.15	1.36
Upper limit of 95% CI	19.2	17.6	6.61	7.55	7.55	5.83	8.41	8.41	6.01
OR Quartile 4	5.71	4.60	2.52	4.33	4.33	1.72	3.73	3.73	1.84
p Value	0.0020	0.0032	0.016	8.9E-4	8.9E-4	0.16	0.0015	0.0015	0.12
Lower limit of 95% CI	1.90	1.67	1.18	1.82	1.82	0.802	1.66	1.66	0.849
Upper limit of 95% CI	17.2	12.7	5.35	10.3	10.3	3.68	8.42	8.42	4.01

[0224] Table 15.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	40400	72000	43900	73800	44300	77400
Average	49300	99000	56600	104000	56800	107000
Stdev	39000	134000	40100	146000	40300	150000
p (t-test)		0.014		0.012		0.0076
Min	10500	20700	10500	20700	10500	20700
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	47	103	65	85	70	80

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	41800	71900	45000	71300	45300	72700
Average	63400	93500	67500	96000	67500	98200
Stdev	98400	122000	87500	132000	84700	136000
p (t-test)		0.13		0.13		0.10
Min	10500	20700	10500	20700	10500	20700
Max	689000	1230000	689000	1230000	689000	1230000
n (Patient)	50	100	66	84	72	78

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	49500	81800	49800	81200	50300	77200
Average	62900	117000	64000	118000	64600	122000
Stdev	41600	175000	42100	179000	41900	186000
p (t-test)		0.0049		0.0054		0.0041
Min	10500	24400	10500	24400	10500	34000
Max	265000	1230000	265000	1230000	265000	1230000
n (Patient)	92	57	95	54	99	50

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.79	0.76	0.71	0.73	0.70	0.70	0.74	0.70	0.70
SE	0.036	0.039	0.045	0.040	0.042	0.046	0.040	0.042	0.047
p Value	1.6E-15	1.0E-11	4.3E-6	9.7E-9	2.5E-6	2.3E-5	7.3E-10	1.2E-6	3.7E-5
nCohort Non-persistent	47	50	92	65	66	95	70	72	99
nCohort Persistent	103	100	57	85	84	54	80	78	50
Cutoff Quartile 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
Sensitivity	86%	86%	91%	87%	86%	91%	89%	87%	92%
Specificity	51%	48%	35%	42%	39%	34%	41%	39%	33%
Cutoff Quartile 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
Sensitivity	65%	65%	68%	65%	63%	69%	68%	65%	68%
Specificity	83%	80%	61%	69%	67%	60%	70%	67%	59%
Cutoff Quartile 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
Sensitivity	34%	33%	39%	38%	36%	37%	39%	36%	38%
Specificity	94%	90%	83%	91%	88%	81%	90%	86%	81%
OR Quartile 2	6.63	5.67	5.55	4.78	3.90	4.98	5.58	4.33	5.75
p Value	3.9E-6	1.7E-5	9.2E-4	1.3E-4	6.9E-4	0.0019	6.1E-5	4.3E-4	0.0019
Lower limit of 95% CI	2.97	2.57	2.01	2.14	1.78	1.81	2.41	1.91	1.91
Upper limit of 95% CI	14.8	12.5	15.3	10.7	8.56	13.7	12.9	9.78	17.3
OR Quartile 3	9.07	7.43	3.37	4.12	3.42	3.26	4.85	3.78	3.01
p Value	5.3E-7	1.1E-6	6.5E-4	5.6E-5	3.7E-4	0.0010	8.1E-6	1.2E-4	0.0026
Lower limit of 95% CI	3.83	3.32	1.68	2.07	1.74	1.61	2.42	1.92	1.47
Upper limit of 95% CI	21.5	16.6	6.77	8.22	6.73	6.61	9.69	7.43	6.15
OR Quartile 4	7.55	4.43	2.99	5.94	4.03	2.52	5.69	3.47	2.58
p Value	0.0014	0.0040	0.0047	2.3E-4	0.0016	0.016	1.5E-4	0.0027	0.014
Lower limit of 95% CI	2.19	1.61	1.40	2.30	1.70	1.18	2.31	1.54	1.21
Upper limit of 95% CI	26.0	12.2	6.37	15.3	9.55	5.35	14.0	7.82	5.51

[0225] Example 16. Use of Basigin for evaluating renal status in patients admitted to the ICU: Persistent at RIFLE F

[0226] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Basigin is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0227] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output. Two cohorts are defined to represent a "persistent" and a "non-persistent" population. "Persistent" indicates those patients whose minimum RIFLE stage during a period of 24, 48 or 72 hours is failure (F) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. "Non-persistent" indicates those patients who are not persistent at failure (F) and whose minimum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0), risk of injury (R), or injury (I) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. If a patient dies after failure (F) or is placed on renal replacement

therapy (RRT) at any time from sample collection to 24, 48, 72, 96 or 168 hours after sample collection, the patient is considered "persistent".

[0228] The ability to distinguish the "persistent" and "non-persistent" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0229] Table 16.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8720	16900	8860	16900	9030	15600
Average	13300	20300	14200	19400	14500	19500
Stdev	12900	14700	13800	13800	13500	14800
p (t-test)		0.0027		0.034		0.053
Min	1970	3580	1970	3580	1970	3580
Max	72100	69500	72100	69500	72100	69500
n (Patient)	95	55	103	47	110	40

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8730	16800	8930	16700	9030	14300
Average	13300	20100	14200	19500	14500	19300
Stdev	12900	14600	13600	14200	13400	14900
p (t-test)		0.0038		0.030		0.060
Min	1970	3580	1970	3580	1970	3580
Max	72100	69500	72100	69500	72100	69500
n (Patient)	94	56	103	47	108	42

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	9370	18800	9370	18800	9380	18300
Average	14900	22800	14900	22800	14900	23000
Stdev	13600	15100	13600	15100	13500	15500
p (t-test)		0.020		0.020		0.021
Min	1970	5570	1970	5570	1970	5570
Max	72100	69500	72100	69500	72100	69500
n (Patient)	130	19	130	19	131	18

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.70	0.71	0.68	0.67	0.71	0.65	0.65	0.71

SE	0.046	0.046	0.070	0.049	0.049	0.070	0.053	0.052	0.072
p Value	6.5E-6	1.2E-5	0.0026	2.0E-4	3.9E-4	0.0026	0.0035	0.0050	0.0043
nCohort Non-persistent	95	94	130	103	103	130	110	108	131
nCohort Persistent	55	56	19	47	47	19	40	42	18
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	91%	91%	95%	91%	91%	95%	90%	90%	94%
Specificity	35%	35%	28%	33%	33%	28%	31%	31%	27%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	75%	73%	84%	74%	72%	84%	72%	69%	83%
Specificity	64%	64%	55%	61%	60%	55%	58%	57%	54%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	36%	36%	42%	34%	34%	42%	30%	29%	44%
Specificity	81%	81%	77%	79%	79%	77%	76%	76%	77%
OR Quartile 2	5.32	5.52	6.89	5.30	5.30	6.89	4.03	4.36	6.44
p Value	0.0012	9.3E-4	0.065	0.0031	0.0031	0.065	0.014	0.0091	0.075
Lower limit of 95% CI	1.94	2.01	0.887	1.76	1.76	0.887	1.33	1.44	0.827
Upper limit of 95% CI	14.6	15.2	53.6	16.0	16.0	53.6	12.2	13.2	50.2
OR Quartile 3	5.25	4.82	6.42	4.59	3.95	6.42	3.67	3.01	5.92
p Value	1.0E-5	2.1E-5	0.0044	9.6E-5	3.3E-4	0.0044	0.0013	0.0044	0.0068
Lower limit of 95% CI	2.51	2.33	1.78	2.14	1.87	1.78	1.66	1.41	1.63
Upper limit of 95% CI	11.0	9.97	23.1	9.88	8.38	23.1	8.09	6.41	21.4
OR Quartile 4	2.44	2.35	2.42	1.90	1.90	2.42	1.38	1.26	2.69
p Value	0.020	0.026	0.082	0.10	0.10	0.082	0.43	0.57	0.056
Lower limit of 95% CI	1.15	1.11	0.894	0.884	0.884	0.894	0.618	0.566	0.976
Upper limit of 95% CI	5.18	4.97	6.58	4.09	4.09	6.58	3.10	2.81	7.43

[0230] Table 16.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8330	16200	8730	16800	8930	16700
Average	12600	20500	13100	20500	13500	20700
Stdev	11600	15700	12400	15300	12100	16200
p (t-test)		4.6E-4		0.0016		0.0027
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	88	62	94	56	101	49

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8580	15100	8740	15700	8930	14100
Average	12800	20200	13400	19900	13800	19900
Stdev	11700	15700	12600	15200	12300	16000
p (t-test)		0.0013		0.0047		0.011
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	88	62	93	57	99	51

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	9260	17500	9260	17500	9310	17200
Average	14700	21500	14700	21500	14800	21600
Stdev	13700	14300	13700	14300	13600	14600
p (t-test)		0.024		0.024		0.026
Min	1970	4850	1970	4850	1970	4850
Max	72100	69500	72100	69500	72100	69500
n (Patient)	123	26	123	26	124	25

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.70	0.70	0.71	0.69	0.70	0.68	0.66	0.69
SE	0.044	0.044	0.061	0.045	0.046	0.061	0.048	0.048	0.063
p Value	1.1E-6	7.7E-6	0.0015	4.7E-6	2.1E-5	0.0015	2.0E-4	7.7E-4	0.0025
nCohort Non-persistent	88	88	123	94	93	123	101	99	124
nCohort Persistent	62	62	26	56	57	26	49	51	25
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	89%	89%	92%	89%	89%	92%	88%	88%	92%
Specificity	35%	35%	28%	34%	34%	28%	32%	32%	28%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	74%	73%	81%	75%	74%	81%	73%	71%	80%
Specificity	67%	66%	56%	65%	65%	56%	61%	61%	56%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	35%	34%	38%	36%	33%	38%	33%	29%	40%
Specificity	82%	81%	77%	81%	80%	77%	78%	77%	77%
OR Quartile 2	4.27	4.27	4.77	4.30	4.46	4.77	3.32	3.58	4.52
p Value	0.0016	0.0016	0.040	0.0026	0.0020	0.040	0.013	0.0085	0.048
Lower limit of 95% CI	1.74	1.74	1.07	1.67	1.73	1.07	1.28	1.38	1.01
Upper limit of 95% CI	10.5	10.5	21.3	11.1	11.5	21.3	8.61	9.26	20.2
OR Quartile 3	5.85	5.12	5.37	5.55	5.09	5.37	4.40	3.69	5.02
p Value	1.6E-6	6.8E-6	0.0015	5.4E-6	1.1E-5	0.0015	1.1E-4	4.1E-4	0.0024
Lower limit of 95% CI	2.84	2.51	1.90	2.65	2.46	1.90	2.08	1.79	1.77
Upper limit of 95% CI	12.0	10.4	15.2	11.6	10.5	15.2	9.32	7.62	14.2
OR Quartile 4	2.48	2.14	2.12	2.35	1.95	2.12	1.74	1.38	2.29
p Value	0.018	0.046	0.100	0.026	0.080	0.100	0.15	0.41	0.073
Lower limit of 95% CI	1.17	1.01	0.866	1.11	0.923	0.866	0.813	0.643	0.925
Upper limit of 95% CI	5.25	4.51	5.19	4.97	4.11	5.19	3.73	2.95	5.65

[0231] Table 16.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8000	15700	8050	16200	8730	16800
Average	11900	20800	11900	21100	12300	21900
Stdev	11000	15600	11000	15700	10700	16600
p (t-test)		6.4E-5		4.5E-5		3.1E-5
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	83	67	86	64	94	56

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8010	15100	8160	15100	8740	14500
Average	11900	20600	12300	20700	12600	21100
Stdev	11100	15600	11300	15700	11000	16500
p (t-test)		9.9E-5		2.0E-4		2.2E-4
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	82	68	86	64	93	57

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	9000	18300	9000	18300	9030	17700
Average	13400	24500	13400	24500	13400	24700
Stdev	11700	17400	11700	17400	11700	17600
p (t-test)		2.7E-5		2.7E-5		2.8E-5
Min	1970	4850	1970	4850	1970	4850
Max	67300	72100	67300	72100	67300	72100
n (Patient)	115	34	115	34	116	33

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.74	0.73	0.74	0.74	0.73	0.74	0.73	0.71	0.74
SE	0.041	0.042	0.053	0.042	0.042	0.053	0.044	0.045	0.053
p Value	7.7E-9	1.6E-8	4.5E-6	3.9E-9	6.4E-8	4.5E-6	3.4E-7	4.2E-6	9.4E-6
nCohort Non-persistent	83	82	115	86	86	115	94	93	116
nCohort Persistent	67	68	34	64	64	34	56	57	33
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	90%	90%	94%	91%	91%	94%	89%	89%	94%
Specificity	37%	38%	30%	37%	37%	30%	34%	34%	30%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	76%	75%	82%	78%	77%	82%	77%	74%	82%
Specificity	71%	71%	59%	71%	70%	59%	66%	65%	59%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	36%	35%	44%	36%	34%	44%	36%	33%	45%
Specificity	83%	83%	80%	83%	81%	80%	81%	80%	80%
OR Quartile 2	5.11	5.30	7.00	5.73	5.73	7.00	4.30	4.46	6.70
p Value	3.8E-4	2.9E-4	0.010	3.1E-4	3.1E-4	0.010	0.0026	0.0020	0.012
Lower limit of 95% CI	2.08	2.15	1.59	2.22	2.22	1.59	1.67	1.73	1.52
Upper limit of 95% CI	12.6	13.0	30.8	14.8	14.8	30.8	11.1	11.5	29.5
OR Quartile 3	7.84	7.25	6.75	8.71	7.54	6.75	6.41	5.09	6.38
p Value	4.1E-8	9.0E-8	9.2E-5	1.8E-8	8.5E-8	9.2E-5	1.3E-6	1.1E-5	1.5E-4
Lower limit of 95% CI	3.76	3.51	2.59	4.10	3.60	2.59	3.02	2.46	2.44
Upper limit of 95% CI	16.3	15.0	17.6	18.5	15.8	17.6	13.6	10.5	16.6
OR Quartile 4	2.75	2.65	3.16	2.66	2.29	3.16	2.35	1.95	3.37
p Value	0.0092	0.012	0.0058	0.011	0.030	0.0058	0.026	0.080	0.0038
Lower limit of 95% CI	1.28	1.24	1.40	1.25	1.08	1.40	1.11	0.923	1.48
Upper limit of 95% CI	5.89	5.67	7.15	5.65	4.85	7.15	4.97	4.11	7.68

[0232] Table 16.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	7920	16700	8000	16700	8440	16900
Average	11400	21000	11900	21100	12100	21600
Stdev	10700	15500	11100	15600	10800	16200
p (t-test)		1.6E-5		4.0E-5		3.3E-5
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	81	69	85	65	91	59

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	7920	15700	8010	16200	8580	16800
Average	11800	20600	11900	20900	12200	21400
Stdev	11100	15400	11100	15600	10900	16200
p (t-test)		8.7E-5		6.3E-5		5.5E-5
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	81	69	84	66	90	60

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8930	18400	8940	18000	8950	17900
Average	12600	24800	12900	24500	12900	24600
Stdev	10500	18000	10700	18100	10700	18300
p (t-test)		1.0E-6		4.3E-6		4.5E-6
Min	1970	4850	1970	4850	1970	4850
Max	60400	72100	60400	72100	60400	72100
n (Patient)	109	40	110	39	111	38

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.76	0.74	0.75	0.75	0.75	0.74	0.73	0.73	0.74
SE	0.040	0.041	0.049	0.041	0.041	0.050	0.043	0.043	0.050
p Value	1.9E-10	4.8E-9	2.2E-7	1.1E-9	2.6E-9	1.2E-6	5.9E-8	1.3E-7	2.8E-6
nCohort Non-persistent	81	81	109	85	84	110	91	90	111
nCohort Persistent	69	69	40	65	66	39	59	60	38
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	90%	90%	92%	91%	91%	92%	90%	90%	92%
Specificity	38%	38%	31%	38%	38%	31%	35%	36%	31%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	77%	75%	82%	78%	77%	82%	76%	75%	82%
Specificity	73%	72%	61%	72%	71%	61%	67%	67%	60%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	36%	35%	42%	35%	35%	41%	36%	35%	42%
Specificity	84%	83%	81%	82%	82%	80%	81%	81%	80%
OR Quartile 2	5.49	5.49	5.59	5.94	6.15	5.37	4.79	4.97	5.15
p Value	2.1E-4	2.1E-4	0.0067	2.3E-4	1.7E-4	0.0082	0.0012	9.2E-4	0.0099
Lower limit of 95% CI	2.23	2.23	1.61	2.30	2.39	1.55	1.86	1.93	1.48
Upper limit of 95% CI	13.5	13.5	19.4	15.3	15.9	18.6	12.4	12.8	17.9
OR Quartile 3	8.88	7.71	7.52	9.26	8.50	7.12	6.54	6.00	6.74
p Value	8.4E-9	4.2E-8	1.2E-5	8.2E-9	1.8E-8	2.0E-5	7.1E-7	1.5E-6	3.5E-5
Lower limit of 95% CI	4.23	3.72	3.05	4.34	4.03	2.89	3.11	2.89	2.73
Upper limit of 95% CI	18.7	16.0	18.5	19.7	17.9	17.6	13.7	12.5	16.7

OR Quartile 4	2.97	2.55	3.10	2.56	2.46	2.78	2.41	2.31	2.94
p Value	0.0056	0.016	0.0049	0.015	0.019	0.011	0.022	0.028	0.0078
Lower limit of 95% CI	1.38	1.19	1.41	1.20	1.16	1.26	1.14	1.09	1.33
Upper limit of 95% CI	6.42	5.46	6.81	5.44	5.23	6.14	5.09	4.89	6.52

[0233] Table 16.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	7630	15100	7700	15700	8330	16800
Average	11500	20500	11700	20800	11900	21400
Stdev	10900	15400	10900	15500	10600	16100
p (t-test)		5.7E-5		4.2E-5		2.5E-5
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	78	72	81	69	88	62

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	7700	14500	7810	15100	8330	15600
Average	11900	20300	12000	20500	12300	21000
Stdev	11200	15300	11200	15500	11000	16100
p (t-test)		1.8E-4		1.4E-4		1.3E-4
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	79	71	82	68	88	62

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8900	18000	8900	18000	8930	17900
Average	12600	24600	12600	24600	12700	24700
Stdev	10600	17900	10600	17900	10500	18100
p (t-test)		1.5E-6		1.5E-6		1.6E-6
Min	1970	4850	1970	4850	1970	4850
Max	60400	72100	60400	72100	60400	72100
n (Patient)	108	41	108	41	109	40

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.75	0.73	0.75	0.75	0.74	0.75	0.74	0.72	0.75
SE	0.040	0.041	0.048	0.040	0.041	0.048	0.043	0.043	0.049
p Value	1.2E-9	1.2E-8	1.9E-7	6.8E-10	6.9E-9	1.9E-7	3.1E-8	3.1E-7	4.5E-7
nCohort Non-persistent	78	79	108	81	82	108	88	88	109
nCohort Persistent	72	71	41	69	68	41	62	62	40

Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	90%	90%	93%	91%	91%	93%	90%	90%	92%
Specificity	40%	39%	31%	40%	39%	31%	36%	36%	31%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	74%	73%	83%	75%	75%	83%	74%	73%	82%
Specificity	72%	71%	62%	72%	71%	62%	67%	66%	61%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	35%	34%	41%	35%	34%	41%	35%	34%	42%
Specificity	83%	82%	81%	83%	82%	81%	82%	81%	81%
OR Quartile 2	6.12	5.90	5.82	6.86	6.61	5.82	5.33	5.33	5.59
p Value	8.2E-5	1.1E-4	0.0055	6.9E-5	9.4E-5	0.0055	5.3E-4	5.3E-4	0.0067
Lower limit of 95% CI	2.49	2.40	1.68	2.66	2.56	1.68	2.07	2.07	1.61
Upper limit of 95% CI	15.1	14.5	20.2	17.7	17.1	20.2	13.8	13.8	19.4
OR Quartile 3	7.10	6.66	7.94	7.71	7.25	7.94	5.85	5.12	7.52
p Value	9.4E-8	2.0E-7	6.7E-6	4.2E-8	9.0E-8	6.7E-6	1.6E-6	6.8E-6	1.2E-5
Lower limit of 95% CI	3.46	3.26	3.22	3.72	3.51	3.22	2.84	2.51	3.05
Upper limit of 95% CI	14.6	13.6	19.6	16.0	15.0	19.6	12.0	10.4	18.5
OR Quartile 4	2.66	2.37	2.93	2.55	2.28	2.93	2.48	2.14	3.10
p Value	0.013	0.026	0.0070	0.016	0.031	0.0070	0.018	0.046	0.0049
Lower limit of 95% CI	1.23	1.11	1.34	1.19	1.08	1.34	1.17	1.01	1.41
Upper limit of 95% CI	5.73	5.06	6.42	5.46	4.84	6.42	5.25	4.51	6.81

[0234] Example 17. Use of Basigin for evaluating renal status in patients admitted to the ICU: Persistent at RIFLE I or F

[0235] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Basigin is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0236] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output. Two cohorts are defined to represent a "persistent" and a "non-persistent" population. "Persistent" indicates those patients whose minimum RIFLE stage during a period of 24, 48 or 72 hours is injury (I) or failure (F) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. "Non-persistent" indicates those patients who are not persistent at injury (I) or failure (F) and whose minimum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0) or risk of injury (R) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. If a patient dies after injury (I) or failure (F) or is placed on renal replacement therapy (RRT) at any time from sample collection to 24, 48, 72, 96 or 168 hours after sample collection, the patient is considered "persistent".

[0237] The ability to distinguish the "persistent" and "non-persistent" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0238] Table 17.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	5980	14300	7700	14500	8440	16700
Average	6980	20300	11700	20000	12100	20700
Stdev	4140	15000	11300	15100	10900	16000
p (t-test)		6.6E-9		2.1E-4		1.3E-4
Min	1970	3580	1970	3580	1970	3580
Max	25700	72100	60400	72100	60400	72100
n (Patient)	50	100	75	75	85	65

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	6250	14100	7530	14500	8580	15000
Average	8250	19900	11300	20100	12800	19900
Stdev	7670	14800	11200	15000	12200	15200
p (t-test)		4.3E-7		8.3E-5		0.0019
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	60400	72100	60400	72100
n (Patient)	52	98	73	77	86	64

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	9030	18000	9190	19600	9370	21700
Average	14200	21200	14400	22300	14500	23100
Stdev	13700	13600	13600	14100	13400	15000
p (t-test)		0.0077		0.0054		0.0052
Min	1970	3580	1970	3580	1970	3580
Max	72100	69500	72100	69500	72100	69500
n (Patient)	112	37	120	29	125	24

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.87	0.84	0.70	0.73	0.75	0.71	0.71	0.70	0.71
SE	0.028	0.032	0.053	0.041	0.039	0.058	0.043	0.044	0.063
p Value	0	0	1.7E-4	1.2E-8	1.7E-10	3.4E-4	1.9E-6	9.5E-6	0.0011
nCohort Non-persistent	50	52	112	75	73	120	85	86	125
nCohort Persistent	100	98	37	75	77	29	65	64	24
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	91%	91%	92%	88%	90%	90%	86%	88%	92%
Specificity	58%	56%	30%	39%	41%	28%	34%	35%	28%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	69%	68%	78%	71%	71%	79%	71%	70%	79%
Specificity	88%	85%	59%	71%	73%	57%	66%	65%	55%

Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	37%	36%	43%	36%	36%	48%	38%	36%	50%
Specificity	98%	94%	80%	85%	86%	80%	85%	83%	79%
OR Quartile 2	14.0	12.5	4.94	4.62	6.02	3.43	3.22	3.75	4.28
p Value	5.4E-9	1.7E-8	0.012	3.4E-4	5.1E-5	0.055	0.0060	0.0027	0.057
Lower limit of 95% CI	5.76	5.19	1.42	2.00	2.53	0.973	1.40	1.58	0.955
Upper limit of 95% CI	33.9	30.0	17.2	10.7	14.3	12.1	7.42	8.89	19.2
OR Quartile 3	16.3	11.9	5.20	5.80	6.62	5.01	4.68	4.42	4.68
p Value	9.1E-9	2.1E-8	2.0E-4	9.4E-7	2.1E-7	0.0011	1.5E-5	2.8E-5	0.0038
Lower limit of 95% CI	6.30	5.00	2.18	2.87	3.25	1.90	2.33	2.20	1.64
Upper limit of 95% CI	42.3	28.2	12.4	11.7	13.5	13.2	9.39	8.87	13.3
OR Quartile 4	28.8	9.07	3.12	3.27	3.60	3.73	3.46	2.66	3.81
p Value	0.0011	4.7E-4	0.0054	0.0035	0.0020	0.0025	0.0017	0.011	0.0040
Lower limit of 95% CI	3.81	2.63	1.40	1.48	1.60	1.59	1.60	1.25	1.53
Upper limit of 95% CI	217	31.3	6.94	7.25	8.12	8.78	7.50	5.65	9.45

[0239] Table 17.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	5750	14100	7520	15000	8000	16700
Average	6860	20200	10900	20200	11400	20800
Stdev	4090	14900	10900	14900	10600	15500
p (t-test)		7.0E-9		3.3E-5		2.1E-5
Min	1970	3580	1970	3580	1970	3580
Max	25700	72100	60400	72100	60400	72100
n (Patient)	49	101	70	80	79	71

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	6200	14100	7520	14300	8090	15600
Average	8160	19800	11400	19800	12400	19800
Stdev	7720	14800	11400	14800	12300	14700
p (t-test)		4.7E-7		1.7E-4		0.0010
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	60400	72100	60400	72100
n (Patient)	51	99	70	80	79	71

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8860	18400	8950	21700	9030	24500
Average	12500	23500	12900	24800	13100	25800
Stdev	11200	16500	11300	17200	11200	18000
p (t-test)		5.4E-6		2.4E-6		1.9E-6
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	103	46	111	38	116	33

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.88	0.84	0.74	0.77	0.75	0.75	0.74	0.72	0.75
SE	0.028	0.031	0.046	0.038	0.039	0.050	0.041	0.042	0.053
p Value	0	0	1.6E-7	4.5E-12	2.1E-10	4.8E-7	3.5E-9	3.0E-7	2.6E-6
nCohort Non-persistent	49	51	103	70	70	111	79	79	116
nCohort Persistent	101	99	46	80	80	38	71	71	33
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	91%	91%	91%	89%	89%	89%	87%	87%	91%
Specificity	59%	57%	32%	41%	41%	30%	37%	37%	29%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	69%	69%	80%	72%	71%	82%	73%	72%	82%
Specificity	90%	86%	63%	76%	74%	60%	71%	70%	59%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	37%	35%	46%	36%	35%	50%	38%	35%	52%
Specificity	98%	94%	83%	87%	86%	83%	86%	84%	82%
OR Quartile 2	14.8	13.2	4.95	5.58	5.58	3.60	4.00	4.00	4.15
p Value	3.0E-9	9.7E-9	0.0046	6.1E-5	6.1E-5	0.024	0.0012	0.0012	0.026
Lower limit of 95% CI	6.08	5.46	1.64	2.41	2.41	1.18	1.73	1.73	1.19
Upper limit of 95% CI	36.1	31.8	15.0	12.9	12.9	10.9	9.21	9.21	14.5
OR Quartile 3	19.9	13.8	7.03	8.22	7.16	6.74	6.66	5.84	6.38
p Value	8.4E-9	1.3E-8	4.2E-6	1.9E-8	9.2E-8	3.5E-5	2.0E-7	9.3E-7	1.5E-4
Lower limit of 95% CI	7.19	5.59	3.06	3.94	3.48	2.73	3.26	2.89	2.44
Upper limit of 95% CI	54.9	34.0	16.1	17.1	14.7	16.7	13.6	11.8	16.6
OR Quartile 4	27.8	8.75	4.25	3.85	3.23	4.84	3.79	2.76	4.81
p Value	0.0013	5.9E-4	2.7E-4	0.0015	0.0046	1.2E-4	0.0010	0.0097	2.1E-4
Lower limit of 95% CI	3.68	2.54	1.95	1.67	1.43	2.16	1.71	1.28	2.10
Upper limit of 95% CI	209	30.1	9.26	8.88	7.28	10.8	8.42	5.95	11.0

[0240] Table 17.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	5750	14100	7500	14500	7700	15600
Average	6860	20200	10900	20000	11300	20400
Stdev	4090	14900	11000	14900	10800	15200
p (t-test)		7.0E-9		4.5E-5		4.4E-5
Min	1970	3580	1970	3580	1970	3580
Max	25700	72100	60400	72100	60400	72100
n (Patient)	49	101	69	81	75	75

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	6200	14100	7500	14100	7700	14500
Average	8160	19800	11400	19700	11700	20000
Stdev	7720	14800	11500	14800	11300	15200
p (t-test)		4.7E-7		2.2E-4		2.1E-4
Min	1970	3580	1970	3580	1970	3580

Max	42400	72100	60400	72100	60400	72100
n (Patient)	51	99	69	81	75	75

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8730	18000	8860	19200	8940	18800
Average	11700	24100	12100	25000	12400	25800
Stdev	9830	17000	10000	17600	10100	18300
p (t-test)		8.3E-8		9.4E-8		8.0E-8
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	98	51	105	44	110	39

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.88	0.84	0.77	0.77	0.75	0.76	0.75	0.73	0.76
SE	0.028	0.031	0.043	0.038	0.039	0.046	0.040	0.041	0.049
p Value	0	0	5.1E-10	4.2E-12	2.1E-10	1.5E-8	4.6E-10	1.1E-8	1.3E-7
nCohort Non-persistent	49	51	98	69	69	105	75	75	110
nCohort Persistent	101	99	51	81	81	44	75	75	39
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	91%	91%	92%	89%	89%	91%	88%	88%	92%
Specificity	59%	57%	34%	42%	42%	31%	39%	39%	31%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	69%	69%	82%	72%	70%	82%	73%	72%	82%
Specificity	90%	86%	66%	75%	74%	63%	73%	72%	61%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	37%	35%	45%	36%	35%	48%	36%	35%	49%
Specificity	98%	94%	85%	87%	86%	84%	85%	84%	83%
OR Quartile 2	14.8	13.2	5.97	5.80	5.80	4.58	4.62	4.62	5.37
p Value	3.0E-9	9.7E-9	0.0015	4.3E-5	4.3E-5	0.0070	3.4E-4	3.4E-4	0.0082
Lower limit of 95% CI	6.08	5.46	1.98	2.50	2.50	1.51	2.00	2.00	1.55
Upper limit of 95% CI	36.1	31.8	18.0	13.5	13.5	13.9	10.7	10.7	18.6
OR Quartile 3	19.9	13.8	9.19	7.71	6.73	7.62	7.56	6.61	7.12
p Value	8.4E-9	1.3E-8	1.8E-7	4.2E-8	2.0E-7	3.9E-6	4.3E-8	2.1E-7	2.0E-5
Lower limit of 95% CI	7.19	5.59	4.00	3.72	3.28	3.22	3.67	3.24	2.89
Upper limit of 95% CI	54.9	34.0	21.1	16.0	13.8	18.0	15.6	13.5	17.6
OR Quartile 4	27.8	8.75	4.55	3.72	3.12	4.73	3.27	2.79	4.55
p Value	0.0013	5.9E-4	1.4E-4	0.0021	0.0061	1.1E-4	0.0035	0.0100	2.0E-4
Lower limit of 95% CI	3.68	2.54	2.09	1.61	1.38	2.15	1.48	1.28	2.05
Upper limit of 95% CI	209	30.1	9.90	8.57	7.02	10.4	7.25	6.07	10.1

[0241] Table 17.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “persistent” and “non-persistent” cohorts where persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	5750	14100	7330	15000	7630	15700
Average	6860	20200	10800	20000	11200	20400
Stdev	4090	14900	11000	14800	10900	15100

p (t-test)		7.0E-9		3.7E-5		3.7E-5
Min	1970	3580	1970	3580	1970	3580
Max	25700	72100	60400	72100	60400	72100
n (Patient)	49	101	68	82	74	76

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	6200	14100	7330	14300	7630	15000
Average	8160	19800	11300	19700	11600	20000
Stdev	7720	14800	11500	14700	11300	15100
p (t-test)		4.7E-7		1.9E-4		1.8E-4
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	60400	72100	60400	72100
n (Patient)	51	99	68	82	74	76

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8720	17900	8800	18000	8860	17900
Average	11700	23300	12100	23700	12400	24300
Stdev	9930	16800	10200	17200	10200	17800
p (t-test)		3.7E-7		8.1E-7		9.1E-7
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	95	54	100	49	105	44

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.88	0.84	0.76	0.77	0.76	0.75	0.75	0.74	0.74
SE	0.028	0.031	0.043	0.038	0.039	0.045	0.039	0.040	0.047
p Value	0	0	2.5E-9	5.4E-13	3.6E-11	3.6E-8	9.8E-11	2.9E-9	3.8E-7
nCohort Non-persistent	49	51	95	68	68	100	74	74	105
nCohort Persistent	101	99	54	82	82	49	76	76	44
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	91%	91%	91%	89%	89%	90%	88%	88%	91%
Specificity	59%	57%	34%	43%	43%	32%	39%	39%	31%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	69%	69%	80%	72%	71%	80%	74%	72%	80%
Specificity	90%	86%	66%	76%	75%	64%	74%	73%	62%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	37%	35%	43%	35%	34%	43%	36%	34%	43%
Specificity	98%	94%	84%	87%	85%	83%	85%	84%	82%
OR Quartile 2	14.8	13.2	4.98	6.03	6.03	4.14	4.80	4.80	4.58
p Value	3.0E-9	9.7E-9	0.0019	2.9E-5	2.9E-5	0.0061	2.4E-4	2.4E-4	0.0070
Lower limit of 95% CI	6.08	5.46	1.81	2.60	2.60	1.50	2.08	2.08	1.51
Upper limit of 95% CI	36.1	31.8	13.7	14.0	14.0	11.4	11.1	11.1	13.9
OR Quartile 3	19.9	13.8	7.70	8.34	7.25	6.93	8.11	7.07	6.32
p Value	8.4E-9	1.3E-8	3.7E-7	1.9E-8	9.0E-8	2.5E-6	1.9E-8	9.4E-8	1.4E-5
Lower limit of 95% CI	7.19	5.59	3.50	3.98	3.51	3.10	3.91	3.45	2.75
Upper limit of 95% CI	54.9	34.0	16.9	17.5	15.0	15.5	16.8	14.5	14.5
OR Quartile 4	27.8	8.75	3.96	3.59	3.01	3.66	3.16	2.69	3.44
p Value	0.0013	5.9E-4	4.7E-4	0.0027	0.0078	9.5E-4	0.0046	0.013	0.0018
Lower limit of 95% CI	3.68	2.54	1.83	1.56	1.34	1.70	1.43	1.23	1.58
Upper limit of 95% CI	209	30.1	8.56	8.27	6.77	7.91	6.98	5.85	7.48

[0242] Table 17.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “persistent” and “non-persistent” cohorts where

persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	5750	14100	7010	14500	7520	15700
Average	6870	20000	10400	20000	10700	20400
Stdev	4170	14900	10500	14800	10400	15100
p (t-test)		2.3E-8		1.8E-5		1.2E-5
Min	1970	3580	1970	3580	1970	3580
Max	25700	72100	60400	72100	60400	72100
n (Patient)	47	103	65	85	70	80

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	6250	14000	7330	14000	7630	14300
Average	8220	19700	11400	19400	11700	19600
Stdev	7790	14800	11700	14600	11500	15000
p (t-test)		8.9E-7		4.2E-4		4.3E-4
Min	1970	3580	1970	3580	1970	3580
Max	42400	72100	60400	72100	60400	72100
n (Patient)	50	100	66	84	72	78

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	8350	17700	8440	18400	8720	18400
Average	11400	23100	11400	23800	11700	24300
Stdev	9790	16600	9650	16800	9670	17200
p (t-test)		2.6E-7		6.4E-8		5.1E-8
Min	1970	3580	1970	3580	1970	3580
Max	60400	72100	60400	72100	60400	72100
n (Patient)	92	57	95	54	99	50

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.87	0.84	0.76	0.78	0.75	0.77	0.77	0.73	0.77
SE	0.028	0.032	0.042	0.037	0.039	0.042	0.038	0.041	0.044
p Value	0	0	3.9E-10	3.3E-14	4.0E-10	1.7E-10	1.7E-12	2.3E-8	8.7E-10
nCohort Non-persistent	47	50	92	65	66	95	70	72	99
nCohort Persistent	103	100	57	85	84	54	80	78	50
Cutoff Quartile 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
Sensitivity	90%	90%	91%	89%	88%	91%	89%	87%	92%
Specificity	60%	56%	35%	45%	42%	34%	41%	39%	33%
Cutoff Quartile 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
Sensitivity	68%	68%	79%	71%	69%	80%	72%	71%	80%
Specificity	89%	86%	67%	77%	74%	66%	76%	72%	65%
Cutoff Quartile 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
Sensitivity	36%	35%	42%	35%	33%	44%	36%	33%	46%
Specificity	98%	94%	85%	88%	85%	85%	87%	83%	85%
OR Quartile 2	13.7	11.5	5.55	6.80	5.45	4.98	5.58	4.33	5.75

p Value	4.4E-9	2.7E-8	9.2E-4	9.0E-6	5.2E-5	0.0019	6.1E-5	4.3E-4	0.0019
Lower limit of 95% CI	5.72	4.85	2.01	2.92	2.40	1.81	2.41	1.91	1.91
Upper limit of 95% CI	32.9	27.1	15.3	15.9	12.4	13.7	12.9	9.78	17.3
OR Quartile 3	17.8	13.1	7.75	8.00	6.43	7.70	8.22	6.22	7.31
p Value	2.7E-8	2.4E-8	2.0E-7	4.0E-8	4.1E-7	3.7E-7	1.9E-8	4.4E-7	1.3E-6
Lower limit of 95% CI	6.45	5.29	3.58	3.81	3.13	3.50	3.94	3.06	3.27
Upper limit of 95% CI	49.2	32.2	16.8	16.8	13.2	16.9	17.1	12.6	16.4
OR Quartile 4	25.8	8.44	4.05	3.89	2.80	4.63	3.85	2.50	4.77
p Value	0.0016	7.3E-4	4.0E-4	0.0021	0.013	1.2E-4	0.0015	0.021	9.0E-5
Lower limit of 95% CI	3.42	2.45	1.87	1.64	1.24	2.12	1.67	1.15	2.18
Upper limit of 95% CI	195	29.1	8.79	9.22	6.30	10.1	8.88	5.44	10.4

[0243] Example 18. Use of Cathepsin B for evaluating renal status in patients admitted to the ICU: Persistent at RIFLE F

[0244] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Cathepsin B is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0245] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output. Two cohorts are defined to represent a "persistent" and a "non-persistent" population. "Persistent" indicates those patients whose minimum RIFLE stage during a period of 24, 48 or 72 hours is failure (F) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. "Non-persistent" indicates those patients who are not persistent at failure (F) and whose minimum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0), risk of injury (R), or injury (I) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. If a patient dies after failure (F) or is placed on renal replacement therapy (RRT) at any time from sample collection to 24, 48, 72, 96 or 168 hours after sample collection, the patient is considered "persistent".

[0246] The ability to distinguish the "persistent" and "non-persistent" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0247] Table 18.1: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	2.42	8.44	2.42	8.44	2.83	7.78
Average	6.51	22.2	7.06	23.8	8.21	23.5
Stdev	10.3	29.0	10.9	30.7	14.2	30.1
p (t-test)		3.8E-6		2.6E-6		5.9E-5
Min	0.0435	0.240	0.0435	0.366	0.0435	0.366
Max	57.5	111	57.5	111	103	111
n (Patient)	97	51	105	43	112	36

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	2.46	8.29	2.51	8.44	3.04	6.80
Average	6.57	21.8	6.84	24.3	8.05	23.1
Stdev	10.4	28.8	10.4	30.8	13.9	29.8
p (t-test)		7.2E-6		7.9E-7		5.4E-5
Min	0.0435	0.172	0.0435	0.172	0.0435	0.172
Max	57.5	111	57.5	111	103	111
n (Patient)	96	52	105	43	110	38

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.62	6.68	3.61	8.62	3.61	8.62
Average	10.2	25.1	10.1	26.4	10.1	26.4
Stdev	17.9	30.5	17.9	30.8	17.9	30.8
p (t-test)		0.0032		0.0016		0.0016
Min	0.0435	0.592	0.0435	0.592	0.0435	0.592
Max	111	91.6	111	91.6	111	91.6
n (Patient)	129	18	130	17	130	17

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.70	0.68	0.64	0.71	0.70	0.66	0.68	0.66	0.66
SE	0.047	0.047	0.074	0.049	0.050	0.076	0.054	0.054	0.076
p Value	2.9E-5	1.4E-4	0.052	2.4E-5	9.8E-5	0.038	8.1E-4	0.0029	0.038
nCohort Non-persistent	97	96	129	105	105	130	112	110	130
nCohort Persistent	51	52	18	43	43	17	36	38	17
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	86%	85%	83%	88%	86%	82%	86%	84%	82%
Specificity	31%	30%	26%	30%	30%	26%	29%	28%	26%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	67%	65%	56%	70%	67%	59%	67%	63%	59%
Specificity	59%	58%	50%	58%	57%	51%	55%	55%	51%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	43%	42%	44%	42%	44%	47%	44%	45%	47%
Specificity	85%	84%	78%	82%	83%	78%	81%	82%	78%
OR Quartile 2	2.81	2.38	1.79	3.33	2.58	1.65	2.48	2.09	1.65
p Value	0.025	0.051	0.38	0.021	0.052	0.45	0.084	0.13	0.45
Lower limit of 95% CI	1.14	0.997	0.488	1.20	0.990	0.447	0.886	0.797	0.447
Upper limit of 95% CI	6.97	5.68	6.57	9.25	6.74	6.11	6.94	5.50	6.11
OR Quartile 3	2.85	2.64	1.27	3.20	2.76	1.47	2.48	2.06	1.47
p Value	0.0038	0.0065	0.64	0.0026	0.0076	0.46	0.024	0.062	0.46
Lower limit of 95% CI	1.40	1.31	0.471	1.50	1.31	0.528	1.13	0.963	0.528
Upper limit of 95% CI	5.79	5.33	3.42	6.82	5.82	4.11	5.45	4.39	4.11

OR Quartile 4	4.15	3.96	2.76	3.26	3.83	3.10	3.47	3.64	3.10
p Value	3.6E-4	5.3E-4	0.051	0.0031	8.4E-4	0.033	0.0027	0.0016	0.033
Lower limit of 95% CI	1.90	1.82	0.997	1.49	1.74	1.10	1.54	1.63	1.10
Upper limit of 95% CI	9.06	8.63	7.63	7.13	8.41	8.74	7.80	8.13	8.74

[0248] Table 18.2: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	2.30	8.29	2.37	8.44	2.57	7.54
Average	5.93	21.2	6.29	22.6	7.68	21.9
Stdev	9.88	27.6	10.1	28.9	13.9	28.2
p (t-test)		4.0E-6		1.4E-6		6.5E-5
Min	0.0435	0.240	0.0435	0.366	0.0435	0.366
Max	57.5	111	57.5	111	103	111
n (Patient)	90	58	97	51	104	44

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	2.40	7.97	2.40	7.97	2.83	6.80
Average	6.34	20.6	6.66	21.6	8.10	20.4
Stdev	10.4	27.7	10.6	28.8	14.3	27.8
p (t-test)		1.9E-5		1.0E-5		5.3E-4
Min	0.0435	0.172	0.0435	0.172	0.0435	0.172
Max	57.5	111	57.5	111	103	111
n (Patient)	90	58	96	52	102	46

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.63	4.73	3.62	6.43	3.62	6.43
Average	10.1	21.0	10.1	21.8	10.1	21.8
Stdev	18.1	27.5	18.1	27.8	18.1	27.8
p (t-test)		0.014		0.0091		0.0091
Min	0.0435	0.592	0.0435	0.592	0.0435	0.592
Max	111	91.6	111	91.6	111	91.6
n (Patient)	122	25	123	24	123	24

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.68	0.60	0.72	0.69	0.61	0.68	0.65	0.61
SE	0.045	0.046	0.065	0.046	0.047	0.066	0.050	0.050	0.066
p Value	4.9E-6	8.5E-5	0.13	3.3E-6	4.3E-5	0.10	3.1E-4	0.0031	0.10
nCohort Non-persistent	90	90	122	97	96	123	104	102	123
nCohort Persistent	58	58	25	51	52	24	44	46	24

Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	84%	83%	76%	86%	85%	75%	84%	83%	75%
Specificity	31%	30%	25%	31%	30%	25%	29%	28%	25%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	67%	66%	52%	69%	67%	54%	66%	63%	54%
Specificity	61%	60%	50%	60%	59%	50%	57%	56%	50%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	43%	41%	40%	43%	40%	42%	43%	39%	42%
Specificity	87%	86%	78%	85%	83%	78%	83%	81%	78%
OR Quartile 2	2.46	2.06	1.08	2.81	2.38	1.01	2.14	1.89	1.01
p Value	0.036	0.084	0.88	0.025	0.051	0.98	0.10	0.16	0.98
Lower limit of 95% CI	1.06	0.909	0.395	1.14	0.997	0.368	0.860	0.786	0.368
Upper limit of 95% CI	5.69	4.66	2.94	6.97	5.68	2.77	5.34	4.53	2.77
OR Quartile 3	3.23	2.85	1.08	3.25	3.01	1.20	2.53	2.16	1.20
p Value	9.3E-4	0.0028	0.86	0.0013	0.0023	0.68	0.013	0.035	0.68
Lower limit of 95% CI	1.61	1.43	0.458	1.59	1.48	0.500	1.22	1.06	0.500
Upper limit of 95% CI	6.45	5.66	2.56	6.67	6.11	2.89	5.28	4.42	2.89
OR Quartile 4	4.92	4.18	2.35	4.15	3.39	2.54	3.63	2.81	2.54
p Value	9.3E-5	3.6E-4	0.065	3.6E-4	0.0019	0.046	0.0013	0.0089	0.046
Lower limit of 95% CI	2.21	1.90	0.947	1.90	1.57	1.02	1.66	1.30	1.02
Upper limit of 95% CI	11.0	9.18	5.81	9.06	7.33	6.35	7.95	6.09	6.35

[0249] Table 18.3: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "persistent" and "non-persistent" cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	2.23	8.44	2.20	8.46	2.42	8.14
Average	5.84	20.1	5.84	21.1	7.59	20.2
Stdev	10.0	26.8	9.98	27.4	14.3	26.6
p (t-test)		1.3E-5		3.7E-6		2.6E-4
Min	0.0435	0.240	0.0435	0.267	0.0435	0.267
Max	57.5	111	57.5	111	103	111
n (Patient)	85	63	89	59	97	51

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	2.30	8.29	2.23	8.44	2.57	7.37
Average	5.91	19.8	6.04	20.8	7.84	19.4
Stdev	10.1	26.7	10.1	27.5	14.4	26.6
p (t-test)		2.2E-5		8.4E-6		7.4E-4
Min	0.0435	0.172	0.0435	0.172	0.0435	0.172
Max	57.5	111	57.5	111	103	111
n (Patient)	84	64	89	59	96	52

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.60	8.30	3.46	8.46	3.46	8.46

Average	10.2	18.5	10.1	19.0	10.1	19.0
Stdev	18.6	24.8	18.5	25.1	18.5	25.1
p (t-test)		0.041		0.030		0.030
Min	0.0435	0.267	0.0435	0.267	0.0435	0.267
Max	111	91.6	111	91.6	111	91.6
n (Patient)	115	32	116	31	116	31

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.70	0.69	0.61	0.73	0.71	0.61	0.68	0.66	0.61
SE	0.044	0.045	0.058	0.044	0.045	0.059	0.048	0.048	0.059
p Value	4.0E-6	2.1E-5	0.066	1.6E-7	3.9E-6	0.054	1.1E-4	0.0013	0.054
nCohort Non-persistent	85	84	115	89	89	116	97	96	116
nCohort Persistent	63	64	32	59	59	31	51	52	31
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	84%	83%	78%	86%	85%	77%	84%	83%	77%
Specificity	32%	31%	26%	33%	31%	26%	30%	29%	26%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	67%	66%	56%	69%	68%	58%	67%	63%	58%
Specificity	62%	62%	51%	63%	62%	52%	59%	57%	52%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	41%	41%	38%	42%	41%	39%	41%	38%	39%
Specificity	87%	87%	78%	87%	85%	78%	84%	82%	78%
OR Quartile 2	2.47	2.16	1.26	3.08	2.55	1.20	2.29	1.97	1.20
p Value	0.030	0.058	0.63	0.011	0.029	0.71	0.062	0.12	0.71
Lower limit of 95% CI	1.09	0.973	0.494	1.29	1.10	0.468	0.959	0.847	0.468
Upper limit of 95% CI	5.58	4.79	3.21	7.33	5.90	3.06	5.48	4.57	3.06
OR Quartile 3	3.31	3.10	1.35	3.87	3.41	1.48	2.85	2.33	1.48
p Value	5.9E-4	0.0011	0.45	1.6E-4	5.3E-4	0.33	0.0038	0.017	0.33
Lower limit of 95% CI	1.67	1.57	0.616	1.92	1.70	0.666	1.40	1.16	0.666
Upper limit of 95% CI	6.56	6.11	2.98	7.80	6.81	3.30	5.79	4.67	3.30
OR Quartile 4	4.73	4.54	2.16	4.72	4.01	2.30	3.54	2.90	2.30
p Value	1.6E-4	2.4E-4	0.073	1.4E-4	5.2E-4	0.054	0.0013	0.0064	0.054
Lower limit of 95% CI	2.11	2.03	0.931	2.12	1.83	0.985	1.63	1.35	0.985
Upper limit of 95% CI	10.6	10.2	5.01	10.5	8.79	5.37	7.68	6.25	5.37

[0250] Table 18.4: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "persistent" and "non-persistent" cohorts where persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	2.22	8.29	2.20	8.46	2.42	8.14
Average	5.83	19.9	5.84	21.1	6.65	21.4
Stdev	10.1	26.7	9.98	27.4	10.6	28.6
p (t-test)		1.7E-5		3.7E-6		1.4E-5
Min	0.0435	0.240	0.0435	0.267	0.0435	0.267
Max	57.5	111	57.5	111	57.5	111
n (Patient)	84	64	89	59	95	53

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent	Persistent Cohort	Non-persistent	Persistent Cohort	Non-persistent	Persistent Cohort

	Cohort		Cohort		Cohort	
Median	2.30	8.29	2.22	8.45	2.46	7.97
Average	5.91	19.8	5.90	20.7	6.72	21.0
Stdev	10.1	26.7	10.0	27.3	10.6	28.5
p (t-test)		2.2E-5		6.7E-6		2.4E-5
Min	0.0435	0.172	0.0435	0.172	0.0435	0.172
Max	57.5	111	57.5	111	57.5	111
n (Patient)	84	64	88	60	94	54

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.29	7.34	3.29	8.30	3.29	8.30
Average	9.60	19.3	9.51	20.2	9.51	20.2
Stdev	17.4	26.4	17.3	26.9	17.3	26.9
p (t-test)		0.012		0.0067		0.0067
Min	0.0435	0.267	0.0435	0.267	0.0435	0.267
Max	111	91.6	111	91.6	111	91.6
n (Patient)	111	36	113	34	113	34

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.69	0.63	0.73	0.71	0.63	0.69	0.68	0.63
SE	0.044	0.045	0.056	0.044	0.044	0.057	0.047	0.047	0.057
p Value	2.6E-6	2.1E-5	0.024	1.6E-7	1.2E-6	0.022	4.3E-5	1.9E-4	0.022
nCohort Non-persistent	84	84	111	89	88	113	95	94	113
nCohort Persistent	64	64	36	59	60	34	53	54	34
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	84%	83%	81%	86%	85%	79%	85%	83%	79%
Specificity	32%	31%	27%	33%	32%	27%	31%	30%	27%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	67%	66%	61%	69%	68%	62%	66%	65%	62%
Specificity	63%	62%	53%	63%	62%	53%	59%	59%	53%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	41%	41%	36%	42%	42%	38%	42%	41%	38%
Specificity	87%	87%	78%	87%	86%	79%	84%	84%	79%
OR Quartile 2	2.56	2.16	1.53	3.08	2.64	1.39	2.47	2.12	1.39
p Value	0.024	0.058	0.36	0.011	0.023	0.48	0.041	0.080	0.48
Lower limit of 95% CI	1.13	0.973	0.608	1.29	1.14	0.550	1.04	0.915	0.550
Upper limit of 95% CI	5.78	4.79	3.87	7.33	6.12	3.53	5.90	4.92	3.53
OR Quartile 3	3.50	3.10	1.78	3.87	3.60	1.83	2.79	2.60	1.83
p Value	3.3E-4	0.0011	0.14	1.6E-4	3.0E-4	0.13	0.0041	0.0069	0.13
Lower limit of 95% CI	1.77	1.57	0.828	1.92	1.80	0.835	1.39	1.30	0.835
Upper limit of 95% CI	6.94	6.11	3.84	7.80	7.20	4.01	5.62	5.20	4.01
OR Quartile 4	4.54	4.54	2.05	4.72	4.52	2.30	3.78	3.62	2.30
p Value	2.4E-4	2.4E-4	0.085	1.4E-4	2.0E-4	0.049	7.8E-4	0.0011	0.049
Lower limit of 95% CI	2.03	2.03	0.906	2.12	2.04	1.01	1.74	1.67	1.01
Upper limit of 95% CI	10.2	10.2	4.64	10.5	10.0	5.24	8.23	7.85	5.24

[0251] Table 18.5: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the “persistent” and “non-persistent” cohorts where persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	2.20	8.44	2.13	8.46	2.40	7.97
Average	5.32	19.9	5.34	20.8	6.69	20.5
Stdev	9.01	26.4	9.01	26.9	10.8	28.0
p (t-test)		7.4E-6		2.2E-6		3.8E-5
Min	0.0435	0.172	0.0435	0.172	0.0435	0.172
Max	57.5	111	57.5	111	57.5	111
n (Patient)	81	67	85	63	92	56

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	2.22	8.45	2.17	8.53	2.40	8.30
Average	5.34	20.1	5.36	21.0	6.23	21.3
Stdev	8.96	26.6	8.95	27.1	9.78	28.2
p (t-test)		5.7E-6		1.6E-6		6.5E-6
Min	0.0435	0.172	0.0435	0.172	0.0435	0.172
Max	57.5	111	57.5	111	57.5	111
n (Patient)	82	66	86	62	92	56

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.17	8.14	3.05	8.30	3.05	8.30
Average	8.68	21.8	8.62	22.4	8.62	22.4
Stdev	14.5	30.1	14.5	30.3	14.5	30.3
p (t-test)		5.5E-4		3.4E-4		3.4E-4
Min	0.0435	0.267	0.0435	0.267	0.0435	0.267
Max	103	111	103	111	103	111
n (Patient)	110	37	111	36	111	36

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.71	0.64	0.73	0.73	0.65	0.68	0.69	0.65
SE	0.043	0.043	0.055	0.043	0.043	0.055	0.046	0.046	0.055
p Value	1.3E-6	2.1E-6	0.0097	4.6E-8	8.0E-8	0.0075	7.7E-5	2.9E-5	0.0075
nCohort Non-persistent	81	82	110	85	86	111	92	92	111
nCohort Persistent	67	66	37	63	62	36	56	56	36
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	84%	83%	81%	86%	85%	81%	84%	84%	81%
Specificity	32%	32%	27%	33%	33%	27%	30%	30%	27%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	67%	67%	62%	70%	69%	64%	66%	66%	64%
Specificity	64%	63%	54%	65%	64%	54%	60%	60%	54%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	40%	41%	38%	41%	42%	39%	39%	41%	39%
Specificity	88%	88%	79%	87%	87%	79%	84%	85%	79%
OR Quartile 2	2.41	2.32	1.61	2.95	2.84	1.53	2.28	2.28	1.53
p Value	0.031	0.038	0.31	0.011	0.015	0.36	0.054	0.054	0.36
Lower limit of 95% CI	1.08	1.05	0.638	1.27	1.23	0.608	0.986	0.986	0.608
Upper limit of 95% CI	5.34	5.15	4.05	6.81	6.57	3.87	5.29	5.29	3.87
OR Quartile 3	3.67	3.47	1.90	4.25	4.02	2.08	2.89	2.89	2.08
p Value	1.9E-4	3.5E-4	0.099	4.9E-5	9.2E-5	0.064	0.0026	0.0026	0.064
Lower limit of 95% CI	1.85	1.75	0.886	2.11	2.00	0.958	1.45	1.45	0.958
Upper limit of 95% CI	7.26	6.85	4.08	8.53	8.06	4.52	5.79	5.79	4.52
OR Quartile 4	4.79	4.98	2.30	4.73	4.92	2.43	3.32	3.88	2.43
p Value	1.9E-4	1.3E-4	0.043	1.6E-4	1.1E-4	0.032	0.0023	6.4E-4	0.032

Lower limit of 95% CI	2.11	2.19	1.03	2.11	2.19	1.08	1.54	1.78	1.08
Upper limit of 95% CI	10.9	11.4	5.16	10.6	11.1	5.49	7.18	8.46	5.49

[0252] Table 18.6: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	90.7	129	94.2	135	94.2	136
Average	102	133	103	136	105	137
Stdev	53.6	79.7	55.0	81.2	55.4	85.0
p (t-test)		0.0056		0.0045		0.0085
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	253	401	253	401	253	401
n (Patient)	95	55	103	47	110	40

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	92.4	128	94.2	129	95.2	124
Average	103	131	104	133	107	131
Stdev	53.5	80.0	55.4	81.5	56.1	84.5
p (t-test)		0.010		0.012		0.044
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	253	401	253	401	253	401
n (Patient)	94	56	103	47	108	42

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	97.5	157	97.5	157	98.9	148
Average	108	155	108	155	108	154
Stdev	59.5	91.2	59.5	91.2	59.5	93.8
p (t-test)		0.0034		0.0034		0.0056
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	284	401	284	401	284	401
n (Patient)	130	19	130	19	131	18

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.61	0.60	0.66	0.62	0.60	0.66	0.60	0.57	0.65
SE	0.049	0.049	0.072	0.051	0.051	0.072	0.054	0.053	0.074
p Value	0.021	0.041	0.022	0.021	0.054	0.022	0.057	0.20	0.041
nCohort Non-persistent	95	94	130	103	103	130	110	108	131
nCohort Persistent	55	56	19	47	47	19	40	42	18
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	80%	79%	84%	81%	79%	84%	80%	76%	83%

Specificity	28%	28%	26%	28%	27%	26%	27%	26%	26%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	62%	61%	68%	62%	62%	68%	62%	60%	67%
Specificity	57%	56%	52%	55%	55%	52%	55%	54%	52%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	36%	36%	53%	36%	34%	53%	38%	33%	50%
Specificity	81%	81%	78%	80%	79%	78%	79%	78%	78%
OR Quartile 2	1.59	1.40	1.89	1.65	1.38	1.89	1.50	1.12	1.75
p Value	0.26	0.40	0.34	0.24	0.44	0.34	0.37	0.79	0.40
Lower limit of 95% CI	0.716	0.641	0.518	0.711	0.607	0.518	0.621	0.488	0.478
Upper limit of 95% CI	3.52	3.06	6.89	3.85	3.14	6.89	3.62	2.57	6.43
OR Quartile 3	2.13	2.00	2.38	2.00	2.00	2.38	2.00	1.71	2.16
p Value	0.029	0.044	0.098	0.055	0.055	0.098	0.067	0.15	0.15
Lower limit of 95% CI	1.08	1.02	0.851	0.987	0.987	0.851	0.952	0.828	0.764
Upper limit of 95% CI	4.20	3.92	6.63	4.04	4.04	6.63	4.20	3.52	6.10
OR Quartile 4	2.44	2.35	4.05	2.21	1.90	4.05	2.27	1.75	3.52
p Value	0.020	0.026	0.0058	0.042	0.10	0.0058	0.041	0.16	0.015
Lower limit of 95% CI	1.15	1.11	1.50	1.03	0.884	1.50	1.03	0.798	1.28
Upper limit of 95% CI	5.18	4.97	10.9	4.75	4.09	10.9	4.99	3.84	9.67

[0253] Table 18.7: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	89.6	121	92.5	120	94.3	118
Average	101	131	103	131	105	131
Stdev	53.2	77.7	54.7	78.7	55.1	81.7
p (t-test)		0.0063		0.012		0.025
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	253	401	253	401	253	401
n (Patient)	88	62	94	56	101	49

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	92.5	119	96.1	113	98.9	111
Average	103	127	105	126	108	124
Stdev	55.2	76.9	56.7	77.4	56.9	79.9
p (t-test)		0.029		0.059		0.15
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	253	401	253	401	253	401
n (Patient)	88	62	93	57	99	51

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	101	124	101	124	101	111
Average	109	137	109	137	109	136
Stdev	58.7	90.7	58.7	90.7	58.7	92.3

p (t-test)		0.046		0.046		0.067
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	284	401	284	401	284	401
n (Patient)	123	26	123	26	124	25

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.61	0.59	0.58	0.60	0.57	0.58	0.58	0.54	0.56
SE	0.047	0.048	0.064	0.049	0.049	0.064	0.051	0.050	0.065
p Value	0.021	0.072	0.22	0.046	0.15	0.22	0.12	0.41	0.32
nCohort Non-persistent	88	88	123	94	93	123	101	99	124
nCohort Persistent	62	62	26	56	57	26	49	51	25
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	82%	81%	81%	82%	81%	81%	82%	78%	80%
Specificity	31%	30%	26%	30%	29%	26%	29%	27%	26%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	60%	58%	54%	59%	56%	54%	59%	55%	52%
Specificity	57%	56%	50%	55%	54%	50%	54%	53%	50%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	34%	32%	42%	32%	30%	42%	33%	29%	40%
Specificity	81%	80%	78%	79%	77%	78%	78%	77%	77%
OR Quartile 2	2.05	1.75	1.48	1.95	1.71	1.48	1.79	1.36	1.39
p Value	0.076	0.16	0.47	0.11	0.19	0.47	0.18	0.45	0.54
Lower limit of 95% CI	0.928	0.802	0.514	0.864	0.772	0.514	0.771	0.612	0.482
Upper limit of 95% CI	4.54	3.81	4.24	4.41	3.79	4.24	4.15	3.04	4.01
OR Quartile 3	1.95	1.74	1.19	1.78	1.49	1.19	1.73	1.35	1.08
p Value	0.048	0.098	0.69	0.093	0.24	0.69	0.12	0.39	0.86
Lower limit of 95% CI	1.01	0.902	0.508	0.909	0.767	0.508	0.868	0.684	0.458
Upper limit of 95% CI	3.77	3.36	2.77	3.47	2.89	2.77	3.46	2.65	2.56
OR Quartile 4	2.14	1.85	2.61	1.75	1.46	2.61	1.74	1.38	2.29
p Value	0.046	0.10	0.034	0.14	0.32	0.034	0.15	0.41	0.073
Lower limit of 95% CI	1.01	0.881	1.07	0.830	0.690	1.07	0.813	0.643	0.925
Upper limit of 95% CI	4.51	3.89	6.33	3.70	3.08	6.33	3.73	2.95	5.65

[0254] Table 18.8: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	88.6	122	89.6	124	94.2	120
Average	98.0	132	98.0	134	102	132
Stdev	50.6	77.1	50.5	77.9	53.8	79.5
p (t-test)		0.0013		8.3E-4		0.0083
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	253	401
n (Patient)	83	67	86	64	94	56

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	89.6	121	92.5	120	96.1	113

Average	98.7	131	99.8	131	105	127
Stdev	50.5	77.3	51.3	78.3	54.4	79.6
p (t-test)		0.0026		0.0035		0.038
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	253	401
n (Patient)	82	68	86	64	93	57

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	99.1	121	99.1	121	99.8	113
Average	107	135	107	135	108	134
Stdev	58.0	85.1	58.0	85.1	58.0	86.2
p (t-test)		0.028		0.028		0.041
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	284	401	284	401	284	401
n (Patient)	115	34	115	34	116	33

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.63	0.62	0.59	0.63	0.61	0.59	0.60	0.57	0.58
SE	0.046	0.046	0.057	0.046	0.047	0.057	0.048	0.049	0.058
p Value	0.0046	0.0099	0.13	0.0039	0.017	0.13	0.039	0.16	0.19
nCohort Non-persistent	83	82	115	86	86	115	94	93	116
nCohort Persistent	67	68	34	64	64	34	56	57	33
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	84%	82%	82%	84%	83%	82%	84%	81%	82%
Specificity	33%	32%	27%	33%	31%	27%	31%	29%	27%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	60%	59%	56%	59%	58%	56%	59%	56%	55%
Specificity	58%	57%	51%	57%	56%	51%	55%	54%	51%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	34%	34%	38%	34%	33%	38%	32%	30%	36%
Specificity	82%	82%	78%	81%	80%	78%	79%	77%	78%
OR Quartile 2	2.45	2.17	1.72	2.61	2.20	1.72	2.33	1.71	1.64
p Value	0.026	0.051	0.27	0.021	0.051	0.27	0.048	0.19	0.32
Lower limit of 95% CI	1.11	0.995	0.651	1.16	0.998	0.651	1.01	0.772	0.619
Upper limit of 95% CI	5.42	4.72	4.56	5.87	4.87	4.56	5.38	3.79	4.35
OR Quartile 3	2.03	1.92	1.33	1.94	1.73	1.33	1.78	1.49	1.24
p Value	0.034	0.050	0.46	0.049	0.100	0.46	0.093	0.24	0.58
Lower limit of 95% CI	1.06	1.000	0.618	1.00	0.900	0.618	0.909	0.767	0.572
Upper limit of 95% CI	3.91	3.68	2.88	3.73	3.33	2.88	3.47	2.89	2.70
OR Quartile 4	2.37	2.28	2.23	2.29	1.98	2.23	1.75	1.46	1.98
p Value	0.025	0.031	0.056	0.030	0.072	0.056	0.14	0.32	0.11
Lower limit of 95% CI	1.12	1.08	0.980	1.08	0.942	0.980	0.830	0.690	0.860
Upper limit of 95% CI	5.03	4.84	5.07	4.85	4.17	5.07	3.70	3.08	4.55

[0255] Table 18.9: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “persistent” and “non-persistent” cohorts where persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent	Persistent Cohort	Non-persistent	Persistent Cohort	Non-persistent	Persistent Cohort

	Cohort		Cohort		Cohort	
Median	87.0	122	88.6	127	94.2	122
Average	96.4	133	96.5	135	100	133
Stdev	49.1	77.0	48.8	78.2	51.3	79.8
p (t-test)		5.4E-4		2.7E-4		0.0023
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	253	401
n (Patient)	81	69	85	65	91	59

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	88.6	122	89.6	124	94.2	120
Average	97.1	132	97.1	134	101	132
Stdev	48.7	77.7	48.7	78.4	51.2	80.1
p (t-test)		9.4E-4		5.8E-4		0.0043
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	253	401
n (Patient)	81	69	84	66	90	60

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	94.3	123	95.2	129	96.1	123
Average	104	139	104	140	105	139
Stdev	55.7	83.5	55.5	84.3	55.6	85.3
p (t-test)		0.0038		0.0030		0.0048
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	274	401	274	401	274	401
n (Patient)	109	40	110	39	111	38

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.64	0.63	0.62	0.64	0.63	0.62	0.61	0.60	0.61
SE	0.045	0.046	0.054	0.046	0.046	0.054	0.048	0.048	0.055
p Value	0.0019	0.0044	0.027	0.0016	0.0037	0.026	0.016	0.031	0.043
nCohort Non-persistent	81	81	109	85	84	110	91	90	111
nCohort Persistent	69	69	40	65	66	39	59	60	38
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	84%	83%	85%	85%	83%	85%	83%	82%	84%
Specificity	33%	32%	28%	33%	32%	28%	31%	30%	28%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	59%	59%	60%	60%	59%	62%	59%	58%	61%
Specificity	58%	58%	53%	58%	57%	54%	56%	56%	53%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	35%	35%	38%	35%	35%	38%	34%	33%	37%
Specificity	83%	83%	79%	82%	82%	79%	80%	80%	78%
OR Quartile 2	2.64	2.25	2.25	2.70	2.37	2.16	2.18	1.91	2.07
p Value	0.017	0.042	0.098	0.016	0.033	0.12	0.061	0.11	0.14
Lower limit of 95% CI	1.19	1.03	0.860	1.20	1.07	0.823	0.966	0.863	0.787
Upper limit of 95% CI	5.83	4.89	5.90	6.08	5.23	5.66	4.91	4.22	5.43
OR Quartile 3	2.02	2.02	1.71	2.04	1.93	1.85	1.86	1.75	1.74
p Value	0.034	0.034	0.15	0.033	0.049	0.11	0.067	0.097	0.15
Lower limit of 95% CI	1.05	1.05	0.817	1.06	1.00	0.878	0.957	0.904	0.822
Upper limit of 95% CI	3.89	3.89	3.56	3.94	3.70	3.90	3.61	3.39	3.68
OR Quartile 4	2.55	2.55	2.24	2.56	2.46	2.36	2.08	2.00	2.11
p Value	0.016	0.016	0.045	0.015	0.019	0.033	0.054	0.068	0.066
Lower limit of 95% CI	1.19	1.19	1.02	1.20	1.16	1.07	0.986	0.950	0.951
Upper limit of 95% CI	5.46	5.46	4.94	5.44	5.23	5.22	4.39	4.21	4.70

[0256] Table 18.10: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	86.1	121	87.0	122	92.8	120
Average	96.0	132	96.0	133	100.0	132
Stdev	48.8	76.4	48.7	77.1	51.1	79.1
p (t-test)		6.8E-4		4.2E-4		0.0029
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	253	401
n (Patient)	78	72	81	69	88	62

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	87.0	122	87.8	124	92.8	120
Average	96.0	132	96.1	134	100.0	132
Stdev	48.4	76.9	48.4	77.6	51.1	79.1
p (t-test)		5.9E-4		3.6E-4		0.0029
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	246	401	246	401	253	401
n (Patient)	79	71	82	68	88	62

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	94.2	129	94.2	129	94.3	123
Average	103	143	103	143	103	142
Stdev	53.5	85.1	53.5	85.1	53.7	86.0
p (t-test)		8.4E-4		8.4E-4		0.0014
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	260	401	260	401	260	401
n (Patient)	108	41	108	41	109	40

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.64	0.64	0.63	0.64	0.64	0.63	0.61	0.61	0.62
SE	0.045	0.045	0.053	0.045	0.046	0.053	0.047	0.047	0.053
p Value	0.0022	0.0022	0.012	0.0019	0.0018	0.012	0.019	0.019	0.021
nCohort Non-persistent	78	79	108	81	82	108	88	88	109
nCohort Persistent	72	71	41	69	68	41	62	62	40
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	83%	83%	85%	84%	84%	85%	82%	82%	85%
Specificity	33%	33%	29%	33%	33%	29%	31%	31%	28%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	58%	59%	61%	58%	59%	61%	58%	58%	60%
Specificity	58%	58%	54%	57%	57%	54%	56%	56%	53%

Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	35%	35%	39%	35%	35%	39%	34%	34%	38%
Specificity	83%	84%	80%	83%	83%	80%	81%	81%	79%
OR Quartile 2	2.50	2.41	2.35	2.64	2.54	2.35	2.05	2.05	2.25
p Value	0.021	0.027	0.082	0.017	0.021	0.082	0.076	0.076	0.098
Lower limit of 95% CI	1.15	1.11	0.898	1.19	1.15	0.898	0.928	0.928	0.860
Upper limit of 95% CI	5.44	5.25	6.14	5.83	5.62	6.14	4.54	4.54	5.90
OR Quartile 3	1.91	2.02	1.81	1.81	1.92	1.81	1.74	1.74	1.71
p Value	0.051	0.034	0.11	0.073	0.050	0.11	0.098	0.098	0.15
Lower limit of 95% CI	0.998	1.05	0.871	0.947	1.000	0.871	0.902	0.902	0.817
Upper limit of 95% CI	3.65	3.87	3.77	3.47	3.68	3.77	3.36	3.36	3.56
OR Quartile 4	2.66	2.76	2.50	2.55	2.65	2.50	2.14	2.14	2.24
p Value	0.013	0.0097	0.022	0.016	0.012	0.022	0.046	0.046	0.045
Lower limit of 95% CI	1.23	1.28	1.14	1.19	1.24	1.14	1.01	1.01	1.02
Upper limit of 95% CI	5.73	5.95	5.47	5.46	5.67	5.47	4.51	4.51	4.94

[0257] Example 19. Use of Cathepsin B for evaluating renal status in patients admitted to the ICU: Persistent at RIFLE I or F

[0258] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Cathepsin B is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0259] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output. Two cohorts are defined to represent a "persistent" and a "non-persistent" population. "Persistent" indicates those patients whose minimum RIFLE stage during a period of 24, 48 or 72 hours is injury (I) or failure (F) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. "Non-persistent" indicates those patients who are not persistent at injury (I) or failure (F) and whose minimum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0) or risk of injury (R) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. If a patient dies after injury (I) or failure (F) or is placed on renal replacement therapy (RRT) at any time from sample collection to 24, 48, 72, 96 or 168 hours after sample collection, the patient is considered "persistent".

[0260] The ability to distinguish the "persistent" and "non-persistent" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0261] Table 19.1: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by

serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.57	7.50	2.42	6.67	2.42	8.44
Average	2.92	17.1	6.68	17.6	6.52	19.6
Stdev	3.60	23.8	10.8	25.9	10.4	27.4
p (t-test)		2.7E-5		9.0E-4		7.7E-5
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	54	94	77	71	87	61

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.74	7.97	2.37	7.81	2.29	8.53
Average	3.01	17.3	5.59	18.4	5.56	21.2
Stdev	3.56	24.0	9.35	25.8	8.93	27.5
p (t-test)		1.9E-5		8.4E-5		1.8E-6
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	56	92	75	73	88	60

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.29	5.69	3.46	8.62	3.46	8.62
Average	10.6	16.7	10.2	19.8	10.1	22.0
Stdev	19.0	24.0	18.5	26.1	18.2	27.6
p (t-test)		0.12		0.026		0.0095
Min	0.0435	0.592	0.0435	0.592	0.0435	0.592
Max	111	91.6	111	91.6	111	91.6
n (Patient)	113	34	120	27	124	23

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.75	0.74	0.61	0.66	0.68	0.64	0.68	0.71	0.65
SE	0.039	0.040	0.057	0.045	0.044	0.062	0.045	0.044	0.066
p Value	1.2E-10	1.5E-9	0.049	5.1E-4	4.8E-5	0.029	7.8E-5	2.2E-6	0.028
nCohort Non-persistent	54	56	113	77	75	120	87	88	124
nCohort Persistent	94	92	34	71	73	27	61	60	23
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	83%	83%	85%	83%	84%	85%	85%	87%	83%
Specificity	39%	38%	28%	32%	33%	28%	32%	33%	27%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	64%	63%	62%	62%	63%	59%	64%	67%	61%
Specificity	74%	71%	53%	61%	63%	52%	60%	61%	52%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	36%	37%	32%	34%	37%	41%	38%	42%	43%
Specificity	94%	95%	77%	83%	87%	78%	84%	86%	78%
OR Quartile 2	3.10	2.85	2.29	2.36	2.54	2.18	2.74	3.19	1.72
p Value	0.0038	0.0072	0.12	0.031	0.020	0.18	0.018	0.0086	0.35
Lower limit of 95% CI	1.44	1.33	0.815	1.08	1.16	0.701	1.19	1.34	0.546

Upper limit of 95% CI	6.68	6.12	6.44	5.17	5.56	6.78	6.34	7.60	5.44
OR Quartile 3	5.04	4.26	1.83	2.55	2.86	1.55	2.63	3.18	1.66
p Value	1.8E-5	7.5E-5	0.13	0.0056	0.0020	0.31	0.0050	9.8E-4	0.27
Lower limit of 95% CI	2.41	2.08	0.835	1.32	1.47	0.667	1.34	1.60	0.669
Upper limit of 95% CI	10.6	8.74	4.01	4.95	5.57	3.63	5.18	6.32	4.12
OR Quartile 4	9.63	10.4	1.60	2.51	3.82	2.49	3.16	4.52	2.76
p Value	3.4E-4	2.1E-4	0.27	0.019	0.0013	0.043	0.0035	2.0E-4	0.032
Lower limit of 95% CI	2.79	3.00	0.690	1.16	1.68	1.03	1.46	2.04	1.09
Upper limit of 95% CI	33.2	35.7	3.71	5.45	8.64	6.00	6.83	10.0	6.99

[0262] Table 19.2: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.55	7.19	2.17	7.37	2.13	8.46
Average	2.90	16.9	5.39	18.1	5.35	19.9
Stdev	3.63	23.8	9.40	25.3	9.10	26.4
p (t-test)		3.5E-5		1.0E-4		8.2E-6
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	53	95	72	76	81	67

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.60	7.81	2.29	7.37	2.20	8.44
Average	2.99	17.2	5.48	18.0	5.50	19.7
Stdev	3.59	23.9	9.38	25.4	9.13	26.5
p (t-test)		2.4E-5		1.3E-4		1.4E-5
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	55	93	72	76	81	67

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.05	6.73	3.30	8.62	3.30	8.62
Average	9.45	18.3	9.15	21.1	9.08	22.8
Stdev	17.6	25.1	17.1	26.6	16.8	27.7
p (t-test)		0.016		0.0022		6.8E-4
Min	0.0435	0.592	0.0435	0.592	0.0435	0.592
Max	111	91.6	111	91.6	111	91.6
n (Patient)	105	42	112	35	116	31

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only

AUC	0.76	0.74	0.63	0.70	0.68	0.65	0.72	0.70	0.66
SE	0.039	0.040	0.053	0.043	0.044	0.056	0.043	0.044	0.058
p Value	7.0E-11	9.2E-10	0.011	4.1E-6	3.3E-5	0.0065	1.9E-7	3.2E-6	0.0064
nCohort Non-persistent	53	55	105	72	72	112	81	81	116
nCohort Persistent	95	93	42	76	76	35	67	67	31
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	83%	83%	83%	84%	83%	83%	87%	85%	81%
Specificity	40%	38%	29%	35%	33%	28%	35%	33%	27%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	64%	63%	62%	64%	63%	60%	67%	66%	61%
Specificity	75%	73%	54%	65%	64%	53%	64%	63%	53%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	36%	37%	36%	37%	37%	43%	40%	39%	45%
Specificity	94%	95%	79%	88%	88%	80%	88%	86%	80%
OR Quartile 2	3.24	2.97	2.00	2.84	2.42	1.85	3.40	2.85	1.52
p Value	0.0027	0.0053	0.14	0.0092	0.025	0.21	0.0042	0.012	0.40
Lower limit of 95% CI	1.50	1.38	0.801	1.29	1.12	0.700	1.47	1.26	0.570
Upper limit of 95% CI	6.99	6.39	5.00	6.22	5.25	4.89	7.87	6.44	4.05
OR Quartile 3	5.52	4.63	1.93	3.41	3.03	1.67	3.67	3.25	1.76
p Value	8.8E-6	3.7E-5	0.078	3.7E-4	0.0012	0.19	1.9E-4	6.3E-4	0.17
Lower limit of 95% CI	2.60	2.23	0.928	1.74	1.55	0.772	1.85	1.65	0.782
Upper limit of 95% CI	11.7	9.58	4.01	6.70	5.93	3.61	7.26	6.40	3.95
OR Quartile 4	9.29	9.99	2.10	4.08	4.08	3.07	4.79	4.04	3.33
p Value	4.2E-4	2.7E-4	0.065	0.0010	0.0010	0.0071	1.9E-4	6.7E-4	0.0051
Lower limit of 95% CI	2.69	2.90	0.954	1.76	1.76	1.36	2.11	1.81	1.43
Upper limit of 95% CI	32.0	34.4	4.60	9.46	9.46	6.94	10.9	9.01	7.73

[0263] Table 19.3: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the "persistent" and "non-persistent" cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.55	7.19	2.13	6.94	2.13	8.14
Average	2.90	16.9	5.41	17.9	5.45	18.9
Stdev	3.63	23.8	9.46	25.2	9.30	25.9
p (t-test)		3.5E-5		1.3E-4		3.5E-5
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	53	95	71	77	77	71

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.60	7.81	2.20	6.94	2.20	8.14
Average	2.99	17.2	5.50	17.8	5.53	18.8
Stdev	3.59	23.9	9.44	25.3	9.28	26.0
p (t-test)		2.4E-5		1.7E-4		4.4E-5
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	55	93	71	77	77	71

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.05	6.73	3.29	8.30	3.29	8.30
Average	9.69	16.7	9.36	18.6	9.27	19.8
Stdev	18.1	23.9	17.6	25.0	17.3	25.9
p (t-test)		0.049		0.013		0.0058
Min	0.0435	0.267	0.0435	0.267	0.0435	0.267
Max	111	91.6	111	91.6	111	91.6
n (Patient)	99	48	105	42	109	38

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.76	0.74	0.61	0.70	0.68	0.63	0.71	0.69	0.63
SE	0.039	0.040	0.051	0.043	0.044	0.053	0.043	0.043	0.054
p Value	7.0E-11	9.2E-10	0.026	3.5E-6	2.9E-5	0.013	9.9E-7	9.3E-6	0.014
nCohort Non-persistent	53	55	99	71	71	105	77	77	109
nCohort Persistent	95	93	48	77	77	42	71	71	38
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	83%	83%	81%	84%	83%	81%	86%	85%	79%
Specificity	40%	38%	28%	35%	34%	28%	35%	34%	27%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	64%	63%	60%	65%	64%	60%	66%	65%	61%
Specificity	75%	73%	55%	66%	65%	53%	65%	64%	53%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	36%	37%	33%	36%	36%	38%	38%	38%	39%
Specificity	94%	95%	79%	87%	87%	80%	87%	87%	80%
OR Quartile 2	3.24	2.97	1.71	2.94	2.51	1.62	3.29	2.78	1.36
p Value	0.0027	0.0053	0.21	0.0070	0.019	0.28	0.0042	0.012	0.50
Lower limit of 95% CI	1.50	1.38	0.733	1.34	1.16	0.672	1.46	1.25	0.559
Upper limit of 95% CI	6.99	6.39	3.98	6.45	5.45	3.91	7.45	6.17	3.30
OR Quartile 3	5.52	4.63	1.83	3.63	3.22	1.68	3.63	3.22	1.74
p Value	8.8E-6	3.7E-5	0.091	2.0E-4	6.6E-4	0.16	2.0E-4	6.6E-4	0.15
Lower limit of 95% CI	2.60	2.23	0.909	1.84	1.64	0.813	1.84	1.64	0.823
Upper limit of 95% CI	11.7	9.58	3.69	7.15	6.31	3.47	7.15	6.31	3.70
OR Quartile 4	9.29	9.99	1.86	3.94	3.94	2.46	4.11	4.11	2.58
p Value	4.2E-4	2.7E-4	0.11	0.0014	0.0014	0.025	7.2E-4	7.2E-4	0.020
Lower limit of 95% CI	2.69	2.90	0.860	1.70	1.70	1.12	1.81	1.81	1.16
Upper limit of 95% CI	32.0	34.4	4.01	9.11	9.11	5.40	9.33	9.33	5.75

[0264] Table 19.4: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the “persistent” and “non-persistent” cohorts where persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.55	7.19	2.13	6.94	2.13	8.14
Average	2.90	16.9	5.41	17.9	5.45	18.9
Stdev	3.63	23.8	9.46	25.2	9.30	25.9
p (t-test)		3.5E-5		1.3E-4		3.5E-5
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	53	95	71	77	77	71

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.60	7.81	2.20	6.94	2.20	8.14
Average	2.99	17.2	5.50	17.8	5.53	18.8
Stdev	3.59	23.9	9.44	25.3	9.28	26.0
p (t-test)		2.4E-5		1.7E-4		4.4E-5
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	55	93	71	77	77	71

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.05	6.20	3.17	7.81	3.17	7.81
Average	9.81	16.2	9.51	17.6	9.42	18.6
Stdev	18.2	23.5	17.8	24.4	17.5	25.3
p (t-test)		0.071		0.026		0.013
Min	0.0435	0.267	0.0435	0.267	0.0435	0.267
Max	111	91.6	111	91.6	111	91.6
n (Patient)	97	50	102	45	106	41

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.76	0.74	0.61	0.70	0.68	0.62	0.71	0.69	0.63
SE	0.039	0.040	0.050	0.043	0.044	0.051	0.043	0.043	0.053
p Value	7.0E-11	9.2E-10	0.031	3.5E-6	2.9E-5	0.015	9.9E-7	9.3E-6	0.017
nCohort Non-persistent	53	55	97	71	71	102	77	77	106
nCohort Persistent	95	93	50	77	77	45	71	71	41
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	83%	83%	82%	84%	83%	82%	86%	85%	80%
Specificity	40%	38%	29%	35%	34%	28%	35%	34%	27%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	64%	63%	60%	65%	64%	60%	66%	65%	61%
Specificity	75%	73%	55%	66%	65%	54%	65%	64%	54%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	36%	37%	32%	36%	36%	36%	38%	38%	37%
Specificity	94%	95%	78%	87%	87%	79%	87%	87%	79%
OR Quartile 2	3.24	2.97	1.85	2.94	2.51	1.84	3.29	2.78	1.55
p Value	0.0027	0.0053	0.15	0.0070	0.019	0.17	0.0042	0.012	0.33
Lower limit of 95% CI	1.50	1.38	0.794	1.34	1.16	0.764	1.46	1.25	0.643
Upper limit of 95% CI	6.99	6.39	4.30	6.45	5.45	4.42	7.45	6.17	3.76
OR Quartile 3	5.52	4.63	1.81	3.63	3.22	1.76	3.63	3.22	1.82
p Value	8.8E-6	3.7E-5	0.094	2.0E-4	6.6E-4	0.12	2.0E-4	6.6E-4	0.11
Lower limit of 95% CI	2.60	2.23	0.904	1.84	1.64	0.861	1.84	1.64	0.872
Upper limit of 95% CI	11.7	9.58	3.61	7.15	6.31	3.58	7.15	6.31	3.79
OR Quartile 4	9.29	9.99	1.70	3.94	3.94	2.13	4.11	4.11	2.20
p Value	4.2E-4	2.7E-4	0.17	0.0014	0.0014	0.057	7.2E-4	7.2E-4	0.050
Lower limit of 95% CI	2.69	2.90	0.792	1.70	1.70	0.979	1.81	1.81	1.000
Upper limit of 95% CI	32.0	34.4	3.66	9.11	9.11	4.63	9.33	9.33	4.85

[0265] Table 19.5: Comparison of marker levels and the area under the ROC curve (AUC) in urine samples for the “persistent” and “non-persistent” cohorts where persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.55	7.19	2.17	6.80	2.13	7.81
Average	2.73	16.8	5.50	17.4	5.54	18.1
Stdev	3.28	23.6	9.62	24.9	9.51	25.5
p (t-test)		4.2E-5		3.1E-4		1.2E-4
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	51	97	68	80	73	75

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	1.57	7.97	2.13	7.81	2.13	8.44
Average	2.78	17.2	5.32	17.7	5.36	18.7
Stdev	3.25	23.8	9.50	25.0	9.34	25.7
p (t-test)		2.0E-5		1.6E-4		4.5E-5
Min	0.0435	0.156	0.0435	0.156	0.0435	0.156
Max	17.5	111	57.5	111	57.5	111
n (Patient)	54	94	69	79	75	73

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	3.03	6.73	3.04	7.81	3.03	7.97
Average	8.75	17.9	8.61	18.7	8.55	19.5
Stdev	15.1	26.6	14.9	27.2	14.7	27.8
p (t-test)		0.0087		0.0041		0.0021
Min	0.0435	0.267	0.0435	0.267	0.0435	0.267
Max	103	111	103	111	103	111
n (Patient)	95	52	98	49	101	46

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.75	0.75	0.63	0.68	0.70	0.63	0.69	0.71	0.64
SE	0.039	0.039	0.049	0.043	0.043	0.050	0.043	0.043	0.051
p Value	1.2E-10	9.8E-11	0.0095	2.6E-5	4.8E-6	0.0082	6.9E-6	1.5E-6	0.0065
nCohort Non-persistent	51	54	95	68	69	98	73	75	101
nCohort Persistent	97	94	52	80	79	49	75	73	46
Cutoff Quartile 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Sensitivity	82%	83%	83%	82%	84%	82%	84%	85%	80%
Specificity	39%	39%	29%	34%	35%	29%	34%	35%	28%
Cutoff Quartile 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
Sensitivity	64%	64%	62%	64%	65%	61%	65%	66%	63%
Specificity	76%	74%	56%	66%	67%	55%	66%	65%	55%
Cutoff Quartile 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
Sensitivity	36%	37%	33%	35%	37%	35%	36%	38%	35%
Specificity	96%	96%	79%	87%	88%	80%	86%	88%	79%
OR Quartile 2	3.04	3.10	2.00	2.41	2.71	1.78	2.73	2.99	1.58
p Value	0.0046	0.0038	0.11	0.024	0.012	0.18	0.012	0.0072	0.29
Lower limit of 95% CI	1.41	1.44	0.859	1.12	1.25	0.763	1.25	1.35	0.675
Upper limit of 95% CI	6.54	6.68	4.64	5.18	5.87	4.14	5.99	6.64	3.68
OR Quartile 3	5.76	5.04	2.02	3.44	3.64	1.94	3.62	3.62	2.12
p Value	8.0E-6	1.8E-5	0.046	3.6E-4	2.0E-4	0.064	2.0E-4	2.0E-4	0.039
Lower limit of 95% CI	2.67	2.41	1.01	1.75	1.84	0.963	1.84	1.84	1.04
Upper limit of 95% CI	12.4	10.6	4.03	6.78	7.19	3.90	7.13	7.13	4.34

OR Quartile 4	13.8	15.4	1.82	3.53	4.42	2.07	3.54	4.56	2.03
p Value	4.8E-4	2.7E-4	0.12	0.0032	7.8E-4	0.062	0.0024	4.0E-4	0.073
Lower limit of 95% CI	3.17	3.54	0.851	1.53	1.86	0.963	1.57	1.97	0.937
Upper limit of 95% CI	60.4	67.3	3.90	8.16	10.5	4.46	8.02	10.6	4.41

[0266] Table 19.6: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	67.7	118	88.6	113	91.4	118
Average	83.0	128	100	126	101	130
Stdev	42.9	70.2	54.3	73.9	51.8	78.0
p (t-test)		4.6E-5		0.017		0.0068
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	174	401	251	401	251	401
n (Patient)	50	100	75	75	85	65

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	77.0	117	88.6	118	92.8	120
Average	87.3	127	99.0	127	101	129
Stdev	44.7	71.1	51.5	74.9	52.8	77.7
p (t-test)		3.4E-4		0.0095		0.0095
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	182	401	246	401	253	401
n (Patient)	52	98	73	77	86	64

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	90.0	136	95.2	136	96.1	132
Average	106	137	107	139	108	142
Stdev	61.7	73.4	60.7	80.5	59.9	87.1
p (t-test)		0.014		0.019		0.020
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	284	401	284	401	284	401
n (Patient)	112	37	120	29	125	24

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.67	0.64	0.60	0.60	0.63	0.60	0.60	0.62
SE	0.043	0.044	0.055	0.046	0.046	0.060	0.047	0.047	0.066
p Value	1.5E-6	1.2E-4	0.0098	0.029	0.024	0.035	0.030	0.039	0.075
nCohort Non-persistent	50	52	112	75	73	120	85	86	125
nCohort Persistent	100	98	37	75	77	29	65	64	24

Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	85%	84%	86%	81%	81%	86%	80%	80%	83%
Specificity	46%	42%	29%	32%	32%	28%	29%	29%	26%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	59%	58%	68%	55%	56%	62%	57%	58%	62%
Specificity	68%	65%	55%	55%	56%	52%	55%	56%	52%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	32%	31%	38%	31%	31%	41%	34%	33%	42%
Specificity	88%	85%	79%	80%	81%	78%	81%	80%	78%
OR Quartile 2	4.83	3.76	2.56	2.05	1.90	2.37	1.67	1.61	1.79
p Value	7.9E-5	7.3E-4	0.073	0.063	0.093	0.13	0.19	0.22	0.32
Lower limit of 95% CI	2.21	1.74	0.916	0.962	0.898	0.767	0.775	0.747	0.571
Upper limit of 95% CI	10.5	8.10	7.16	4.37	4.02	7.33	3.59	3.46	5.63
OR Quartile 3	3.06	2.63	2.58	1.45	1.62	1.81	1.63	1.73	1.81
p Value	0.0022	0.0067	0.017	0.25	0.14	0.16	0.14	0.100	0.20
Lower limit of 95% CI	1.50	1.31	1.18	0.765	0.850	0.788	0.852	0.900	0.736
Upper limit of 95% CI	6.25	5.28	5.65	2.77	3.09	4.15	3.13	3.33	4.43
OR Quartile 4	3.45	2.43	2.23	1.77	1.91	2.55	2.21	1.98	2.47
p Value	0.011	0.045	0.050	0.14	0.094	0.032	0.038	0.072	0.052
Lower limit of 95% CI	1.33	1.02	1.000	0.837	0.896	1.08	1.04	0.942	0.992
Upper limit of 95% CI	8.93	5.78	4.98	3.74	4.07	6.01	4.66	4.17	6.17

[0267] Table 19.7: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	67.1	119	86.1	115	88.6	118
Average	81.4	129	97.7	127	98.3	130
Stdev	41.9	69.9	52.5	73.3	50.3	76.7
p (t-test)		2.3E-5		0.0062		0.0031
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	174	401	246	401	246	401
n (Patient)	49	101	70	80	79	71

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	73.7	118	87.8	115	94.3	113
Average	85.8	127	98.5	126	101	127
Stdev	43.9	70.8	52.1	73.8	52.8	76.0
p (t-test)		1.9E-4		0.0097		0.017
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	182	401	246	401	253	401
n (Patient)	51	99	70	80	79	71

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	91.4	125	96.1	117	97.5	113

Average	105	134	106	136	107	137
Stdev	59.4	75.2	58.4	81.0	57.7	85.9
p (t-test)		0.011		0.016		0.020
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	274	401	274	401	274	401
n (Patient)	103	46	111	38	116	33

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.72	0.68	0.63	0.62	0.61	0.61	0.62	0.59	0.59
SE	0.042	0.044	0.051	0.046	0.046	0.055	0.046	0.047	0.058
p Value	2.7E-7	3.6E-5	0.014	0.0095	0.019	0.050	0.012	0.052	0.10
nCohort Non-persistent	49	51	103	70	70	111	79	79	116
nCohort Persistent	101	99	46	80	80	38	71	71	33
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	85%	84%	87%	82%	81%	87%	82%	80%	85%
Specificity	47%	43%	30%	34%	33%	29%	32%	30%	28%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	59%	59%	63%	55%	55%	58%	56%	55%	58%
Specificity	69%	67%	55%	56%	56%	52%	56%	54%	52%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	33%	31%	35%	31%	31%	37%	34%	32%	36%
Specificity	90%	86%	79%	81%	81%	78%	82%	81%	78%
OR Quartile 2	5.07	3.94	2.87	2.46	2.12	2.67	2.07	1.78	2.13
p Value	5.0E-5	4.9E-4	0.031	0.020	0.050	0.060	0.063	0.14	0.15
Lower limit of 95% CI	2.31	1.82	1.10	1.15	1.00	0.958	0.960	0.834	0.758
Upper limit of 95% CI	11.1	8.50	7.47	5.25	4.49	7.46	4.44	3.78	6.01
OR Quartile 3	3.32	2.83	2.11	1.54	1.54	1.50	1.62	1.46	1.45
p Value	0.0012	0.0039	0.040	0.19	0.19	0.28	0.14	0.25	0.35
Lower limit of 95% CI	1.61	1.40	1.04	0.806	0.806	0.715	0.850	0.765	0.666
Upper limit of 95% CI	6.85	5.73	4.32	2.93	2.93	3.17	3.09	2.77	3.17
OR Quartile 4	4.27	2.87	1.96	1.99	1.99	2.11	2.37	2.04	1.98
p Value	0.0050	0.022	0.085	0.078	0.078	0.066	0.026	0.062	0.11
Lower limit of 95% CI	1.55	1.16	0.911	0.927	0.927	0.951	1.11	0.965	0.860
Upper limit of 95% CI	11.8	7.07	4.23	4.29	4.29	4.70	5.06	4.33	4.55

[0268] Table 19.8: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	67.1	119	85.2	113	88.6	113
Average	81.4	129	97.7	127	98.2	128
Stdev	41.9	69.9	52.9	72.9	51.4	75.0
p (t-test)		2.3E-5		0.0071		0.0046
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	174	401	246	401	246	401
n (Patient)	49	101	69	81	75	75

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent	Persistent Cohort	Non-persistent	Persistent Cohort	Non-persistent	Persistent Cohort

	Cohort		Cohort		Cohort	
Median	73.7	118	87.0	113	91.4	113
Average	85.8	127	98.5	126	98.9	128
Stdev	43.9	70.8	52.4	73.4	51.0	75.6
p (t-test)		1.9E-4		0.011		0.0073
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	182	401	246	401	246	401
n (Patient)	51	99	69	81	75	75

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	92.8	122	98.9	112	99.7	111
Average	103	134	106	133	107	134
Stdev	58.8	74.4	57.8	79.7	57.1	83.9
p (t-test)		0.0073		0.022		0.028
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	274	401	274	401	274	401
n (Patient)	98	51	105	44	110	39

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.72	0.68	0.63	0.62	0.61	0.60	0.62	0.60	0.58
SE	0.042	0.044	0.049	0.046	0.046	0.052	0.046	0.046	0.054
p Value	2.7E-7	3.6E-5	0.0086	0.0099	0.020	0.065	0.012	0.023	0.13
nCohort Non-persistent	49	51	98	69	69	105	75	75	110
nCohort Persistent	101	99	51	81	81	44	75	75	39
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	85%	84%	88%	83%	81%	86%	83%	81%	85%
Specificity	47%	43%	32%	35%	33%	30%	33%	32%	28%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	59%	59%	61%	54%	54%	55%	55%	55%	54%
Specificity	69%	67%	55%	55%	55%	51%	55%	55%	51%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	33%	31%	33%	31%	31%	34%	32%	32%	33%
Specificity	90%	86%	79%	81%	81%	78%	81%	81%	77%
OR Quartile 2	5.07	3.94	3.47	2.55	2.20	2.65	2.38	2.05	2.16
p Value	5.0E-5	4.9E-4	0.010	0.016	0.040	0.046	0.026	0.063	0.12
Lower limit of 95% CI	2.31	1.82	1.34	1.19	1.04	1.02	1.11	0.962	0.823
Upper limit of 95% CI	11.1	8.50	8.99	5.46	4.66	6.91	5.13	4.37	5.66
OR Quartile 3	3.32	2.83	1.90	1.46	1.46	1.27	1.45	1.45	1.21
p Value	0.0012	0.0039	0.067	0.25	0.25	0.51	0.25	0.25	0.61
Lower limit of 95% CI	1.61	1.40	0.955	0.765	0.765	0.627	0.765	0.765	0.582
Upper limit of 95% CI	6.85	5.73	3.79	2.78	2.78	2.57	2.77	2.77	2.52
OR Quartile 4	4.27	2.87	1.83	1.92	1.92	1.84	2.05	2.05	1.70
p Value	0.0050	0.022	0.12	0.094	0.094	0.12	0.063	0.063	0.19
Lower limit of 95% CI	1.55	1.16	0.861	0.894	0.894	0.849	0.962	0.962	0.763
Upper limit of 95% CI	11.8	7.07	3.91	4.14	4.14	4.01	4.37	4.37	3.79

[0269] Table 19.9: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	67.1	119	84.6	115	87.8	115
Average	81.4	129	95.8	128	96.4	130
Stdev	41.9	69.9	50.8	73.3	49.4	75.4
p (t-test)		2.3E-5		0.0028		0.0018
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	174	401	246	401	246	401
n (Patient)	49	101	68	82	74	76

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	73.7	118	86.1	115	90.0	115
Average	85.8	127	96.6	127	97.2	129
Stdev	43.9	70.8	50.4	73.9	49.0	76.0
p (t-test)		1.9E-4		0.0045		0.0029
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	182	401	246	401	246	401
n (Patient)	51	99	68	82	74	76

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	91.4	120	95.2	113	96.1	112
Average	102	133	105	132	106	133
Stdev	58.2	74.3	57.6	77.6	56.9	81.2
p (t-test)		0.0056		0.015		0.020
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	274	401	274	401	274	401
n (Patient)	95	54	100	49	105	44

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.72	0.68	0.63	0.63	0.62	0.60	0.63	0.62	0.59
SE	0.042	0.044	0.048	0.045	0.046	0.050	0.045	0.046	0.052
p Value	2.7E-7	3.6E-5	0.0069	0.0042	0.0091	0.039	0.0052	0.011	0.085
nCohort Non-persistent	49	51	95	68	68	100	74	74	105
nCohort Persistent	101	99	54	82	82	49	76	76	44
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	85%	84%	87%	83%	82%	86%	83%	82%	84%
Specificity	47%	43%	32%	35%	34%	30%	34%	32%	29%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	59%	59%	61%	55%	55%	57%	55%	55%	57%
Specificity	69%	67%	56%	56%	56%	53%	55%	55%	52%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	33%	31%	33%	32%	32%	33%	33%	33%	32%
Specificity	90%	86%	79%	82%	82%	78%	82%	82%	77%
OR Quartile 2	5.07	3.94	3.10	2.65	2.28	2.57	2.47	2.13	2.11
p Value	5.0E-5	4.9E-4	0.014	0.012	0.031	0.041	0.021	0.051	0.11
Lower limit of 95% CI	2.31	1.82	1.25	1.24	1.08	1.04	1.15	0.997	0.849
Upper limit of 95% CI	11.1	8.50	7.65	5.67	4.84	6.37	5.32	4.53	5.26
OR Quartile 3	3.32	2.83	1.98	1.54	1.54	1.50	1.53	1.53	1.45
p Value	0.0012	0.0039	0.049	0.19	0.19	0.25	0.19	0.19	0.31
Lower limit of 95% CI	1.61	1.40	1.00	0.807	0.807	0.755	0.806	0.806	0.712
Upper limit of 95% CI	6.85	5.73	3.92	2.94	2.94	2.99	2.92	2.92	2.94
OR Quartile 4	4.27	2.87	1.88	2.17	2.17	1.72	2.30	2.30	1.58
p Value	0.0050	0.022	0.10	0.051	0.051	0.16	0.033	0.033	0.25

Lower limit of 95% CI	1.55	1.16	0.885	0.995	0.995	0.802	1.07	1.07	0.721
Upper limit of 95% CI	11.8	7.07	3.97	4.72	4.72	3.68	4.95	4.95	3.44

[0270] Table 19.10: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	67.1	118	84.0	118	86.1	118
Average	82.3	127	94.5	128	95.0	129
Stdev	42.4	69.9	50.0	72.9	48.9	74.4
p (t-test)		7.1E-5		0.0020		0.0013
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	174	401	246	401	246	401
n (Patient)	47	103	65	85	70	80

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	71.0	117	86.1	115	90.0	115
Average	86.0	127	95.6	127	96.3	129
Stdev	44.4	70.6	50.0	73.4	48.7	75.4
p (t-test)		2.6E-4		0.0033		0.0022
Min	23.6	13.2	16.4	13.2	16.4	13.2
Max	182	401	246	401	246	401
n (Patient)	50	100	66	84	72	78

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	90.0	122	94.2	118	94.3	115
Average	101	135	102	134	104	134
Stdev	55.1	76.3	55.1	78.2	54.7	80.7
p (t-test)		0.0019		0.0046		0.0079
Min	16.4	13.2	16.4	13.2	16.4	13.2
Max	260	401	260	401	260	401
n (Patient)	92	57	95	54	99	50

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.70	0.68	0.64	0.64	0.62	0.62	0.64	0.62	0.60
SE	0.043	0.044	0.048	0.045	0.045	0.049	0.045	0.045	0.050
p Value	2.2E-6	5.3E-5	0.0036	0.0024	0.0058	0.014	0.0025	0.0073	0.038
nCohort Non-persistent	47	50	92	65	66	95	70	72	99
nCohort Persistent	103	100	57	85	84	54	80	78	50
Cutoff Quartile 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
Sensitivity	84%	84%	86%	82%	82%	85%	82%	82%	84%

Specificity	47%	44%	32%	35%	35%	31%	34%	33%	29%
Cutoff Quartile 3	101	101	101	101	101	101	101	101	101
Sensitivity	58%	58%	61%	55%	55%	59%	56%	55%	58%
Specificity	68%	66%	57%	57%	56%	55%	57%	56%	54%
Cutoff Quartile 4	142	142	142	142	142	142	142	142	142
Sensitivity	32%	31%	35%	33%	32%	35%	34%	33%	34%
Specificity	89%	86%	80%	85%	83%	80%	84%	83%	79%
OR Quartile 2	4.78	4.12	2.82	2.56	2.46	2.53	2.46	2.29	2.17
p Value	8.8E-5	3.3E-4	0.019	0.015	0.019	0.036	0.020	0.033	0.080
Lower limit of 95% CI	2.19	1.90	1.18	1.20	1.16	1.06	1.15	1.07	0.910
Upper limit of 95% CI	10.5	8.94	6.71	5.44	5.23	6.02	5.25	4.88	5.20
OR Quartile 3	2.98	2.68	2.07	1.63	1.54	1.76	1.71	1.54	1.59
p Value	0.0033	0.0063	0.035	0.14	0.19	0.10	0.10	0.19	0.18
Lower limit of 95% CI	1.44	1.32	1.05	0.852	0.807	0.894	0.897	0.806	0.801
Upper limit of 95% CI	6.16	5.44	4.06	3.13	2.95	3.46	3.28	2.93	3.16
OR Quartile 4	3.96	2.76	2.22	2.70	2.37	2.17	2.73	2.50	1.91
p Value	0.0079	0.028	0.037	0.016	0.033	0.043	0.013	0.021	0.093
Lower limit of 95% CI	1.43	1.12	1.05	1.20	1.07	1.02	1.24	1.15	0.897
Upper limit of 95% CI	10.9	6.82	4.70	6.08	5.23	4.60	6.04	5.44	4.08

[0271] Example 20. Use of Tenascin for evaluating renal status in patients admitted to the ICU: Persistent at RIFLE F

[0272] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Tenascin is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0273] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output. Two cohorts are defined to represent a "persistent" and a "non-persistent" population. "Persistent" indicates those patients whose minimum RIFLE stage during a period of 24, 48 or 72 hours is failure (F) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. "Non-persistent" indicates those patients who are not persistent at failure (F) and whose minimum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0), risk of injury (R), or injury (I) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. If a patient dies after failure (F) or is placed on renal replacement therapy (RRT) at any time from sample collection to 24, 48, 72, 96 or 168 hours after sample collection, the patient is considered "persistent".

[0274] The ability to distinguish the "persistent" and "non-persistent" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0275] Table 20.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47000	59300	47500	58200	48100	58800
Average	51400	61900	52200	62100	52800	62200
Stdev	24600	27900	24700	28500	25000	28700
p (t-test)		0.018		0.031		0.051
Min	17100	15600	17100	15600	17100	15600
Max	140000	141000	140000	141000	140000	141000
n (Patient)	95	55	103	47	110	40

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	45800	59600	47500	59300	48100	58800
Average	51200	62200	52200	61900	53100	60900
Stdev	24700	27700	25000	28000	25400	28000
p (t-test)		0.013		0.035		0.10
Min	17100	15600	17100	15600	17100	15600
Max	140000	141000	140000	141000	140000	141000
n (Patient)	94	56	103	47	108	42

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	51300	62000	51300	62000	51700	61000
Average	53600	65600	53600	65600	53800	65100
Stdev	24700	34600	24700	34600	24600	35500
p (t-test)		0.062		0.062		0.085
Min	17100	15600	17100	15600	17100	15600
Max	140000	141000	140000	141000	140000	141000
n (Patient)	130	19	130	19	131	18

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.62	0.62	0.60	0.61	0.61	0.60	0.60	0.59	0.59
SE	0.048	0.048	0.073	0.051	0.051	0.073	0.054	0.053	0.075
p Value	0.015	0.0093	0.17	0.038	0.033	0.17	0.063	0.10	0.24
nCohort Non-persistent	95	94	130	103	103	130	110	108	131
nCohort Persistent	55	56	19	47	47	19	40	42	18
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	80%	80%	79%	81%	81%	79%	82%	81%	78%
Specificity	28%	29%	25%	28%	28%	25%	28%	28%	25%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	60%	61%	63%	60%	62%	63%	60%	60%	61%
Specificity	56%	56%	52%	54%	55%	52%	54%	54%	51%

Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	33%	34%	37%	34%	34%	37%	32%	31%	33%
Specificity	79%	80%	76%	79%	79%	76%	77%	77%	76%
OR Quartile 2	1.59	1.65	1.28	1.65	1.65	1.28	1.85	1.63	1.18
p Value	0.26	0.22	0.68	0.24	0.24	0.68	0.19	0.27	0.78
Lower limit of 95% CI	0.716	0.743	0.395	0.711	0.711	0.395	0.741	0.680	0.362
Upper limit of 95% CI	3.52	3.66	4.12	3.85	3.85	4.12	4.62	3.93	3.83
OR Quartile 3	1.89	2.00	1.82	1.76	2.00	1.82	1.74	1.71	1.65
p Value	0.064	0.044	0.24	0.11	0.055	0.24	0.14	0.15	0.33
Lower limit of 95% CI	0.964	1.02	0.675	0.872	0.987	0.675	0.832	0.828	0.601
Upper limit of 95% CI	3.72	3.92	4.92	3.54	4.04	4.92	3.62	3.52	4.51
OR Quartile 4	1.82	2.03	1.86	1.90	1.90	1.86	1.64	1.49	1.55
p Value	0.12	0.064	0.23	0.10	0.10	0.23	0.23	0.33	0.42
Lower limit of 95% CI	0.863	0.959	0.675	0.884	0.884	0.675	0.737	0.674	0.537
Upper limit of 95% CI	3.86	4.28	5.14	4.09	4.09	5.14	3.64	3.29	4.46

[0276] Table 20.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	45800	58800	47200	58800	47500	59300
Average	49800	63100	50400	63500	51200	63700
Stdev	22700	29100	22900	29500	23400	29900
p (t-test)		0.0021		0.0027		0.0058
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	88	62	94	56	101	49

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	45800	58800	47500	58200	47900	58200
Average	50500	62000	51100	62000	52200	61300
Stdev	24500	27400	24700	27600	25000	27800
p (t-test)		0.0080		0.013		0.043
Min	17100	15600	17100	15600	17100	15600
Max	140000	141000	140000	141000	140000	141000
n (Patient)	88	62	93	57	99	51

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	50800	61000	50800	61000	51300	59900
Average	52600	67100	52600	67100	52800	66800
Stdev	23600	34500	23600	34500	23600	35200
p (t-test)		0.010		0.010		0.014
Min	17100	15600	17100	15600	17100	15600
Max	129000	141000	129000	141000	129000	141000
n (Patient)	123	26	123	26	124	25

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.63	0.63	0.62	0.63	0.62	0.62	0.62	0.60	0.61
SE	0.047	0.047	0.063	0.048	0.048	0.063	0.050	0.050	0.065
p Value	0.0040	0.0059	0.054	0.0056	0.011	0.054	0.013	0.042	0.082
nCohort Non-persistent	88	88	123	94	93	123	101	99	124
nCohort Persistent	62	62	26	56	57	26	49	51	25
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	81%	81%	81%	80%	81%	81%	82%	80%	80%
Specificity	30%	30%	26%	29%	29%	26%	29%	28%	26%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	60%	60%	62%	61%	60%	62%	59%	57%	60%
Specificity	57%	57%	52%	56%	56%	52%	54%	54%	52%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	34%	34%	38%	36%	35%	38%	35%	33%	36%
Specificity	81%	81%	77%	81%	81%	77%	79%	79%	77%
OR Quartile 2	1.75	1.75	1.48	1.65	1.71	1.48	1.79	1.62	1.39
p Value	0.16	0.16	0.47	0.22	0.19	0.47	0.18	0.25	0.54
Lower limit of 95% CI	0.802	0.802	0.514	0.743	0.772	0.514	0.771	0.714	0.482
Upper limit of 95% CI	3.81	3.81	4.24	3.66	3.79	4.24	4.15	3.66	4.01
OR Quartile 3	1.95	1.95	1.74	2.00	1.87	1.74	1.73	1.52	1.60
p Value	0.048	0.048	0.21	0.044	0.066	0.21	0.12	0.23	0.29
Lower limit of 95% CI	1.01	1.01	0.730	1.02	0.960	0.730	0.868	0.769	0.667
Upper limit of 95% CI	3.77	3.77	4.12	3.92	3.66	4.12	3.46	3.00	3.84
OR Quartile 4	2.14	2.14	2.12	2.35	2.25	2.12	2.02	1.86	1.84
p Value	0.046	0.046	0.100	0.026	0.034	0.100	0.069	0.11	0.19
Lower limit of 95% CI	1.01	1.01	0.866	1.11	1.07	0.866	0.947	0.872	0.737
Upper limit of 95% CI	4.51	4.51	5.19	4.97	4.76	5.19	4.33	3.95	4.61

[0277] Table 20.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	43800	59900	44100	60600	45800	61000
Average	48000	64300	48000	65100	48900	66000
Stdev	21700	28700	21500	28900	21800	29700
p (t-test)		1.1E-4		5.3E-5		8.3E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	83	67	86	64	94	56

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	43700	60600	44100	60600	47000	59900
Average	47600	64500	48200	64800	49300	64900
Stdev	21600	28500	22000	28700	22200	29600
p (t-test)		6.7E-5		9.8E-5		3.3E-4
Min	17100	15600	17100	15600	17100	15600

Max	123000	141000	123000	141000	123000	141000
n (Patient)	82	68	86	64	93	57

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47500	64800	47500	64800	47600	64300
Average	50300	71300	50300	71300	50600	71200
Stdev	22200	32500	22200	32500	22200	33000
p (t-test)		2.9E-5		2.9E-5		4.7E-5
Min	17100	15600	17100	15600	17100	15600
Max	129000	141000	129000	141000	129000	141000
n (Patient)	115	34	115	34	116	33

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.67	0.68	0.70	0.68	0.68	0.70	0.67	0.66	0.69
SE	0.045	0.044	0.055	0.045	0.045	0.055	0.047	0.047	0.056
p Value	1.3E-4	5.3E-5	3.5E-4	6.4E-5	8.9E-5	3.5E-4	2.2E-4	7.5E-4	7.0E-4
nCohort Non-persistent	83	82	115	86	86	115	94	93	116
nCohort Persistent	67	68	34	64	64	34	56	57	33
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	82%	82%	85%	83%	83%	85%	84%	82%	85%
Specificity	31%	32%	28%	31%	31%	28%	31%	30%	28%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	63%	63%	71%	64%	64%	71%	62%	61%	70%
Specificity	60%	61%	56%	60%	60%	56%	57%	57%	55%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	37%	38%	47%	39%	39%	47%	39%	39%	45%
Specificity	84%	85%	81%	85%	85%	81%	83%	83%	80%
OR Quartile 2	2.09	2.17	2.24	2.20	2.20	2.24	2.33	2.02	2.13
p Value	0.063	0.051	0.13	0.051	0.051	0.13	0.048	0.089	0.15
Lower limit of 95% CI	0.960	0.995	0.796	0.998	0.998	0.796	1.01	0.897	0.758
Upper limit of 95% CI	4.55	4.72	6.28	4.87	4.87	6.28	5.38	4.57	6.01
OR Quartile 3	2.55	2.69	3.01	2.73	2.73	3.01	2.25	2.11	2.83
p Value	0.0057	0.0035	0.0088	0.0033	0.0033	0.0088	0.019	0.030	0.014
Lower limit of 95% CI	1.31	1.38	1.32	1.40	1.40	1.32	1.14	1.08	1.24
Upper limit of 95% CI	4.94	5.22	6.87	5.32	5.32	6.87	4.43	4.13	6.48
OR Quartile 4	3.21	3.61	3.76	3.60	3.60	3.76	3.15	3.02	3.37
p Value	0.0031	0.0013	0.0015	0.0012	0.0012	0.0015	0.0030	0.0042	0.0038
Lower limit of 95% CI	1.48	1.65	1.66	1.66	1.66	1.66	1.48	1.42	1.48
Upper limit of 95% CI	6.93	7.91	8.52	7.81	7.81	8.52	6.74	6.45	7.68

[0278] Table 20.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “persistent” and “non-persistent” cohorts where persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	43800	59900	44300	59900	47000	59900
Average	48000	63800	48200	64500	48800	65200
Stdev	21800	28600	21500	29100	21300	30000

p (t-test)		1.9E-4		1.2E-4		1.4E-4
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	81	69	85	65	91	59

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	43800	59900	44100	60600	45800	61000
Average	47900	63900	47900	64700	48500	65400
Stdev	21600	28600	21500	28900	21200	29800
p (t-test)		1.5E-4		7.2E-5		8.4E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	81	69	84	66	90	60

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47500	64800	47500	64300	47500	63200
Average	49600	70200	49700	70400	50000	70200
Stdev	21100	32800	21000	33200	21100	33600
p (t-test)		1.3E-5		1.6E-5		2.6E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	109	40	110	39	111	38

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.67	0.67	0.69	0.67	0.68	0.68	0.66	0.67	0.68
SE	0.045	0.045	0.052	0.045	0.045	0.052	0.046	0.046	0.053
p Value	2.0E-4	1.6E-4	2.6E-4	1.9E-4	8.3E-5	4.4E-4	5.3E-4	2.5E-4	8.6E-4
nCohort Non-persistent	81	81	109	85	84	110	91	90	111
nCohort Persistent	69	69	40	65	66	39	59	60	38
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	81%	81%	82%	82%	82%	82%	81%	82%	82%
Specificity	31%	31%	28%	31%	31%	27%	30%	30%	27%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	62%	62%	70%	63%	64%	69%	61%	62%	68%
Specificity	60%	60%	57%	60%	61%	56%	57%	58%	56%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	36%	38%	45%	38%	39%	46%	39%	40%	45%
Specificity	84%	85%	82%	85%	86%	82%	84%	84%	81%
OR Quartile 2	1.92	1.92	1.79	1.95	2.02	1.71	1.84	1.91	1.64
p Value	0.094	0.094	0.21	0.093	0.077	0.25	0.13	0.11	0.29
Lower limit of 95% CI	0.894	0.894	0.715	0.894	0.927	0.684	0.832	0.863	0.653
Upper limit of 95% CI	4.14	4.14	4.48	4.24	4.39	4.30	4.08	4.22	4.12
OR Quartile 3	2.53	2.53	3.08	2.56	2.70	2.91	2.09	2.20	2.74
p Value	0.0058	0.0058	0.0045	0.0055	0.0034	0.0072	0.031	0.021	0.011
Lower limit of 95% CI	1.31	1.31	1.42	1.32	1.39	1.34	1.07	1.13	1.26
Upper limit of 95% CI	4.90	4.90	6.68	4.98	5.26	6.32	4.07	4.29	5.98
OR Quartile 4	2.97	3.48	3.64	3.46	3.90	3.86	3.24	3.62	3.47
p Value	0.0056	0.0018	0.0013	0.0017	6.9E-4	8.7E-4	0.0025	0.0010	0.0022
Lower limit of 95% CI	1.38	1.59	1.65	1.60	1.78	1.74	1.51	1.68	1.56
Upper limit of 95% CI	6.42	7.61	8.02	7.50	8.56	8.54	6.93	7.81	7.69

[0279] Table 20.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the “persistent” and “non-persistent” cohorts where

persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	43200	60600	43500	61300	44500	62800
Average	46900	64300	46900	65100	47700	66000
Stdev	21100	28400	20900	28600	20600	29700
p (t-test)		3.3E-5		1.5E-5		1.8E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	78	72	81	69	88	62

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	43500	59900	43700	60600	44500	61000
Average	47100	64300	47200	65100	47900	65800
Stdev	21000	28600	20900	28800	20700	29700
p (t-test)		4.4E-5		2.0E-5		2.5E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	79	71	82	68	88	62

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47400	65200	47400	65200	47500	64800
Average	49400	70300	49400	70300	49600	70200
Stdev	21000	32400	21000	32400	21100	32800
p (t-test)		7.6E-6		7.6E-6		1.3E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	108	41	108	41	109	40

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.69	0.68	0.70	0.69	0.69	0.70	0.68	0.68	0.69
SE	0.043	0.044	0.051	0.044	0.044	0.051	0.045	0.045	0.052
p Value	1.9E-5	3.8E-5	1.2E-4	9.2E-6	1.9E-5	1.2E-4	4.0E-5	7.0E-5	2.5E-4
nCohort Non-persistent	78	79	108	81	82	108	88	88	109
nCohort Persistent	72	71	41	69	68	41	62	62	40
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	82%	82%	83%	83%	82%	83%	82%	82%	82%
Specificity	32%	32%	28%	32%	32%	28%	31%	31%	28%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	64%	63%	71%	65%	65%	71%	63%	63%	70%
Specificity	63%	62%	57%	63%	62%	57%	59%	59%	57%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	38%	38%	46%	39%	40%	46%	40%	40%	45%
Specificity	86%	86%	82%	86%	87%	82%	85%	85%	82%
OR Quartile 2	2.14	2.07	1.87	2.25	2.17	1.87	2.05	2.05	1.79

p Value	0.051	0.063	0.18	0.042	0.051	0.18	0.076	0.076	0.21
Lower limit of 95% CI	0.995	0.960	0.747	1.03	0.995	0.747	0.928	0.928	0.715
Upper limit of 95% CI	4.61	4.44	4.67	4.89	4.72	4.67	4.54	4.54	4.48
OR Quartile 3	2.99	2.83	3.26	3.19	3.02	3.26	2.45	2.45	3.08
p Value	0.0012	0.0021	0.0028	7.0E-4	0.0012	0.0028	0.0086	0.0086	0.0045
Lower limit of 95% CI	1.54	1.46	1.50	1.63	1.55	1.50	1.26	1.26	1.42
Upper limit of 95% CI	5.81	5.49	7.06	6.23	5.88	7.06	4.78	4.78	6.68
OR Quartile 4	3.65	3.79	4.05	4.09	4.25	4.05	3.90	3.90	3.64
p Value	0.0014	0.0010	5.1E-4	5.5E-4	3.9E-4	5.1E-4	6.0E-4	6.0E-4	0.0013
Lower limit of 95% CI	1.65	1.71	1.84	1.84	1.91	1.84	1.79	1.79	1.65
Upper limit of 95% CI	8.10	8.42	8.90	9.09	9.46	8.90	8.48	8.48	8.02

[0280] Example 21. Use of Tenascin for evaluating renal status in patients admitted to the ICU: Persistent at RIFLE I or F

[0281] Patients from the intensive care unit (ICU) with RIFLE stage of injury (I) or failure (F) are enrolled in the following study. EDTA anti-coagulated blood samples (10 mL) and urine samples (50 mL) are collected from each patient at enrollment, and at every 12 hours up to day 3, and then every 24 hours thereafter up to day 7 while the subject is hospitalized. Tenascin is measured in the enrollment samples by standard immunoassay methods using commercially available assay reagents.

[0282] Kidney status is assessed by RIFLE criteria based on serum creatinine, urine output, or both serum creatinine and urine output. Two cohorts are defined to represent a "persistent" and a "non-persistent" population. "Persistent" indicates those patients whose minimum RIFLE stage during a period of 24, 48 or 72 hours is injury (I) or failure (F) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. "Non-persistent" indicates those patients who are not persistent at injury (I) or failure (F) and whose minimum RIFLE stage during a period of 24, 48 or 72 hours is non-injury (RIFLE 0) or risk of injury (R) where the persistence period can start from the time of sample collection to 24, 48, 72, 96 or 168 hours after sample collection. If a patient dies after injury (I) or failure (F) or is placed on renal replacement therapy (RRT) at any time from sample collection to 24, 48, 72, 96 or 168 hours after sample collection, the patient is considered "persistent".

[0283] The ability to distinguish the "persistent" and "non-persistent" cohorts is determined using receiver operating characteristic (ROC) analysis.

[0284] Table 21.1: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 24 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	37500	57200	43800	58200	47000	58200
Average	44000	60900	49500	61000	50100	62000
Stdev	21400	26800	25000	26400	23900	27800
p (t-test)		1.6E-4		0.0070		0.0058
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	140000	141000	140000	141000
n (Patient)	50	100	75	75	85	65

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	37500	57200	43500	59300	45800	58800
Average	44300	61100	47300	62800	49700	62800
Stdev	21500	26800	22200	27700	22800	28800
p (t-test)		1.5E-4		2.3E-4		0.0024
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	52	98	73	77	86	64

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47800	62000	48300	62000	48400	63200
Average	52400	63400	52900	64300	52900	66700
Stdev	24900	28800	24700	30900	24400	32800
p (t-test)		0.027		0.036		0.018
Min	17100	15600	17100	15600	17100	15600
Max	140000	141000	140000	141000	140000	141000
n (Patient)	112	37	120	29	125	24

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.70	0.70	0.62	0.64	0.67	0.61	0.63	0.63	0.63
SE	0.043	0.043	0.055	0.045	0.044	0.061	0.046	0.046	0.065
p Value	2.9E-6	3.8E-6	0.024	0.0021	8.0E-5	0.063	0.0049	0.0039	0.050
nCohort Non-persistent	50	52	112	75	73	120	85	86	125
nCohort Persistent	100	98	37	75	77	29	65	64	24
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	81%	82%	81%	81%	82%	79%	80%	81%	79%
Specificity	38%	38%	27%	32%	33%	26%	29%	30%	26%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	59%	59%	68%	60%	62%	66%	60%	61%	67%
Specificity	68%	67%	55%	60%	63%	53%	58%	58%	53%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	32%	33%	35%	32%	35%	34%	35%	36%	38%
Specificity	88%	88%	78%	81%	85%	77%	82%	83%	77%
OR Quartile 2	2.61	2.78	1.57	2.05	2.20	1.34	1.67	1.88	1.31
p Value	0.013	0.0082	0.34	0.063	0.041	0.57	0.19	0.11	0.62
Lower limit of 95% CI	1.22	1.30	0.623	0.962	1.03	0.498	0.775	0.862	0.451
Upper limit of 95% CI	5.58	5.92	3.95	4.37	4.70	3.58	3.59	4.09	3.79
OR Quartile 3	3.06	2.99	2.58	2.25	2.82	2.17	2.04	2.17	2.24
p Value	0.0022	0.0024	0.017	0.015	0.0021	0.072	0.033	0.022	0.086
Lower limit of 95% CI	1.50	1.47	1.18	1.17	1.45	0.932	1.06	1.12	0.893
Upper limit of 95% CI	6.25	6.05	5.65	4.32	5.47	5.06	3.94	4.19	5.61

OR Quartile 4	3.45	3.72	1.88	2.05	3.04	1.73	2.56	2.66	1.99
p Value	0.011	0.0067	0.12	0.063	0.0060	0.22	0.015	0.011	0.15
Lower limit of 95% CI	1.33	1.44	0.840	0.962	1.38	0.721	1.20	1.25	0.788
Upper limit of 95% CI	8.93	9.61	4.23	4.37	6.73	4.15	5.44	5.65	5.01

[0285] Table 21.2: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 48 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	37400	58200	42700	59100	43800	59300
Average	43600	60900	47100	62400	48000	63300
Stdev	21400	26600	22700	27200	21900	28500
p (t-test)		1.1E-4		2.9E-4		3.0E-4
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	49	101	70	80	79	71

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	37400	58200	42700	59100	44300	58200
Average	43900	61100	47000	62500	48700	62600
Stdev	21500	26700	22500	27300	22700	28100
p (t-test)		9.9E-5		2.3E-4		0.0011
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	51	99	70	80	79	71

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47500	64000	47700	64000	47800	64600
Average	49900	66900	50600	68300	50700	70600
Stdev	22100	31000	22100	32800	21900	34100
p (t-test)		2.1E-4		2.9E-4		8.9E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	103	46	111	38	116	33

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.71	0.67	0.68	0.68	0.66	0.66	0.65	0.68
SE	0.043	0.042	0.050	0.043	0.043	0.054	0.045	0.045	0.056
p Value	8.2E-7	1.1E-6	6.5E-4	5.6E-5	4.4E-5	0.0025	2.5E-4	9.4E-4	0.0017
nCohort Non-persistent	49	51	103	70	70	111	79	79	116
nCohort Persistent	101	99	46	80	80	38	71	71	33

Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	81%	82%	83%	82%	82%	82%	82%	82%	82%
Specificity	39%	39%	28%	34%	34%	27%	32%	32%	27%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	59%	60%	67%	62%	62%	66%	62%	61%	67%
Specificity	69%	69%	57%	64%	64%	55%	61%	59%	54%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	32%	32%	39%	32%	34%	39%	35%	35%	42%
Specificity	88%	88%	81%	83%	84%	79%	84%	84%	79%
OR Quartile 2	2.73	2.90	1.86	2.46	2.46	1.64	2.07	2.07	1.64
p Value	0.0096	0.0060	0.16	0.020	0.020	0.29	0.063	0.063	0.32
Lower limit of 95% CI	1.28	1.36	0.776	1.15	1.15	0.653	0.960	0.960	0.619
Upper limit of 95% CI	5.85	6.20	4.47	5.25	5.25	4.12	4.44	4.44	4.35
OR Quartile 3	3.32	3.23	2.77	3.00	3.00	2.35	2.52	2.26	2.38
p Value	0.0012	0.0013	0.0062	0.0012	0.0012	0.029	0.0059	0.015	0.036
Lower limit of 95% CI	1.61	1.58	1.34	1.54	1.54	1.09	1.31	1.17	1.06
Upper limit of 95% CI	6.85	6.59	5.75	5.84	5.84	5.05	4.87	4.34	5.35
OR Quartile 4	3.32	3.58	2.67	2.33	2.73	2.50	2.76	2.76	2.82
p Value	0.013	0.0085	0.012	0.033	0.013	0.024	0.0097	0.0097	0.013
Lower limit of 95% CI	1.28	1.38	1.24	1.07	1.24	1.13	1.28	1.28	1.24
Upper limit of 95% CI	8.61	9.26	5.75	5.07	6.04	5.53	5.95	5.95	6.44

[0286] Table 21.3: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 72 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	37400	58200	42700	59300	43500	59300
Average	43600	60900	46600	62600	47200	63300
Stdev	21400	26600	22500	27100	22000	27900
p (t-test)		1.1E-4		1.5E-4		1.4E-4
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	49	101	69	81	75	75

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	37400	58200	42700	59300	43500	59300
Average	43900	61100	46500	62700	47100	63400
Stdev	21500	26700	22300	27200	21800	27900
p (t-test)		9.9E-5		1.2E-4		1.0E-4
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	51	99	69	81	75	75

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47200	64300	47500	64000	47500	64600

Average	48600	67800	49400	68800	49600	70800
Stdev	21200	30500	21400	31700	21200	32700
p (t-test)		1.4E-5		2.7E-5		7.9E-6
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	98	51	105	44	110	39

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.71	0.69	0.68	0.69	0.68	0.68	0.68	0.70
SE	0.043	0.042	0.047	0.043	0.043	0.050	0.044	0.044	0.052
p Value	8.2E-7	1.1E-6	3.9E-5	1.8E-5	1.3E-5	2.4E-4	4.8E-5	3.7E-5	1.5E-4
nCohort Non-persistent	49	51	98	69	69	105	75	75	110
nCohort Persistent	101	99	51	81	81	44	75	75	39
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	81%	82%	84%	83%	83%	84%	83%	83%	85%
Specificity	39%	39%	30%	35%	35%	29%	33%	33%	28%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	59%	60%	69%	63%	63%	68%	63%	63%	69%
Specificity	69%	69%	59%	65%	65%	57%	63%	63%	56%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	32%	32%	41%	33%	35%	41%	36%	37%	44%
Specificity	88%	88%	83%	84%	86%	81%	85%	87%	81%
OR Quartile 2	2.73	2.90	2.26	2.55	2.55	2.11	2.38	2.38	2.16
p Value	0.0096	0.0060	0.067	0.016	0.016	0.11	0.026	0.026	0.12
Lower limit of 95% CI	1.28	1.36	0.946	1.19	1.19	0.849	1.11	1.11	0.823
Upper limit of 95% CI	5.85	6.20	5.39	5.46	5.46	5.26	5.13	5.13	5.66
OR Quartile 3	3.32	3.23	3.17	3.19	3.19	2.86	2.82	2.82	2.91
p Value	0.0012	0.0013	0.0016	7.0E-4	7.0E-4	0.0056	0.0022	0.0022	0.0072
Lower limit of 95% CI	1.61	1.58	1.55	1.63	1.63	1.36	1.45	1.45	1.34
Upper limit of 95% CI	6.85	6.59	6.49	6.23	6.23	6.01	5.46	5.46	6.32
OR Quartile 4	3.32	3.58	3.34	2.64	3.12	2.94	3.27	3.87	3.27
p Value	0.013	0.0085	0.0020	0.017	0.0061	0.0063	0.0035	0.0011	0.0033
Lower limit of 95% CI	1.28	1.38	1.55	1.19	1.38	1.36	1.48	1.72	1.48
Upper limit of 95% CI	8.61	9.26	7.16	5.83	7.02	6.38	7.25	8.74	7.23

[0287] Table 21.4: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 96 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	37400	58200	42700	59100	43700	59100
Average	43600	60900	46900	62200	47500	62800
Stdev	21400	26600	22500	27300	22000	28000
p (t-test)		1.1E-4		3.1E-4		2.8E-4
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	49	101	68	82	74	76

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent	Persistent Cohort	Non-persistent	Persistent Cohort	Non-persistent	Persistent Cohort

	Cohort		Cohort		Cohort	
Median	37400	58200	42700	59100	43700	59100
Average	43900	61100	46800	62300	47400	63000
Stdev	21500	26700	22400	27300	21800	28000
p (t-test)		9.9E-5		2.4E-4		2.2E-4
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	51	99	68	82	74	76

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47500	62800	47500	62000	47500	63200
Average	49200	65600	49700	66200	49800	67800
Stdev	21200	31000	21400	31600	21200	32600
p (t-test)		1.9E-4		2.5E-4		1.1E-4
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	95	54	100	49	105	44

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.71	0.71	0.66	0.67	0.68	0.65	0.67	0.67	0.66
SE	0.043	0.042	0.048	0.043	0.043	0.049	0.044	0.044	0.051
p Value	8.2E-7	1.1E-6	8.0E-4	5.6E-5	4.4E-5	0.0019	1.4E-4	1.1E-4	0.0015
nCohort Non-persistent	49	51	95	68	68	100	74	74	105
nCohort Persistent	101	99	54	82	82	49	76	76	44
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	81%	82%	80%	82%	82%	80%	82%	82%	80%
Specificity	39%	39%	27%	34%	34%	27%	32%	32%	27%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	59%	60%	65%	62%	62%	65%	62%	62%	66%
Specificity	69%	69%	58%	65%	65%	57%	62%	62%	56%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	32%	32%	39%	33%	34%	39%	36%	37%	41%
Specificity	88%	88%	82%	84%	85%	81%	85%	86%	81%
OR Quartile 2	2.73	2.90	1.47	2.28	2.28	1.44	2.13	2.13	1.41
p Value	0.0096	0.0060	0.34	0.031	0.031	0.38	0.051	0.051	0.42
Lower limit of 95% CI	1.28	1.36	0.661	1.08	1.08	0.633	0.997	0.997	0.604
Upper limit of 95% CI	5.85	6.20	3.28	4.84	4.84	3.29	4.53	4.53	3.31
OR Quartile 3	3.32	3.23	2.53	3.02	3.02	2.50	2.66	2.66	2.48
p Value	0.0012	0.0013	0.0084	0.0012	0.0012	0.011	0.0036	0.0036	0.015
Lower limit of 95% CI	1.61	1.58	1.27	1.55	1.55	1.23	1.38	1.38	1.19
Upper limit of 95% CI	6.85	6.59	5.06	5.88	5.88	5.07	5.15	5.15	5.16
OR Quartile 4	3.32	3.58	2.92	2.54	3.01	2.70	3.16	3.73	2.94
p Value	0.013	0.0085	0.0056	0.021	0.0078	0.011	0.0046	0.0015	0.0063
Lower limit of 95% CI	1.28	1.38	1.37	1.15	1.34	1.26	1.43	1.66	1.36
Upper limit of 95% CI	8.61	9.26	6.23	5.62	6.77	5.78	6.98	8.42	6.38

[0288] Table 21.5: Comparison of marker levels and the area under the ROC curve (AUC) in EDTA samples for the "persistent" and "non-persistent" cohorts where persistence starts within 168 hours after sample collection and renal status is assessed by serum creatinine (sCr) only, urine output (UO) only, or serum creatinine or urine output RIFLE criteria.

sCr or UO

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	37100	58200	41000	59900	42700	60600
Average	42700	61000	45100	63100	45600	63700
Stdev	21300	26400	21200	27200	20800	27700
p (t-test)		5.2E-5		2.1E-5		1.5E-5
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	47	103	65	85	70	80

sCr only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	37300	57200	41800	59100	43200	59100
Average	43700	61100	45900	62700	46600	63300
Stdev	21700	26500	21700	27300	21200	28000
p (t-test)		9.7E-5		7.1E-5		6.6E-5
Min	18800	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	50	100	66	84	72	78

UO only

Persistence Period Duration (hr)	24		48		72	
	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort	Non-persistent Cohort	Persistent Cohort
Median	47200	63600	47000	64000	47400	64500
Average	48300	66200	48400	67000	48700	67800
Stdev	20600	30600	20800	30700	20600	31500
p (t-test)		3.7E-5		1.9E-5		1.8E-5
Min	17100	15600	17100	15600	17100	15600
Max	123000	141000	123000	141000	123000	141000
n (Patient)	92	57	95	54	99	50

Persistence Period Duration (hr)	24			48			72		
	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only	sCr or UO	sCr only	UO only
AUC	0.72	0.71	0.68	0.71	0.69	0.68	0.70	0.68	0.68
SE	0.042	0.042	0.046	0.042	0.043	0.047	0.042	0.043	0.048
p Value	8.5E-8	8.2E-7	1.3E-4	7.3E-7	7.7E-6	7.8E-5	1.3E-6	2.5E-5	1.5E-4
nCohort Non-persistent	47	50	92	65	66	95	70	72	99
nCohort Persistent	103	100	57	85	84	54	80	78	50
Cutoff Quartile 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
Sensitivity	82%	82%	81%	82%	82%	81%	82%	82%	80%
Specificity	40%	40%	28%	35%	35%	28%	34%	33%	27%
Cutoff Quartile 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
Sensitivity	60%	60%	65%	64%	63%	67%	64%	63%	66%
Specificity	72%	70%	59%	68%	67%	59%	66%	64%	58%
Cutoff Quartile 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
Sensitivity	32%	32%	40%	35%	35%	41%	38%	37%	42%
Specificity	89%	88%	84%	88%	86%	83%	89%	88%	83%
OR Quartile 2	3.00	3.04	1.65	2.56	2.46	1.75	2.46	2.29	1.50
p Value	0.0050	0.0043	0.22	0.015	0.019	0.18	0.020	0.033	0.33
Lower limit of 95% CI	1.39	1.42	0.741	1.20	1.16	0.770	1.15	1.07	0.659
Upper limit of 95% CI	6.46	6.51	3.66	5.44	5.23	3.96	5.25	4.88	3.41
OR Quartile 3	3.95	3.50	2.63	3.65	3.42	2.87	3.37	2.99	2.63
p Value	3.3E-4	7.1E-4	0.0056	2.0E-4	3.7E-4	0.0031	3.9E-4	0.0012	0.0073
Lower limit of 95% CI	1.87	1.69	1.33	1.85	1.74	1.43	1.72	1.54	1.30
Upper limit of 95% CI	8.38	7.23	5.21	7.22	6.73	5.77	6.60	5.81	5.35
OR Quartile 4	3.96	3.45	3.47	3.89	3.34	3.39	4.65	4.14	3.49

p Value	0.0079	0.011	0.0014	0.0021	0.0046	0.0017	4.9E-4	8.6E-4	0.0014
Lower limit of 95% CI	1.43	1.33	1.62	1.64	1.45	1.58	1.96	1.80	1.62
Upper limit of 95% CI	10.9	8.93	7.47	9.22	7.69	7.29	11.0	9.56	7.52

[0289] While the invention has been described and exemplified in sufficient detail for those skilled in this art to make and use it, various alternatives, modifications, and improvements should be apparent without departing from the spirit and scope of the invention. The examples provided herein are representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Modifications therein and other uses will occur to those skilled in the art. These modifications are encompassed within the spirit of the invention and are defined by the scope of the claims.

[0290] It will be readily apparent to a person skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

[0291] All patents and publications mentioned in the specification are indicative of the levels of those of ordinary skill in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

[0292] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

[0293] Other embodiments are set forth within the following claims.

We claim:

1. A method for evaluating renal status in a subject, comprising:

performing an assay method configured to detect Follistatin-related protein 3, an assay method configured to detect Basigin, an assay method configured to detect Cathepsin B, and an assay method configured to detect Tenascin, on a body fluid sample obtained from the subject to provide one or more assay result(s); and

correlating the assay result(s) to the renal status of the subject.

2. A method according to claim 1, wherein said correlation step comprises correlating the assay result(s) to one or more of risk stratification, diagnosis, staging, prognosis, classifying and monitoring of the renal status of the subject.

3. A method according to claim 1, wherein said correlating step comprises assigning a likelihood of one or more future changes in renal status to the subject based on the assay result(s).

4. A method according to claim 3, wherein said one or more future changes in renal status comprise one or more of a future injury to renal function, future reduced renal function, future improvement in renal function, and future acute renal failure (ARF).

5. A method according to one of claims 1-4, wherein said assay result(s) comprise one or more of a measured concentration of Follistatin-related protein 3, a measured concentration of Basigin, a measured concentration of Cathepsin B, and a measured concentration of Tenascin.

6. A method according to one of claims 1-5, wherein said correlating step comprises combining a plurality of assay results using a function that converts the plurality of assay results into a single composite result.

7. A method according to claim 3, wherein said one or more future changes in renal status comprise a clinical outcome related to a renal injury suffered by the subject.

8. A method according to claim 3, wherein the likelihood of one or more future changes in renal status is that an event of interest is more or less likely to occur within 30 days of the time at which the body fluid sample is obtained from the subject.

9. A method according to claim 8, wherein the likelihood of one or more future changes in renal status is that an event of interest is more or less likely to occur within a period selected from the group consisting of 21 days, 14 days, 7 days, 5 days, 96 hours, 72 hours, 48 hours, 36 hours, 24 hours, and 12 hours.

10. A method according to one of claims 1-5, wherein the subject is selected for evaluation of renal status based on the pre-existence in the subject of one or more known risk factors for prerenal, intrinsic renal, or postrenal ARF.

11. A method according to one of claims 1-5, wherein the subject is selected for evaluation of renal status based on an existing diagnosis of one or more of congestive heart failure, preeclampsia, eclampsia, diabetes mellitus, hypertension, coronary artery disease, proteinuria, renal insufficiency, glomerular filtration below the normal range, cirrhosis, serum creatinine above the normal range, sepsis, injury to renal function, reduced renal function, or ARF, or based on undergoing or having undergone major vascular surgery, coronary artery bypass, or other cardiac surgery, or based on exposure to NSAIDs, cyclosporines, tacrolimus, aminoglycosides, foscarnet, ethylene glycol, hemoglobin, myoglobin, ifosfamide, heavy metals, methotrexate, radiopaque contrast agents, or streptozotocin.

12. A method according to one of claims 1-5, wherein said correlating step comprises assigning a diagnosis of the occurrence or nonoccurrence of one or more of an injury to renal function, reduced renal function, or ARF to the subject based on the assay result.

13. A method according to one of claims 1-5, wherein said correlating step comprises assessing whether or not renal function is improving or worsening in a subject who has suffered from an injury to renal function, reduced renal function, or ARF based on the assay result.

14. A method according to one of claims 1-5, wherein said method is a method of diagnosing the occurrence or nonoccurrence of an injury to renal function in said subject.

15. A method according to one of claims 1-5, wherein said method is a method of diagnosing the occurrence or nonoccurrence of reduced renal function in said subject.

16. A method according to one of claims 1-5, wherein said method is a method of diagnosing the occurrence or nonoccurrence of acute renal failure in said subject.

17. A method according to one of claims 1-5, wherein said method is a method of diagnosing the occurrence or nonoccurrence of a need for renal replacement therapy in said subject.

18. A method according to one of claims 1-5, wherein said method is a method of diagnosing the occurrence or nonoccurrence of a need for renal transplantation in said subject.

19. A method according to one of claims 1-5, wherein said method is a method of assigning a risk of the future occurrence or nonoccurrence of an injury to renal function in said subject.

20. A method according to one of claims 1-5, wherein said method is a method of assigning a risk of the future occurrence or nonoccurrence of reduced renal function in said subject.

21. A method according to one of claims 1-5, wherein said method is a method of assigning a risk of the future occurrence or nonoccurrence of acute renal failure in said subject.

22. A method according to one of claims 1-5, wherein said method is a method of assigning a risk of the future occurrence or nonoccurrence of a need for renal replacement therapy in said subject.

23. A method according to one of claims 1-5, wherein said method is a method of assigning a risk of the future occurrence or nonoccurrence of a need for renal transplantation in said subject.

24. A method according to one of claims 1-5, wherein said one or more future changes in renal status comprise one or more of a future injury to renal function, future reduced renal function, future improvement in renal function, and future acute renal failure (ARF) within 72 hours of the time at which the body fluid sample is obtained.

25. A method according to one of claims 1-5, wherein said one or more future changes in renal status comprise one or more of a future injury to renal function, future reduced renal function, future improvement in renal function, and future acute renal failure (ARF) within 48 hours of the time at which the body fluid sample is obtained.

26. A method according to one of claims 1-5, wherein said one or more future changes in renal status comprise one or more of a future injury to renal function, future reduced renal function, future improvement in renal function, and future acute renal failure (ARF) within 24 hours of the time at which the body fluid sample is obtained.

27. A method according to one of claims 1-5, wherein the subject is in RIFLE stage 0 or R.

28. A method according to claim 27, wherein the subject is in RIFLE stage 0, and said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage R, I or F within 72 hours.

29. A method according to claim 28, wherein the subject is in RIFLE stage 0, and said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage I or F within 72 hours.

30. A method according to claim 28, wherein the subject is in RIFLE stage 0, and said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 72 hours.

31. A method according to claim 27, wherein the subject is in RIFLE stage 0 or R, and said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage I or F within 72 hours.

32. A method according to claim 31, wherein the subject is in RIFLE stage 0 or R, and said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 72 hours.

33. A method according to claim 27, wherein the subject is in RIFLE stage R, and said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage I or F within 72 hours.

34. A method according to claim 33, wherein the subject is in RIFLE stage R, and said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 72 hours.

35. A method according to one of claims 1-5, wherein the subject is in RIFLE stage 0, R, or I, and said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 72 hours.

36. A method according to claim 35, wherein the subject is in RIFLE stage I, and said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 72 hours.

37. A method according to claim 28, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage R, I or F within 48 hours.

38. A method according to claim 29, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage I or F within 48 hours.

39. A method according to claim 30, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 48 hours.

40. A method according to claim 31, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage I or F within 48 hours.

41. A method according to claim 32, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 48 hours.

42. A method according to claim 33, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage I or F within 48 hours.

43. A method according to claim 34, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 48 hours.

44. A method according to claim 35, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 48 hours.

45. A method according to claim 36, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 48 hours.

46. A method according to claim 28, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage R, I or F within 24 hours.

47. A method according to claim 29, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage I or F within 24 hours.

48. A method according to claim 30, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 24 hours.

49. A method according to claim 31, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage I or F within 24 hours.

50. A method according to claim 32, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 24 hours.

51. A method according to claim 33, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage I or F within 24 hours.

52. A method according to claim 34, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 24 hours.

53. A method according to claim 35, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 24 hours.

54. A method according to claim 36, wherein said correlating step comprises assigning a likelihood that the subject will reach RIFLE stage F within 24 hours.

55. A method according to one of claims 1-5, wherein the subject is not in acute renal failure.

56. A method according to one of claims 1-5, wherein the subject has not experienced a 1.5-fold or greater increase in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained.

57. A method according to one of claims 1-5, wherein the subject has a urine output of at least 0.5 ml/kg/hr over the 6 hours preceding the time at which the body fluid sample is obtained.

58. A method according to one of claims 1-5, wherein the subject has not experienced an increase of 0.3 mg/dL or greater in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained.

59. A method according to one of claims 1-5, wherein the subject (i) has not experienced a 1.5-fold or greater increase in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained, (ii) has a urine output of at least 0.5 ml/kg/hr over the 6 hours preceding the time at which the body fluid sample is obtained, and (iii) has not experienced an increase of 0.3 mg/dL or greater in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained.

60. A method according to one of claims 1-5, wherein the subject has not experienced a 1.5-fold or greater increase in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained.

61. A method according to one of claims 1-5, wherein the subject has a urine output of at least 0.5 ml/kg/hr over the 6 hours preceding the time at which the body fluid sample is obtained.

62. A method according to one of claims 1-5, wherein the subject (i) has not experienced a 1.5-fold or greater increase in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained, (ii) has a urine output of at least 0.5 ml/kg/hr over the 12 hours preceding the time at which the body fluid sample is obtained, and (iii) has not experienced an increase of 0.3 mg/dL or greater in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained.

63. A method according to one of claims 1-5, wherein said correlating step comprises assigning one or more of: a likelihood that within 72 hours the subject will (i) experience a 1.5-fold or greater increase in serum creatinine (ii) have a urine output of less than 0.5 ml/kg/hr over a 6 hour period, or (iii) experience an increase of 0.3 mg/dL or greater in serum creatinine.

64. A method according to claim 63, wherein said correlating step comprises assigning one or more of: a likelihood that within 48 hours the subject will (i) experience a 1.5-fold or greater increase in serum creatinine (ii) have a urine output of less than 0.5 ml/kg/hr over a 6 hour period, or (iii) experience an increase of 0.3 mg/dL or greater in serum creatinine.

65. A method according to claim 63, wherein said correlating step comprises assigning one or more of: a likelihood that within 24 hours the subject will (i) experience a 1.5-fold or greater increase in serum creatinine (ii) have a urine output of less than 0.5 ml/kg/hr over a 6 hour period, or (iii) experience an increase of 0.3 mg/dL or greater in serum creatinine.

66. A method according to claim 63, wherein said correlating step comprises assigning a likelihood that within 72 hours the subject will experience a 1.5-fold or greater increase in serum creatinine.

67. A method according to claim 63, wherein said correlating step comprises assigning a likelihood that within 72 hours the subject will have a urine output of less than 0.5 ml/kg/hr over a 6 hour period.

68. A method according to claim 63, wherein said correlating step comprises assigning a likelihood that within 72 hours the subject will experience an increase of 0.3 mg/dL or greater in serum creatinine.

69. A method according to claim 63, wherein said correlating step comprises assigning a likelihood that within 48 hours the subject will experience a 1.5-fold or greater increase in serum creatinine.

70. A method according to claim 63, wherein said correlating step comprises assigning a likelihood that within 48 hours the subject will have a urine output of less than 0.5 ml/kg/hr over a 6 hour period.

71. A method according to claim 63, wherein said correlating step comprises assigning a likelihood that within 48 hours the subject will experience an increase of 0.3 mg/dL or greater in serum creatinine.

72. A method according to claim 63, wherein said correlating step comprises assigning a likelihood that within 24 hours the subject will experience a 1.5-fold or greater increase in serum creatinine.

73. A method according to claim 63, wherein said correlating step comprises assigning a likelihood that within 24 hours the subject will have a urine output of less than 0.5 ml/kg/hr over a 6 hour period.

74. A method according to claim 63, wherein said correlating step comprises assigning a likelihood that within 24 hours the subject will experience an increase of 0.3 mg/dL or greater in serum creatinine.

75. A method according to one of claims 1-5, wherein the subject has not experienced a 2-fold or greater increase in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained.

76. A method according to one of claims 1-5, wherein the subject has a urine output of at least 0.5 ml/kg/hr over the 12 hours preceding the time at which the body fluid sample is obtained.

77. A method according to one of claims 1-5, wherein the subject (i) has not experienced a 2-fold or greater increase in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained, (ii) has a urine output of at least 0.5 ml/kg/hr over the 2 hours preceding the time at which the body fluid

sample is obtained, and (iii) has not experienced an increase of 0.3 mg/dL or greater in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained.

78. A method according to one of claims 1-5, wherein the subject has not experienced a 3-fold or greater increase in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained.

79. A method according to one of claims 1-5, wherein the subject has a urine output of at least 0.3 ml/kg/hr over the 24 hours preceding the time at which the body fluid sample is obtained, or anuria over the 12 hours preceding the time at which the body fluid sample is obtained.

80. A method according to one of claims 1-5, wherein the subject (i) has not experienced a 3-fold or greater increase in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained, (ii) has a urine output of at least 0.3 ml/kg/hr over the 24 hours preceding the time at which the body fluid sample is obtained, or anuria over the 12 hours preceding the time at which the body fluid sample is obtained, and (iii) has not experienced an increase of 0.3 mg/dL or greater in serum creatinine over a baseline value determined prior to the time at which the body fluid sample is obtained.

81. A method according to one of claims 1-5, wherein said correlating step comprises assigning one or more of: a likelihood that within 72 hours the subject will (i) experience a 2-fold or greater increase in serum creatinine (ii) have a urine output of less than 0.5 ml/kg/hr over a 12 hour period, or (iii) experience an increase of 0.3 mg/dL or greater in serum creatinine.

82. A method according to claim 81, wherein said correlating step comprises assigning one or more of: a likelihood that within 48 hours the subject will (i) experience a 2-fold or greater increase in serum creatinine (ii) have a urine output of less than 0.5 ml/kg/hr over a 6 hour period, or (iii) experience an increase of 0.3 mg/dL or greater in serum creatinine.

83. A method according to claim 81, wherein said correlating step comprises assigning one or more of: a likelihood that within 24 hours the subject will (i) experience a 2-fold or greater increase in serum creatinine, or (ii) have a urine output of less than 0.5 ml/kg/hr over a 6 hour period.

84. A method according to claim 81, wherein said correlating step comprises assigning a likelihood that within 72 hours the subject will experience a 2-fold or greater increase in serum creatinine.

85. A method according to claim 81, wherein said correlating step comprises assigning a likelihood that within 72 hours the subject will have a urine output of less than 0.5 ml/kg/hr over a 6 hour period.

86. A method according to claim 81, wherein said correlating step comprises assigning a likelihood that within 48 hours the subject will experience a 2-fold or greater increase in serum creatinine.

87. A method according to claim 81, wherein said correlating step comprises assigning a likelihood that within 48 hours the subject will have a urine output of less than 0.5 ml/kg/hr over a 6 hour period.

88. A method according to claim 81, wherein said correlating step comprises assigning a likelihood that within 24 hours the subject will experience a 2-fold or greater increase in serum creatinine.

89. A method according to claim 81, wherein said correlating step comprises assigning a likelihood that within 24 hours the subject will have a urine output of less than 0.5 ml/kg/hr over a 6 hour period.

90. A method according to one of claims 1-5, wherein said correlating step comprises assigning one or more of: a likelihood that within 72 hours the subject will (i) experience a 3-fold or greater increase in serum creatinine, or (ii) have a urine output of less than 0.3 ml/kg/hr over a 24 hour period or anuria over a 12 hour period.

91. A method according to claim 90, wherein said correlating step comprises assigning one or more of: a likelihood that within 48 hours the subject will (i) experience a 3-fold or greater increase in serum creatinine, or (ii) have a urine output of less than 0.3 ml/kg/hr over a 24 hour period or anuria over a 12 hour period.

92. A method according to claim 90, wherein said correlating step comprises assigning one or more of: a likelihood that within 24 hours the subject will (i) experience a 3-fold or greater increase in serum creatinine, or (ii) have a urine output of less than 0.3 ml/kg/hr over a 24 hour period or anuria over a 12 hour period.

93. A method according to claim 90, wherein said correlating step comprises assigning a likelihood that within 72 hours the subject will experience a 3-fold or greater increase in serum creatinine.

94. A method according to claim 90, wherein said correlating step comprises assigning a likelihood that within 72 hours the subject will have a urine output of less than 0.3 ml/kg/hr over a 24 hour period or anuria over a 12 hour period.

95. A method according to claim 90, wherein said correlating step comprises assigning a likelihood that within 48 hours the subject will experience a 3-fold or greater increase in serum creatinine.

96. A method according to claim 90, wherein said correlating step comprises assigning a likelihood that within 48 hours the subject will have a urine output of less than 0.3 ml/kg/hr over a 24 hour period or anuria over a 12 hour period.

97. A method according to claim 90, wherein said correlating step comprises assigning a likelihood that within 24 hours the subject will experience a 3-fold or greater increase in serum creatinine.

98. A method according to claim 90, wherein said correlating step comprises assigning a likelihood that within 24 hours the subject will have a urine output of less than 0.3 ml/kg/hr over a 24 hour period or anuria over a 12 hour period.

99. A method according to one of claims 1-98, wherein the body fluid sample is a urine sample.

100. A method according to one of claims 1-98, wherein the body fluid sample is a blood, serum, or plasma sample.

101. A method according to one of claims 1-100, wherein the assay method comprises introducing the body fluid sample obtained from the subject into an assay instrument which (i) contacts the body fluid sample with one or more reagents which specifically bind for detection one or more of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin; (ii) generates one or more assay results indicative of one or more of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin in the urine sample, and (iii) uses the assay result(s) to assign the subject to a predetermined subpopulation of individuals having a known predisposition of a current or future acute renal injury or current or future acute renal failure.

102. A method according to claim 101, further comprising treating the subject based on the predetermined subpopulation of individuals to which the patient is assigned, wherein the treatment comprises one or more of initiating renal replacement therapy, withdrawing delivery of compounds that are known to be damaging to the kidney, delaying or avoiding procedures that are known to be damaging to the kidney, and modifying diuretic administration.

103. A method according to claim 101 or 102, wherein the subject does not have a current acute renal injury or acute renal failure, and the assay result is used to assign the subject to a predetermined subpopulation of individuals having a known predisposition of a future acute renal injury or future acute renal failure.

104. A method according to claim 103, wherein the future acute renal injury or future acute renal failure is within a period selected from the group consisting of 21 days, 14 days, 7 days, 5 days, 96 hours, 72 hours, 48 hours, 36 hours, 24 hours, and 12 hours

105. A method according to claim 101 or 102, wherein the subject has a current acute renal injury or acute renal failure, and the assay result is used to assign the subject to a predetermined subpopulation of individuals having a known predisposition of future recovery from acute renal injury or acute renal failure.

106. A method according to claim 105, wherein the future recovery from acute renal injury or acute renal failure is within a period selected from the group consisting of 21 days, 14 days, 7 days, 5 days, 96 hours, 72 hours, 48 hours, 36 hours, 24 hours, and 12 hours

107. A method according to claim 101 or 102, wherein the assay result is used to assign the subject to a predetermined subpopulation of individuals having a known predisposition of future persistence of an acute renal injury or acute renal failure.

108. A method according to claim 107, wherein the future persistence is over a period selected from the group consisting of 21 days, 14 days, 7 days, 5 days, 96 hours, 72 hours, 48 hours, 36 hours, 24 hours, and 12 hours.

109. A method according to claim 107 or 108, wherein the subject has an acute renal injury or acute renal failure at the time the body fluid sample is obtained.

110. Measurement of one or more of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin for the evaluation of renal injury, particularly acute renal injury.

111. A kit, comprising:

reagents for performing one or more assays configured to detect one or more of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin, and

a device which contains one or more encoded calibration curves for correlating results from performing said assay(s) to a concentration of one or more of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin, wherein the concentration range of said calibration curve(s) comprise a normal concentration of one or more of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin and a threshold concentration of one or more of Follistatin-related protein 3, Basigin, Cathepsin B, and Tenascin that indicates acute renal injury in a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/37053

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/53 (2016.01)
CPC - G01N 2800/56, G01N 33/564, G01N 2800/328
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (8): G01N 33/53 (2016.01)
CPC: G01N 2800/56, G01N 33/564, G01N 2800/328

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/7.1, 435/7.2

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Google patents, Google scholar, Google web, PatBase, Proquest Dialog
acute renal failure/ARF/acute kidney injury/AKI; evaluate/analyze; renal/kidney; status/condition; assay/method; detect/measure; Follistatin-related protein 3/FSTL3/Basigin/CD147/Cathepsin B/Tenascin; risk/diagnosis/staging/prognosis/classifying/monitoring

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/0231476 A1 (ASTUTE MEDICAL, INC) 13 September 2012 (13.09.2012) para [0051]; claim 1; Abstract; para [0043]; claim 2; claim 4; para [0022]	110
Y		1-5, 7-9
X	US 2014/0147864 A1 (ASTUTE MEDICAL, INC) 29 May 2014 (29.05.2014) para [0045]; claim 12; para [0046]; Abstract; para [0080]; para [0141]; para [0094]; para [0037]; para [0146]; para [0033]; para [0108]; para [0086]; claim 8; claim 9	111
Y		1-5, 7-9
Y	MAGISTRONI et al. "Interstitial fluid obtained from kidney biopsy as new source of renal biomarkers" J Nephrol. 2011 Vol. 24. No. 3. pp 329-337 especially, Abstract; page 335, Table II	1-5, 7-9
Y	NAGAYA et al. "CD147/basigin reflects renal dysfunction in patients with acute kidney injury" Clin Exp Nephrol. October 2014. Vol. 18 No. 5. pp 746-754 especially, Abstract	1-5, 7-9
A	WO 2003/065993 A2 (GENE LOGIC INC) 14 August 2003 (14.08.2003), whole document	1-5, 7-9, 110-111
A	WO 2013/183596 A1 (UNIV NAGOYA NAT UNIV CORP) 12 December 2013 (12.12.2013), whole document	1-5, 7-9, 110-111

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 September 2016 (07.09.2016)	29 SEP 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/37053

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6, 10-109
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

(12)发明专利申请

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用于肾损伤和肾衰竭的诊断和预后的方法和组合物

(57)摘要

本发明涉及用于罹患或怀疑患有肾损伤的受试者的监测、诊断、预后和治疗方案确定的方法和组合物。具体地讲，本发明涉及使用检测卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白中的一者或多者的测定作为肾损伤中的诊断和预后生物标志物测定。

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1.一种用于评价受试者的肾状态的方法，其包括：

对从受试者获取的体液样品进行被设定为检测卵泡抑素相关蛋白3的测定方法，被设定为检测Basigin的测定方法，被设定为检测组织蛋白酶B的测定方法，以及被设定为检测腱生蛋白的测定方法，从而提供一个或多个测定结果；以及

将所述测定结果与所述受试者的所述肾状态关联。

2.根据权利要求1所述的方法，其中所述关联步骤包括将所述测定结果与所述受试者的所述肾状态的危险分级、诊断、分期、预后、分类和监测中的一者或多者关联。

3.根据权利要求1所述的方法，其中所述关联步骤包括根据所述测定结果对所述受试者指定肾状态的一种或多种日后变化的可能性。

4.根据权利要求3所述的方法，其中所述肾状态的一种或多种日后变化包括日后肾功能损伤、日后肾功能衰弱、日后肾功能改善和日后急性肾衰竭(ARF)中的一者或多者。

5.根据权利要求1-4中一项所述的方法，其中所述测定结果包括卵泡抑素相关蛋白3的测量浓度、Basigin的测量浓度、组织蛋白酶B的测量浓度和腱生蛋白的测量浓度中的一者或多者。

6.根据权利要求1-5中一项所述的方法，其中所述关联步骤包括使用将多个测定结果转换为单个复合结果的功能组合所述多个测定结果。

7.根据权利要求3所述的方法，其中所述肾状态的一种或多种日后变化包括与所述受试者罹患的肾损伤相关的临床结局。

8.根据权利要求3所述的方法，其中所述肾状态的一种或多种日后变化的可能性为从所述受试者获取所述体液样品之时起30天内，所关注的事件较可能或较不可能发生。

9.根据权利要求8所述的方法，其中所述肾状态的一种或多种日后变化的可能性为在选自21天、14天、7天、5天、96小时、72小时、48小时、36小时、24小时和12小时的时间段内，所关注的事件较可能或较不可能发生。

10.根据权利要求1-5中一项所述的方法，其中根据所述受试者中肾前性、肾性或肾后性ARF的一种或多种已知的危险因素的预先存在来选择所述受试者进行肾状态评价。

11.根据权利要求1-5中一项所述的方法，其中根据充血性心力衰竭、子痫前期、子痫、糖尿病、高血压、冠状动脉疾病、蛋白尿、肾功能不全、肾小球过滤低于正常范围、肝硬化、血清肌酸酐高于正常范围、败血症、肾功能损伤、肾功能衰弱或ARF中的一者或多者的现有诊断，或根据正在经历或经历过大血管手术、冠状动脉搭桥或其他心脏手术，或根据暴露至NSAID、环孢菌素、他克莫司、氨基糖苷类、膦甲酸、乙二醇、血红蛋白、肌红蛋白、异环磷酰胺、重金属、甲氨蝶呤、不透射线的造影剂或链脲佐菌素来选择所述受试者进行肾状态评价。

12.根据权利要求1-5中一项所述的方法，其中所述关联步骤包括根据所述测定结果对所述受试者指定是否出现肾功能损伤、肾功能衰弱或ARF中的一者或多者的诊断。

13.根据权利要求1-5中一项所述的方法，其中所述关联步骤包括根据所述测定结果评估罹患肾功能损伤、肾功能衰弱或ARF的受试者的肾功能是否改善或恶化。

14.根据权利要求1-5中一项所述的方法，其中所述方法是诊断所述受试者是否出现肾功能损伤的方法。

15.根据权利要求1-5中一项所述的方法，其中所述方法是诊断所述受试者是否出现肾

功能衰弱的方法。

16.根据权利要求1-5中一项所述的方法，其中所述方法是诊断所述受试者是否出现急性肾衰竭的方法。

17.根据权利要求1-5中一项所述的方法，其中所述方法是诊断所述受试者是否出现对肾替代疗法的需求的方法。

18.根据权利要求1-5中一项所述的方法，其中所述方法是诊断所述受试者是否出现对肾移植的需求的方法。

19.根据权利要求1-5中一项所述的方法，其中所述方法是指定所述受试者日后是否出现肾功能损伤的危险的方法。

20.根据权利要求1-5中一项所述的方法，其中所述方法是指定所述受试者日后是否出现肾功能衰弱的危险的方法。

21.根据权利要求1-5中一项所述的方法，其中所述方法是指定所述受试者日后是否出现急性肾衰竭的危险的方法。

22.根据权利要求1-5中一项所述的方法，其中所述方法是指定所述受试者日后是否出现对肾替代疗法的需求的危险的方法。

23.根据权利要求1-5中一项所述的方法，其中所述方法是指定所述受试者日后是否出现对肾移植的需求的危险的方法。

24.根据权利要求1-5中一项所述的方法，其中所述肾状态的一种或多种日后变化包括从获取所述体液样品之时起72小时内日后肾功能损伤、日后肾功能衰弱、日后肾功能改善和日后急性肾衰竭(ARF)中的一者或多者。

25.根据权利要求1-5中一项所述的方法，其中所述肾状态的一种或多种日后变化包括从获取所述体液样品之时起48小时内日后肾功能损伤、日后肾功能衰弱、日后肾功能改善和日后急性肾衰竭(ARF)中的一者或多者。

26.根据权利要求1-5中一项所述的方法，其中所述肾状态的一种或多种日后变化包括从获取所述体液样品之时起24小时内日后肾功能损伤、日后肾功能衰弱、日后肾功能改善和日后急性肾衰竭(ARF)中的一者或多者。

27.根据权利要求1-5中一项所述的方法，其中所述受试者处于RIFLE阶段0或R。

28.根据权利要求27所述的方法，其中所述受试者处于RIFLE阶段0，并且所述关联步骤包括指定所述受试者将在72小时内达到RIFLE阶段R、I或F的可能性。

29.根据权利要求28所述的方法，其中所述受试者处于RIFLE阶段0，并且所述关联步骤包括指定所述受试者将在72小时内达到RIFLE阶段I或F的可能性。

30.根据权利要求28所述的方法，其中所述受试者处于RIFLE阶段0，并且所述关联步骤包括指定所述受试者将在72小时内达到RIFLE阶段F的可能性。

31.根据权利要求27所述的方法，其中所述受试者处于RIFLE阶段0或R，并且所述关联步骤包括指定所述受试者将在72小时内达到RIFLE阶段I或F的可能性。

32.根据权利要求31所述的方法，其中所述受试者处于RIFLE阶段0或R，并且所述关联步骤包括指定所述受试者将在72小时内达到RIFLE阶段F的可能性。

33.根据权利要求27所述的方法，其中所述受试者处于RIFLE阶段R，并且所述关联步骤包括指定所述受试者将在72小时内达到RIFLE阶段I或F的可能性。

34.根据权利要求33所述的方法，其中所述受试者处于RIFLE阶段R，并且所述关联步骤包括指定所述受试者将在72小时内达到RIFLE阶段F的可能性。

35.根据权利要求1-5中一项所述的方法，其中所述受试者处于RIFLE阶段0、R或I，并且所述关联步骤包括指定所述受试者将在72小时内达到RIFLE阶段F的可能性。

36.根据权利要求35所述的方法，其中所述受试者处于RIFLE阶段I，并且所述关联步骤包括指定所述受试者将在72小时内达到RIFLE阶段F的可能性。

37.根据权利要求28所述的方法，其中所述关联步骤包括指定所述受试者将在48小时内达到RIFLE阶段R、I或F的可能性。

38.根据权利要求29所述的方法，其中所述关联步骤包括指定所述受试者将在48小时内达到RIFLE阶段I或F的可能性。

39.根据权利要求30所述的方法，其中所述关联步骤包括指定所述受试者将在48小时内达到RIFLE阶段F的可能性。

40.根据权利要求31所述的方法，其中所述关联步骤包括指定所述受试者将在48小时内达到RIFLE阶段I或F的可能性。

41.根据权利要求32所述的方法，其中所述关联步骤包括指定所述受试者将在48小时内达到RIFLE阶段F的可能性。

42.根据权利要求33所述的方法，其中所述关联步骤包括指定所述受试者将在48小时内达到RIFLE阶段I或F的可能性。

43.根据权利要求34所述的方法，其中所述关联步骤包括指定所述受试者将在48小时内达到RIFLE阶段F的可能性。

44.根据权利要求35所述的方法，其中所述关联步骤包括指定所述受试者将在48小时内达到RIFLE阶段F的可能性。

45.根据权利要求36所述的方法，其中所述关联步骤包括指定所述受试者将在48小时内达到RIFLE阶段F的可能性。

46.根据权利要求28所述的方法，其中所述关联步骤包括指定所述受试者将在24小时内达到RIFLE阶段R、I或F的可能性。

47.根据权利要求29所述的方法，其中所述关联步骤包括指定所述受试者将在24小时内达到RIFLE阶段I或F的可能性。

48.根据权利要求30所述的方法，其中所述关联步骤包括指定所述受试者将在24小时内达到RIFLE阶段F的可能性。

49.根据权利要求31所述的方法，其中所述关联步骤包括指定所述受试者将在24小时内达到RIFLE阶段I或F的可能性。

50.根据权利要求32所述的方法，其中所述关联步骤包括指定所述受试者将在24小时内达到RIFLE阶段F的可能性。

51.根据权利要求33所述的方法，其中所述关联步骤包括指定所述受试者将在24小时内达到RIFLE阶段I或F的可能性。

52.根据权利要求34所述的方法，其中所述关联步骤包括指定所述受试者将在24小时内达到RIFLE阶段F的可能性。

53.根据权利要求35所述的方法，其中所述关联步骤包括指定所述受试者将在24小时

内达到RIFLE阶段F的可能性。

54.根据权利要求36所述的方法，其中所述关联步骤包括指定所述受试者将在24小时内达到RIFLE阶段F的可能性。

55.根据权利要求1-5中一项所述的方法，其中所述受试者不处于急性肾衰竭。

56.根据权利要求1-5中一项所述的方法，其中所述受试者未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加1.5倍或更多。

57.根据权利要求1-5中一项所述的方法，其中所述受试者在获取所述体液样品的时间之前的6小时内具有的排尿量为至少0.5ml/kg/h。

58.根据权利要求1-5中一项所述的方法，其中所述受试者未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加0.3mg/dL或更多。

59.根据权利要求1-5中一项所述的方法，其中所述受试者(i)未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加1.5倍或更多，(ii)在获取所述体液样品的时间之前的6小时内具有的排尿量为至少0.5ml/kg/h，以及(iii)未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加0.3mg/dL或更多。

60.根据权利要求1-5中一项所述的方法，其中所述受试者未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加1.5倍或更多。

61.根据权利要求1-5中一项所述的方法，其中所述受试者在获取所述体液样品的时间之前的6小时内具有的排尿量为至少0.5ml/kg/h。

62.根据权利要求1-5中一项所述的方法，其中所述受试者(i)未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加1.5倍或更多，(ii)在获取所述体液样品的时间之前的12小时内具有的排尿量为至少0.5ml/kg/h，以及(iii)未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加0.3mg/dL或更多。

63.根据权利要求1-5中一项所述的方法，其中所述关联步骤包括指定以下中的一者或多者：所述受试者在72小时内将(i)经历血清肌酸酐增加1.5倍或更多(ii)在6小时的时间段内具有的排尿量小于0.5ml/kg/h，或(iii)经历血清肌酸酐增加0.3mg/dL或更多的可能性。

64.根据权利要求63所述的方法，其中所述关联步骤包括指定以下中的一者或多者：所述受试者在48小时内将(i)经历血清肌酸酐增加1.5倍或更多(ii)在6小时的时间段内具有的排尿量小于0.5ml/kg/h，或(iii)经历血清肌酸酐增加0.3mg/dL或更多的可能性。

65.根据权利要求63所述的方法，其中所述关联步骤包括指定以下中的一者或多者：所述受试者在24小时内将(i)经历血清肌酸酐增加1.5倍或更多(ii)在6小时的时间段内具有的排尿量小于0.5ml/kg/h，或(iii)经历血清肌酸酐增加0.3mg/dL或更多的可能性。

66.根据权利要求63所述的方法，其中所述关联步骤包括指定所述受试者在72小时内将经历血清肌酸酐增加1.5倍或更多的可能性。

67.根据权利要求63所述的方法，其中所述关联步骤包括指定所述受试者在72小时内将在6小时的时间段内具有的排尿量小于0.5ml/kg/h的可能性。

68.根据权利要求63所述的方法，其中所述关联步骤包括指定所述受试者在72小时内将经历血清肌酸酐增加0.3mg/dL或更多的可能性。

69.根据权利要求63所述的方法，其中所述关联步骤包括指定所述受试者在48小时内

将经历血清肌酸酐增加1.5倍或更多的可能性。

70.根据权利要求63所述的方法，其中所述关联步骤包括指定所述受试者在48小时内将在6小时的时间段内具有的排尿量小于0.5ml/kg/h的可能性。

71.根据权利要求63所述的方法，其中所述关联步骤包括指定所述受试者在48小时内将经历血清肌酸酐增加0.3mg/dL或更多的可能性。

72.根据权利要求63所述的方法，其中所述关联步骤包括指定所述受试者在24小时内将经历血清肌酸酐增加1.5倍或更多的可能性。

73.根据权利要求63所述的方法，其中所述关联步骤包括指定所述受试者在24小时内将在6小时的时间段内具有的排尿量小于0.5ml/kg/h的可能性。

74.根据权利要求63所述的方法，其中所述关联步骤包括指定所述受试者在24小时内将经历血清肌酸酐增加0.3mg/dL或更多的可能性。

75.根据权利要求1-5中一项所述的方法，其中所述受试者未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加2倍或更多。

76.根据权利要求1-5中一项所述的方法，其中所述受试者在获取所述体液样品的时间之前的12小时内具有的排尿量为至少0.5ml/kg/h。

77.根据权利要求1-5中一项所述的方法，其中所述受试者(i)未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加2倍或更多，(ii)在获取所述体液样品的时间之前的2小时内具有的排尿量为至少0.5ml/kg/h，以及(iii)未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加0.3mg/dL或更多。

78.根据权利要求1-5中一项所述的方法，其中所述受试者未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加3倍或更多。

79.根据权利要求1-5任一项所述的方法，其中所述受试者在获取所述体液样品的时间之前的24小时内具有的排尿量为至少0.3ml/kg/h，或在获取所述体液样品的时间之前的12小时内无尿。

80.根据权利要求1-5中一项所述的方法，其中所述受试者(i)未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加3倍或更多，(ii)在获取所述体液样品的时间之前的24小时内具有的排尿量为至少0.3ml/kg/h，或在获取所述体液样品的时间之前的12小时内无尿，以及(iii)未经历血清肌酸酐相对于在获取所述体液样品的时间之前确定的基线值增加0.3mg/dL或更多。

81.根据权利要求1-5中一项所述的方法，其中所述关联步骤包括指定以下中的一者或多者：所述受试者在72小时内将(i)经历血清肌酸酐增加2倍或更多(ii)在12小时的时间段内具有的排尿量小于0.5ml/kg/h，或(iii)经历血清肌酸酐增加0.3mg/dL或更多的可能性。

82.根据权利要求81所述的方法，其中所述关联步骤包括指定以下中的一者或多者：所述受试者在48小时内将(i)经历血清肌酸酐增加2倍或更多(ii)在6小时的时间段内具有的排尿量小于0.5ml/kg/h，或(iii)经历血清肌酸酐增加0.3mg/dL或更多的可能性。

83.根据权利要求81所述的方法，其中所述关联步骤包括指定以下中的一者或多者：所述受试者在24小时内将(i)经历血清肌酸酐增加2倍或更多，或(ii)在6小时的时间段内具有的排尿量小于0.5ml/kg/h的可能性。

84.根据权利要求81所述的方法，其中所述关联步骤包括指定所述受试者在72小时内

将经历血清肌酸酐增加2倍或更多的可能性。

85.根据权利要求81所述的方法，其中所述关联步骤包括指定所述受试者在72小时内将在6小时的时间段内具有的排尿量小于0.5ml/kg/h的可能性。

86.根据权利要求81所述的方法，其中所述关联步骤包括指定所述受试者在48小时内经历血清肌酸酐增加2倍或更多的可能性。

87.根据权利要求81所述的方法，其中所述关联步骤包括指定所述受试者在48小时内将在6小时的时间段内具有的排尿量小于0.5ml/kg/h的可能性。

88.根据权利要求81所述的方法，其中所述关联步骤包括指定所述受试者在24小时内经历血清肌酸酐增加2倍或更多的可能性。

89.根据权利要求81所述的方法，其中所述关联步骤包括指定所述受试者在24小时内将在6小时的时间段内具有的排尿量小于0.5ml/kg/h的可能性。

90.根据权利要求1-5中一项所述的方法，其中所述关联步骤包括指定以下中的一者或多者：所述受试者在72小时内将(i)经历血清肌酸酐增加3倍或更多，或(ii)在24小时的时间段内具有的排尿量小于0.3ml/kg/h或在12小时的时间段内无尿的可能性。

91.根据权利要求90所述的方法，其中所述关联步骤包括指定以下中的一者或多者：所述受试者在48小时内将(i)经历血清肌酸酐增加3倍或更多，或(ii)在24小时的时间段内具有的排尿量小于0.3ml/kg/h或在12小时的时间段内无尿的可能性。

92.根据权利要求90所述的方法，其中所述关联步骤包括指定以下中的一者或多者：所述受试者在24小时内将(i)经历血清肌酸酐增加3倍或更多，或(ii)在24小时的时间段内具有的排尿量小于0.3ml/kg/h或在12小时的时间段内无尿的可能性。

93.根据权利要求90所述的方法，其中所述关联步骤包括指定所述受试者在72小时内将经历血清肌酸酐增加3倍或更多的可能性。

94.根据权利要求90所述的方法，其中所述关联步骤包括指定所述受试者在72小时内将在24小时的时间段内具有的排尿量小于0.3ml/kg/h或在12小时的时间段内无尿的可能性。

95.根据权利要求90所述的方法，其中所述关联步骤包括指定所述受试者在48小时内经历血清肌酸酐增加3倍或更多的可能性。

96.根据权利要求90所述的方法，其中所述关联步骤包括指定所述受试者在48小时内将在24小时的时间段内具有的排尿量小于0.3ml/kg/h或在12小时的时间段内无尿的可能性。

97.根据权利要求90所述的方法，其中所述关联步骤包括指定所述受试者在24小时内将经历血清肌酸酐增加3倍或更多的可能性。

98.根据权利要求90所述的方法，其中所述关联步骤包括指定所述受试者在24小时内将在24小时的时间段内具有的排尿量小于0.3ml/kg/h或在12小时的时间段内无尿的可能性。

99.根据权利要求1-98中一项所述的方法，其中所述体液样品是尿样。

100.根据权利要求1-98中一项所述的方法，其中所述体液样品是血液、血清或血浆样品。

101.根据权利要求1-100中一项所述的方法，其中所述测定方法包括将从所述受试者

获取的所述体液样品引入测定仪器，所述测定仪器(i)使所述体液样品与一种或多种试剂接触，所述试剂特异性地结合以检测卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白中的一者或多者；(ii)产生表示所述尿样中的卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白中的一者或多者的一个或多个测定结果，以及(iii)使用所述测定结果将所述受试者指定到预定的个体亚群，所述个体具有目前或日后急性肾损伤或者目前或日后急性肾衰竭的已知倾向。

102.根据权利要求101所述的方法，还包括根据所述患者被指定到的所述预定的个体亚群治疗所述受试者，其中所述治疗包括开始肾替代疗法、取消递送已知对所述肾脏有伤害的化合物、延迟或避免已知对所述肾脏有伤害的程序以及改变利尿剂的施用中的一者或多者。

103.根据权利要求101或102所述的方法，其中所述受试者不具有目前急性肾损伤或急性肾衰竭，并且所述测定结果用于将所述受试者指定到预定的个体亚群，所述个体具有日后急性肾损伤或日后急性肾衰竭的已知倾向。

104.根据权利要求103所述的方法，其中所述日后急性肾损伤或日后急性肾衰竭在选自21天、14天、7天、5天、96小时、72小时、48小时、36小时、24小时和12小时的时间段内。

105.根据权利要求101或102所述的方法，其中所述受试者具有目前急性肾损伤或急性肾衰竭，并且所述测定结果用于将所述受试者指定到预定的个体亚群，所述个体具有日后从急性肾损伤或急性肾衰竭恢复的已知倾向。

106.根据权利要求105所述的方法，其中所述日后从急性肾损伤或急性肾衰竭恢复在选自21天、14天、7天、5天、96小时、72小时、48小时、36小时、24小时和12小时的时间段内。

107.根据权利要求101或102所述的方法，其中所述测定结果用于将所述受试者指定到预定的个体亚群，所述个体具有急性肾损伤或急性肾衰竭日后持续的已知倾向。

108.根据权利要求107所述的方法，其中所述日后持续在选自21天、14天、7天、5天、96小时、72小时、48小时、36小时、24小时和12小时的时间段内。

109.根据权利要求107或108所述的方法，其中所述受试者在获取所述体液样品时具有急性肾损伤或急性肾衰竭。

110.卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白中的一者或多者的测量值，用于评价肾损伤，特别是急性肾损伤。

111.一种试剂盒，其包括：

用于进行一个或多个测定的试剂，所述测定被设定为检测卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白中的一者或多者，以及

装置，其包含一条或多条编码校正曲线，所述曲线用于将进行所述测定所得到的结果与卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白中的一者或多者的浓度关联，其中所述校正曲线的浓度范围包括卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白中的一者或多者的正常浓度，以及表明人体中的急性肾损伤的卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白中的一者或多者的阈值浓度。

用于肾损伤和肾衰竭的诊断和预后的方法和组合物

[0001] 本发明要求于2015年6月11日提交的美国临时申请No.62/174,456、于2015年6月11日提交的美国临时申请No.62/174,458、于2015年6月11日提交的美国临时申请No.62/174,460和于2015年6月11日提交的美国临时申请No.62/174,461的优先权，上述每个临时申请全文包括所有表格、附图和权利要求据此并入。

[0002] 发明背景

[0003] 本发明的背景技术的以下讨论仅用于帮助读者理解本发明且并非认同描述或构成本发明的现有技术。

[0004] 肾脏负责从身体排泄水和溶解物。它的功能包括维持酸碱平衡、调节电解质浓度、控制血容量和调节血压。因此，肾脏功能因损伤和/或疾病的丧失导致实质上发病和死亡。肾损伤的详细讨论提供于Harrison's Principles of Internal Medicine，第17版，McGraw Hill，New York，第1741-1830页，该文献全文据此以引用的方式并入。肾病和/或肾损伤可为急性的或慢性的。急性和慢性肾病描述如下(来自Current Medical Diagnosis& Treatment 2008，第47版，McGraw Hill，New York，第785-815页，该文献全文据此以引用的方式并入)：“急性肾衰竭是肾功能在几小时至几天内恶化，导致含氮废物(诸如尿素氮)和肌酸酐滞留在血液中。这些物质的滞留被称为氮血症。慢性肾衰竭(慢性肾病)因肾功能在几个月至几年内的异常丧失而引起。”

[0005] 急性肾衰竭(ARF，也称为急性肾损伤或AKI)是肾小球过滤急剧(通常在约48小时至1周内检测到)降低。该过滤能力的丧失导致了肾脏正常排泄的含氮(尿素和肌酸酐)和不含氮废物的滞留、尿排出量减少，或两者兼而有之。据报道，ARF导致约5％需入院治疗，4-15％需进行心肺旁路手术，以及最多30％需进行重症监护治疗。ARF按起因可分为肾前性、肾性或肾后性ARF。肾性疾病可进一步分为肾小球、肾小管、间质和血管异常。ARF的主要原因描述于下表中，该表改自Merck Manual，第17版，第222章，其全文据此以引用的方式并入：

[0006]

类型	危险因素
肾前性	
ECF 容量不足	过度利尿、出血、GI 损失、血管内流体流失到血管外间隙中（由于腹水、腹膜炎、胰腺炎或烧伤）、皮肤和粘膜损失、肾耗盐和耗水状态
心输出量低	心肌病、MI、心脏填塞、肺栓塞、肺动脉高压、正压机械通气
全身血管阻力低	败血性休克、肝功能衰竭、降压药
肾血管阻力增大	NSAID、环孢菌素、他克莫司(tacrolimus)、高钙血症、过敏反应、麻醉剂、肾动脉阻塞、肾静脉血栓形成、败血症、肝肾综合征
出球小动脉张力减小（由肾小球经毛细血管压力降低导致 GFR 降低，尤其是患有双侧肾动脉狭窄的患者）	ACE 抑制剂或血管紧张素 II 受体阻滞剂
肾性	
急性肾小管损伤	缺血（长期或严重肾前性状态）：手术、出血、动脉或静脉梗阻；毒素：NSAID、环孢菌素、他克莫司、氨基糖苷、膦甲酸、乙二醇、血红蛋白、肌红蛋白、异环磷酰胺、重金属、甲氨蝶呤、不透射线的造影剂、链脲佐菌素
急性肾小球肾炎	ANCA 相关：新月体性肾小球肾炎、结节性多动脉炎、韦格纳氏肉芽肿病(Wegener's granulomatosis)；抗 GBM 肾小球肾炎：古德帕斯特综合征(Goodpasture's syndrome)；免疫

类型	危险因素
	复合物：狼疮性肾小球肾炎、感染后肾小球肾炎、冷球蛋白血症性肾小球肾炎
急性肾小管间质性肾炎	药物反应（如，β-内酰胺、NSAID、磺胺类药物、环丙沙星、噻嗪类利尿剂、呋塞米(furosemide)、苯妥英、别嘌醇、肾盂肾炎、肾乳头坏死
急性血管性肾病	血管炎、恶性高血压、血栓性微血管病、硬皮病、动脉粥样硬化栓塞
侵润性疾病	淋巴瘤、结节病、白血病
肾后性	
肾小管沉积	尿酸（肿瘤溶解）、磺胺类药物、氨苯蝶啶、阿昔洛韦(acyclovir)、茚地那韦(indinavir)、甲氨蝶呤、乙二醇摄入、骨髓瘤蛋白、肌红蛋白
输尿管梗阻	内因性：结石、凝血、脱落的肾组织、真菌球、水肿、恶性疾病、先天性缺陷；外因性：恶性疾病、腹膜后纤维化、手术期间的输尿管创伤或高撞击损伤
膀胱梗阻	机械性：良性前列腺增生、前列腺癌、膀胱癌、尿道狭窄、包茎、嵌顿包茎、尿道瓣膜、梗阻性留置导尿管；神经性：抗胆碱能药物、上或下运动神经元病变

[0007]

[0008] 在缺血性ARF的情况下，病程可分成四个阶段。在持续几小时至几天的起始阶段期间，肾脏灌注降低正发展为损伤。肾小球超滤减少，滤液流量由于肾小管内的碎片而减少，并且滤液通过受损上皮发生回漏。在此阶段期间，肾损伤可通过肾脏再灌注介导。起始阶段之后是扩展阶段，该阶段的特征是持续的缺血性损伤和炎症，并且可涉及内皮损伤和血管充血。在持续1至2周的维持阶段期间，肾细胞出现损伤，并且肾小球过滤和尿排出量达到最小。随后可以是恢复阶段，其中肾上皮细胞得以修复，并且GFR逐渐恢复。尽管如此，但患有ARF的受试者的存活率可低至约60％。

[0009] 放射性造影剂(也称为造影介质)和其他肾毒素(诸如环孢霉素)、抗生素(包括氨基糖苷类)和抗癌药(诸如顺铂)引起的急性肾损伤在几天至大约一周的时间段内显现出来。造影诱发的肾病(CIN，它是由放射性造影剂引起的AKI)被认为是肾内血管收缩(导致缺血性损伤)且因产生对肾小管上皮细胞具有直接毒性的活性氧物质而引起的。CIN传统上表现为血尿素氮和血清肌酸酐的急剧(在24-48h内发作)但可逆(峰值3-5天，在1周内消除)的升高。

[0010] 通常报导的用于确定和检测AKI的标准是血清肌酸酐的急剧(通常在约2-7天内或在住院期间)升高。虽然使用血清肌酸酐的升高来确定和检测AKI已充分建立，但血清肌酸

酐升高的幅度和确定AKI的测量时间在不同的出版物之间却有很大的差异。传统上，使用相对较大的血清肌酸酐增长(诸如100％、200％，增长至少100％达到2mg/dL以上的值和其他定义)确定AKI。然而，目前的趋势是使用较小的血清肌酸酐升高来确定AKI。血清肌酸酐升高、AKI与相关的健康危险之间的关系的综述于Praught和Shlipak，Curr Opin Nephrol Hypertens 14:265-270，2005和Chertow等人，J Am Soc Nephrol 16:3365-3370，2005，上述文献与其中所列的参考文献全文据此以引用的方式并入。如这些出版物中所述，现在已知急性恶化的肾功能(AKI)和增加的死亡危险以及其他不利结果与血清肌酸酐的极小增长有关。这些增加可确定为相对(百分比)值或标称值。已报道，血清肌酸酐较损伤前的值相对增长低至20％表明了肾功能急性恶化(AKI)和健康危险增加，但更常见报道的确定AKI和健康危险增加的值是相对增长至少25％。已报道，低至0.3mg/dL、0.2mg/dL或甚至0.1mg/dL的标称增加表明肾功能恶化和死亡危险增加。已使用血清肌酸酐升高至这些阈值的不同时间段来确定AKI，例如从2天、3天、7天的范围或定义为患者住院或入住重症监护室时间的变化时间段。这些研究表明，对于恶化的肾功能或AKI，不存在特定的血清肌酸酐升高阈值(或升高所用的时间段)，而是危险随血清肌酸酐升高幅度的增加而连续增加。

[0011] 一项研究(Lassnigg等人，J Am Soc Nephrol 15:1597-1605，2004，其全文据此以引用的方式并入)对血清肌酸酐的增加和减少进行了研究。心脏手术后具有-0.1至-0.3mg/dL的血清肌酸酐轻微下降的患者死亡率最低。血清肌酸酐下降较大(超过或等于-0.4mg/dL)或血清肌酸酐有任何增加的患者死亡率较高。这些研究结果使作者得出结论，即使肾功能的非常微小的变化(如在手术48小时内通过肌酸酐的小变化来检测)也严重影响患者的结局。为了对用于在临床试验和临床实践中利用血清肌酸酐来确定AKI的统一分类系统达成共识，Bellomo等人，Crit Care.8(4):R204-12，2004(该文献全文据此以引用的方式并入)提出了用于将AKI患者分级的以下分类：

[0012] “危险”：血清肌酸酐较基线增加1.5倍，或6小时尿量<0.5ml/kg体重/h；

[0013] “损伤”：血清肌酸酐较基线增加2.0倍，或12小时尿量<0.5ml/kg/h；

[0014] “衰竭”：血清肌酸酐较基线增加3.0倍，或肌酸酐>355μmol/l(升高>44)，或24h排尿量少于0.3ml/kg/h，或至少12小时无尿；

[0015] 并且包括两种临床结局：

[0016] “丧失”：对肾替代疗法的持续需求超过四周。

[0017] “ESRD”：晚期肾病—对透析的需求超过3个月。

[0018] 这些标准称为RIFLE标准，它们提供了适用于对肾状态进行分类的临床工具。如Kellum，Crit.Care Med.36:S141-45，2008和Ricci等人，Kidney Int.73，538-546，2008所讨论(每个文献全文据此以引用的方式并入)，RIFLE标准提供了已在许多研究中得到确认的AKI的统一定义。

[0019] 最近，Mehta等人，Crit.Care 11:R31(doi:10.1186.cc5713)，2007(该文献全文据此以引用的方式并入)提出了用于将AKI患者分级的以下类似分类，该分类修改自RIFLE：

[0020] “阶段I”：血清肌酸酐增加超过或等于0.3mg/dL(≥26.4μmol/L)，或增加至超过或等于基线的150％(1.5倍)，或超过6小时的排尿量少于0.5mL/kg/小时；

[0021] “阶段II”：血清肌酸酐增加至超过基线的200％(>2倍)，或超过12小时的排尿量少于0.5mL/kg/小时；

[0022] “阶段III”:血清肌酸酐增加至超过基线的300%(>3倍),或血清肌酸酐≥354μmol/L,伴有至少44μmol/L的急性增长,或24小时的排尿量少于0.3mL/kg/小时,或12小时无尿。

[0023] CIN协调工作组(CIN Consensus Working Panel)(McCollough等人,Rev Cardiovasc Med.2006;7(4):177-197,该文献全文据此以引用的方式并入)使用25%的血清肌酸酐升高来确定造影剂诱发的肾病(它是一种类型的AKI)。虽然各组提出的使用血清肌酸酐检测AKI的标准略有不同,但达成以下共识:血清肌酸酐的小变化(诸如0.3mg/dL或25%)足以检测AKI(肾功能恶化),并且血清肌酸酐变化的幅度是AKI严重程度和死亡危险的指标。

[0024] 虽然在若干天内连续测量血清肌酸酐是接受的检测和诊断AKI的方法,并且被认为是评价AKI患者的最重要的工具之一,但一般认为血清肌酸酐在诊断、评估和监测AKI患者时具有许多局限性。根据所用定义的情况,血清肌酸酐升至被视为AKI诊断值(例如,0.3mg/dL或25%的升高)的时间段可为48小时或更长。由于AKI中的细胞损伤可在数小时内发生,在48小时或更长时间点所检测到的血清肌酸酐升高可为损伤的晚期指标,因此依赖血清肌酸酐可延误AKI的诊断。此外,当肾功能快速变化时,血清肌酸酐不是准确的肾脏状态和AKI的最严重阶段期间的治疗需求的良好指标。一些AKI患者会完全恢复,一些将需要透析(短期或长期),而一些则会有其他不利结果,包括死亡、严重的不良心脏事件和慢性肾病。因为血清肌酸酐是过滤速度的标志物,所以它并不区分AKI的起因(肾前性、肾性、肾后性梗阻、粥样栓塞性等)或肾性疾病中损伤的类别或位置(例如,起源于肾小管、肾小球或间质)。排尿量受到类似的限制,了解这些对管理和治疗AKI患者而言可为至关重要的。

[0025] 这些限制强调了需要更好的方法来检测和评估AKI,特别是在早期和亚临床阶段,而且在后期可出现肾脏的痊愈和恢复时。此外,需要更好地鉴别具有患上AKI危险的患者。

发明内容

[0026] 本发明的目的是提供用于评价受试者的肾功能的方法和组合物。如本文中所述,对选自以下的一种或多种标志物的测量可用于对罹患肾功能损伤、肾功能衰弱和/或急性肾衰竭(也称急性肾损伤)或具有罹患上述疾病危险的受试者进行诊断、预后、危险分级、分期、监测、分类和确定进一步诊断和治疗方案:卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白(本文中统称为“肾损伤标志物”,单独称为一种“肾损伤标志物”)。

[0027] 这些肾损伤标志物可单独使用,或以包含多种肾损伤标志物的组合形式使用,用于危险分级(即,鉴别日后有罹患肾功能损伤危险、日后发展为肾功能衰弱、日后发展为ARF、日后肾功能改善等的受试者);用于诊断现有的疾病(即,鉴别罹患肾功能损伤、已发展为肾功能衰弱、已发展为ARF等的受试者);用于监测肾功能的恶化或改善;以及用于预测日后的医疗结局,诸如肾功能的改善或恶化、死亡危险减少或增加、受试者需进行肾替代疗法(即,血液透析、腹膜透析、血液过滤和/或肾移植)的危险减少或增加、受试者肾功能损伤痊愈的危险减少或增加、受试者ARF痊愈的危险减少或增加、受试者发展为晚期肾病的危险减少或增加、受试者发展为慢性肾衰竭的危险减少或增加、受试者的移植肾发生排斥反应的危险减少或增加等。

[0028] 在第一方面,本发明涉及用于评价受试者肾状态的方法。这些方法包括执行一种

测定，该测定被设定为检测取自受试者体液样品中的一种或多种本发明的肾损伤标志物。然后将测定结果与受试者的肾状态关联，所述测定结果例如选自以下的一种或多种标志物的测量浓度：卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白。这种与肾状态关联可包括将测定结果与本文所述的受试者的危险分级、诊断、预后、分期、分类和监测中的一者或多者关联。因此，本发明利用一种或多种本发明的肾损伤标志物来评价肾损伤。

[0029] 在某些实施方案中，用于评价本文所述的肾状态的方法是对受试者进行危险分级的方法；即，对受试者指定肾状态的一种或多种日后变化的可能性。在这些实施方案中，将测定结果与一种或多种此类日后变化关联。以下是优选的危险分级实施方案。

[0030] 在优选的危险分级实施方案中，这些方法包括确定受试者日后出现肾功能损伤的危险，并且将测定结果(例如一种或多种标志物的测量浓度，所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与出现此类日后肾功能损伤的可能性关联。例如，可以将每个测量浓度与阈值相比较。对于“阳向(positive going)”肾损伤标志物，相对于当测量浓度小于阈值时指定的日后罹患肾功能损伤的可能性来说，当测量浓度大于阈值时，对受试者指定日后罹患肾功能损伤的可能性增加。对于“阴向(negative going)”肾损伤标志物，相对于当测量浓度大于阈值时指定的日后罹患肾功能损伤的可能性来说，当测量浓度小于阈值时，对受试者指定日后罹患肾功能损伤的可能性增加。

[0031] 在其他优选的危险分级实施方案中，这些方法包括确定受试者日后肾功能衰弱的危险，并且将测定结果(例如一种或多种标志物的测量浓度，所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与此类肾功能衰弱的可能性关联。例如，可以将每个测量浓度与阈值相比较。对于“阳向”肾损伤标志物，相对于当测量浓度小于阈值时指定的日后肾功能衰弱的可能性来说，当测量浓度大于阈值时，对受试者指定日后肾功能衰弱的可能性增加。对于“阴向”肾损伤标志物，相对于当测量浓度大于阈值时指定的日后肾功能衰弱的可能性来说，当测量浓度小于阈值时，对受试者指定日后肾功能衰弱的可能性增加。

[0032] 在其他优选的危险分级实施方案中，这些方法包括确定受试者日后肾功能改善的可能性，并且将测定结果(例如一种或多种标志物的测量浓度，所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与此类日后肾功能改善的可能性关联。例如，可以将每个测量浓度与阈值相比较。对于“阳向”肾损伤标志物，相对于当测量浓度大于阈值时指定的日后肾功能改善的可能性来说，当测量浓度小于阈值时，对受试者指定日后肾功能改善的可能性增加。对于“阴向”肾损伤标志物，相对于当测量浓度小于阈值时指定的日后肾功能改善的可能性来说，当测量浓度大于阈值时，对受试者指定日后肾功能改善的可能性增加。

[0033] 在其他优选的危险分级实施方案中，这些方法包括确定受试者发展为ARF的危险，并且将结果(例如一种或多种标志物的测量浓度，所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与此类发展为ARF的可能性关联。例如，可以将每个测量浓度与阈值相比较。对于“阳向”肾损伤标志物，相对于当测量浓度小于阈值时指定的发展为ARF的可能性来说，当测量浓度大于阈值时，对受试者指定发展为ARF的可能性增加。对于“阴向”肾损伤标志物，相对于当测量浓度大于阈值时指定的发展为ARF的可能性来说，当测量浓度小于阈值时，对受试者指定发展为ARF的可能性增加。

[0034] 并且在其他优选的危险分级实施方案中，这些方法包括确定受试者结局的危险，并且将测定结果(例如一种或多种标志物的测量浓度，所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与出现同受试者罹患的肾损伤相关的临床结局的可能性关联。例如，可以将每个测量浓度与阈值相比较。对于“阳向”肾损伤标志物，相对于当测量浓度小于阈值时指定的可能性来说，当测量浓度大于阈值时，对受试者指定出现以下一种或多种情况的可能性增加：急性肾损伤、发展为AKI的恶化阶段、死亡、需进行肾替代疗法、需移除肾毒素、晚期肾病、心力衰竭、中风、心肌梗塞、发展为慢性肾病等。对于“阴向”肾损伤标志物，相对于当测量浓度大于阈值时指定的可能性来说，当测量浓度小于阈值时，对受试者指定出现以下一种或多种情况的可能性增加：急性肾损伤、发展为AKI的恶化阶段、死亡、需进行肾替代疗法、需移除肾毒素、晚期肾病、心力衰竭、中风、心肌梗塞、发展为慢性肾病等。

[0035] 在此类危险分级实施方案中，优选地，指定的可能性或危险为从受试者获取体液样品之时起180天内，所关注的事件较可能或较不可能发生。在特别优选的实施方案中，确定的可能性或危险涉及在较短的时间段内，诸如18个月、120天、90天、60天、45天、30天、21天、14天、7天、5天、96小时、72小时、48小时、36小时、24小时、12小时或更短发生的所关注的事件。从受试者获取体液样品起0小时的危险相当于目前症状的诊断。

[0036] 在优选的危险分级实施方案中，根据受试者中肾前性、肾性或肾后性ARF的一种或多种已知的危险因素的预先存在来选择受试者进行危险分级。例如，正在经历或经历过大血管手术、冠状动脉搭桥或其他心脏手术的受试者；具有预先存在的充血性心力衰竭、子痫前期、子痫、糖尿病、高血压、冠状动脉疾病、蛋白尿、肾功能不全、肾小球过滤低于正常范围、肝硬化、血清肌酸酐高于正常范围或败血症的受试者；或暴露至NSAID、环孢菌素、他克莫司、氨基糖苷类、膦甲酸、乙二醇、血红蛋白、肌红蛋白、异环磷酰胺、重金属、甲氨蝶呤、不透射线的造影剂或链脲佐菌素的受试者都是根据本文所述的方法监测危险的优选受试者。该列表并非意味着进行限制。在该语境下，所谓“预先存在”意指在从受试者获取体液样品时就存在危险因素。在特别优选的实施方案中，根据肾功能损伤、肾功能衰弱或ARF的现有诊断来选择进行危险分级的受试者。

[0037] 在其他实施方案中，本文所述的用于评价肾状态的方法是用于诊断受试者的肾损伤的方法；即，评估受试者是否已罹患肾功能损伤、肾功能衰弱或ARF。在这些实施方案中，将测定结果与是否出现肾状态变化关联。以下是优选的诊断实施方案。

[0038] 在优选的诊断实施方案中，这些方法包括诊断是否出现肾功能损伤，并且将测定结果(例如一种或多种标志物的测量浓度，所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与是否出现此类损伤关联。例如，可以将每个测量浓度与阈值相比较。对于阳向标志物，当测量浓度大于阈值时，对受试者指定出现肾功能损伤的可能性增加(相对于当测量浓度小于阈值时指定的可能性)；或者，当测量浓度小于阈值时，可对受试者指定不出现肾功能损伤的可能性增加(相对于当测量浓度大于阈值时指定的可能性)。对于阴向标志物，当测量浓度小于阈值时，对受试者指定出现肾功能损伤的可能性增加(相对于当测量浓度大于阈值时指定的可能性)；或者，当测量浓度大于阈值时，可对受试者指定不出现肾功能损伤的可能性增加(相对于当测量浓度小于阈值时指定的可能性)。

[0039] 在其他优选的诊断实施方案中，这些方法包括诊断是否出现肾功能衰弱，并且将

测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与是否出现损伤引起的肾功能衰弱关联。例如,可以将每个测量浓度与阈值相比较。对于阳向标志物,当测量浓度大于阈值时,对受试者指定出现损伤引起的肾功能衰弱的可能性增加(相对于当测量浓度小于阈值时指定的可能性);或者,当测量浓度小于阈值时,可对受试者指定不出现损伤引起的肾功能衰弱的可能性增加(相对于当测量浓度大于阈值时指定的可能性)。对于阴向标志物,当测量浓度小于阈值时,对受试者指定出现损伤引起的肾功能衰弱的可能性增加(相对于当测量浓度大于阈值时指定的可能性);或者,当测量浓度大于阈值时,可对受试者指定不出现损伤引起的肾功能衰弱的可能性增加(相对于当测量浓度小于阈值时指定的可能性)。

[0040] 在其他优选的诊断实施方案中,这些方法包括诊断是否出现ARF,并且将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与是否出现损伤引起的ARF关联。例如,可以将每个测量浓度与阈值相比较。对于阳向标志物,当测量浓度大于阈值时,对受试者指定出现ARF的可能性增加(相对于当测量浓度小于阈值时指定的可能性);或者,当测量浓度小于阈值时,可对受试者指定不出现ARF的可能性增加(相对于当测量浓度大于阈值时指定的可能性)。对于阴向标志物,当测量浓度小于阈值时,对受试者指定出现ARF的可能性增加(相对于当测量浓度大于阈值时指定的可能性);或者,当测量浓度大于阈值时,可对受试者指定不出现ARF的可能性增加(相对于当测量浓度小于阈值时指定的可能性)。

[0041] 在其他优选的诊断实施方案中,这些方法包括诊断需进行肾替代疗法的受试者,并且将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与肾替代疗法的需求关联。例如,可以将每个测量浓度与阈值相比较。对于阳向标志物,当测量浓度大于阈值时,对受试者指定出现由损伤引起需求肾替代疗法的可能性增加(相对于当测量浓度小于阈值时指定的可能性);或者,当测量浓度小于阈值时,可对受试者指定不出现由损伤引起需求肾替代疗法的可能性增加(相对于当测量浓度大于阈值时指定的可能性)。对于阴向标志物,当测量浓度小于阈值时,对受试者指定出现由损伤引起需求肾替代疗法的可能性增加(相对于当测量浓度大于阈值时指定的可能性);或者,当测量浓度大于阈值时,可对受试者指定不出现由损伤引起需求肾替代疗法的可能性增加(相对于当测量浓度小于阈值时指定的可能性)。

[0042] 在其他优选的诊断实施方案中,这些方法包括诊断需进行肾移植的受试者,并且将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与肾移植的需求关联。例如,可以将每个测量浓度与阈值相比较。对于阳向标志物,当测量浓度大于阈值时,对受试者指定出现由损伤引起需求肾移植的可能性增加(相对于当测量浓度小于阈值时指定的可能性);或者,当测量浓度小于阈值时,可对受试者指定不出现由损伤引起需求肾移植的可能性增加(相对于当测量浓度大于阈值时指定的可能性)。对于阴向标志物,当测量浓度小于阈值时,对受试者指定出现由损伤引起需求肾移植的可能性增加(相对于当测量浓度大于阈值时指定的可能性);或者,当测量浓度大于阈值时,可对受试者指定不出现由损伤引起需求肾移植的可能性增加(相对于当测量浓度小于阈值时指定的可能性)。

[0043] 在其他实施方案中,本文所述的用于评价肾状态的方法是用于监测受试者肾损伤

的方法;即,评估罹患肾功能损伤、肾功能衰弱或ARF受试者的肾功能改善还是恶化。在这些实施方案中,将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与是否出现肾状态变化关联。以下是优选的监测实施方案。

[0044] 在优选的监测实施方案中,这些方法包括监测罹患肾功能损伤的受试者的肾状态,并且将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与受试者是否出现肾状态变化关联。例如,可以将测量浓度与阈值相比较。对于阳向标志物,当测量浓度大于阈值时,可以对受试者指定肾功能恶化;或者,当测量浓度小于阈值时,可以对受试者指定肾功能改善。对于阴向标志物,当测量浓度小于阈值时,可以对受试者指定肾功能恶化;或者,当测量浓度大于阈值时,可以对受试者指定肾功能改善。

[0045] 在其他优选的监测实施方案中,这些方法包括监测罹患肾功能衰弱的受试者的肾状态,并且将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与受试者是否出现肾状态变化关联。例如,可以将测量浓度与阈值相比较。对于阳向标志物,当测量浓度大于阈值时,可以对受试者指定肾功能恶化;或者,当测量浓度小于阈值时,可以对受试者指定肾功能改善。对于阴向标志物,当测量浓度小于阈值时,可以对受试者指定肾功能恶化;或者,当测量浓度大于阈值时,可以对受试者指定肾功能改善。

[0046] 在其他优选的监测实施方案中,这些方法包括监测罹患急性肾衰竭的受试者的肾状态,并且将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与受试者是否出现肾状态变化关联。例如,可以将测量浓度与阈值相比较。对于阳向标志物,当测量浓度大于阈值时,可以对受试者指定肾功能恶化;或者,当测量浓度小于阈值时,可以对受试者指定肾功能改善。对于阴向标志物,当测量浓度小于阈值时,可以对受试者指定肾功能恶化;或者,当测量浓度大于阈值时,可以对受试者指定肾功能改善。

[0047] 在其他另外优选的监测实施方案中,这些方法包括监测由于肾前性、肾性或肾后性ARF的一种或多种已知危险因素的预先存在而存在肾功能损伤危险的受试者的肾状态,并将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与受试者是否出现肾状态变化关联。例如,可以将测量浓度与阈值相比较。对于阳向标志物,当测量浓度大于阈值时,可以对受试者指定肾功能恶化;或者,当测量浓度小于阈值时,可以对受试者指定肾功能改善。对于阴向标志物,当测量浓度小于阈值时,可以对受试者指定肾功能恶化;或者,当测量浓度大于阈值时,可以对受试者指定肾功能改善。

[0048] 在其他优选的监测实施方案中,这些方法包括监测具有或存在肾功能损伤危险的受试者肾状态的急性肾损伤的日后持续。如本文所用,“日后持续”是指现有的急性肾损伤将延续选自21天、14天、7天、5天、96小时、72小时、48小时、36小时、24小时和12小时的时间段。在某些实施方案中,受试者在获取样品时具有急性肾损伤。这并不意味着暗示,受试者必须在获取样品时具有急性肾损伤,而是受试者在急性肾损伤发作时罹患将会持续的急性肾损伤。在各种实施方案中,将测定结果(例如一种或多种标志物的测量浓度,所述标志物

选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与受试者中急性肾损伤的日后持续关联。例如,可以将测量浓度与阈值相比较。对于阳向标志物,当测量浓度大于阈值时,可以对受试者指定急性肾损伤的日后持续;或者,当测量浓度小于阈值时,可以对受试者指定肾功能的日后改善。对于阴向标志物,当测量浓度小于阈值时,可以对受试者指定急性肾损伤的日后持续;或者,当测量浓度大于阈值时,可以对受试者指定肾功能的日后改善。

[0049] 在其他的实施方案中,本文所述的用于评价肾状态的方法是用于对受试者的肾损伤进行分类的方法;即,确定受试者的肾损伤是肾前性、肾性还是肾后性的;和/或将这些类别进一步细分为子类,诸如急性肾小管损伤、急性肾小球肾炎急性肾小管间质肾炎、急性血管性肾病或浸润性疾病;和/或对受试者指定发展到特定RIFLE阶段的可能性。在这些实施方案中,将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与具体类别和/或子类关联。以下是优选的分类实施方案。

[0050] 在优选的分类实施方案中,这些方法包括确定受试者的肾损伤是肾前性、肾性还是肾后性的;和/或将这些类别进一步细分为子类,诸如急性肾小管损伤、急性肾小球肾炎急性肾小管间质肾炎、急性血管性肾病或浸润性疾病;和/或对受试者指定发展到特定RIFLE阶段的可能性,并且将测定结果(例如一种或多种标志物的测量浓度,所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和/或腱生蛋白)与受试者的损伤分类关联。例如,可以将测量浓度与阈值相比较,并且当测量浓度大于阈值时,指定具体的分类;或者,当测量浓度小于阈值时,可以对受试者指定不同分类。

[0051] 技术人员可采用多种方法得出用于这些方法的所需阈值。例如,可以由正常受试者群通过选择代表在此类正常受试者中测定的肾损伤标志物的第75、第85、第90、第95或第99百分位的浓度确定阈值。或者,阈值可从“患病”的受试者群中确定,例如罹患损伤或易感损伤(例如,发展为ARF或一些其他临床结局,诸如死亡、透析、肾移植等)的受试者群体,确定方式为选择代表在此类受试者中测定的肾损伤标志物的第75、第85、第90、第95或第99百分位的浓度。在另一个替代方案中,阈值可以从相同受试者的肾损伤标志物的先前测量值确定;即,可以使用受试者肾损伤标志物水平的时间变化来对受试者指定危险。

[0052] 然而,上述讨论并不意味着暗示必须将本发明的肾损伤标志物与相应的单个阈值相比较。用于组合测定结果的方法可包括采用多变量逻辑回归、对数线性建模、神经网络分析、n-of-m分析、决策树分析、计算标志物比例等。该列表并非意味着进行限制。在这些方法中,可以处理通过组合单个标志物确定的复合结果,如同其本身为标志物;即,可以如本文针对单个标志物所述的那样对复合结果确定阈值,并将单个患者的复合结果与该阈值相比较。

[0053] 可以利用ROC分析建立特定测试区分两个群的能力。例如,从“第一”亚群和“第二”亚群建立的ROC曲线可用于计算ROC曲线,并且曲线下面积提供了测试质量的度量,所述“第一”亚群的肾状态日后易发生一种或多种变化,所述“第二”亚群则不那么易于发生。优选地,本文所述的测试提供的ROC曲线面积大于0.5,优选为至少0.6,更优选为0.7,还更优选为至少0.8,甚至更优选为至少0.9,并且最优选为至少0.95。

[0054] 在某些方面,可将一种或多种肾损伤标志物或此类标志物的复合物的测量浓度作

为连续变量处理。例如，可将任何具体浓度转换为受试者日后出现肾功能衰弱、出现损伤、分类等的相应概率。在又一个替代方案中，阈值可提供在将受试者群分为“多个群体(bins)”时可接受的特异性和灵敏度水平，诸如分为“第一”亚群(例如，易于发生肾状态的一种或多种日后变化、发生损伤、分类等的亚群)和不那么易于发生上述情况的“第二”亚群。通过一种或多种以下测试精确度的度量选择阈值，以将第一群与第二群分开：比值比大于1，优选为至少约2或更大，或约0.5或更小，更优选为至少约3或更大，或约0.33或更小，还更优选为至少约4或更大，或约0.25或更小，甚至更优选为至少约5或更大，或约0.2或更小，最优选为至少约10或更大，或约0.1或更小；

[0055] 特异性大于0.5，优选为至少约0.6，更优选为至少约0.7，还更优选为至少约0.8，甚至更优选为至少约0.9，最优选为至少约0.95，相应的灵敏度大于0.2，优选为大于约0.3，更优选为大于约0.4，还更优选为至少约0.5，甚至更优选为约0.6，又更优选为大于约0.7，又更优选为大于约0.8，更优选为大于约0.9，最优选为大于约0.95；

[0056] 灵敏度大于0.5，优选为至少约0.6，更优选为至少约0.7，还更优选为至少约0.8，甚至更优选为至少约0.9，最优选为至少约0.95，相应的特异性大于0.2，优选为大于约0.3，更优选为大于约0.4，还更优选为至少约0.5，甚至更优选为约0.6，又更优选为大于约0.7，还更优选为大于约0.8，更优选为大于约0.9，最优选为大于约0.95；

[0057] 至少约75％灵敏度与至少约75％特异性的组合；

[0058] 阳性概率比(以公式灵敏度/(1-特异性)计算)大于1，至少约2，更优选为至少约3，还更优选为至少约5，最优选为至少约10；或

[0059] 阴性概率比(以公式(1-灵敏度)/特异性计算)小于1，小于或等于约0.5，更优选为小于或等于约0.3，最优选为小于或等于约0.1。

[0060] 在任何上述测量语境中，术语“约”是指指定测定值+/-5％。

[0061] 多个阈值也可用于评估受试者的肾状态。例如，可将“第一”亚群(易于发生肾状态的一种或多种日后变化、出现损伤、分类等)和“第二”亚群(不那么易于发生上述情况)合并成单组。然后将该组细分为三个或更多个等份(称为三分位数、四分位数、五分位数等，取决于细分的次数)。根据归属的细分组对受试者指定的比值比。如果考虑三分位，则最低或最高三分位可用作比较其他细分的参考。该参考细分的比值比指定为1。相对于该第一个三分位来指定第二个三分位的比值比。即，与第一个三分位中的某人相比，第二个三分位中的某人日后罹患肾状态的一或种多种变化的可能性大3倍。还相对于该第一个三分位来指定第三个三分位的比值比。

[0062] 在某些实施方案中，测定方法是免疫测定。用于此类测定的抗体特异性地结合所关注的全长肾损伤标志物，并且也可结合一种或多种其“相关”的多肽，该术语将在下文中定义。许多免疫测定形式是本领域技术人员已知的。优选的体液样品选自尿液、血液、血清、唾液、眼泪和血浆。

[0063] 不应将上述方法步骤解释为意指将肾损伤标志物测定结果孤立地用于本文所述的方法中。相反，另外的变量或其他临床标识物可以包括在本文所述的方法中。例如，危险分级、诊断、分类、监测等方法可将测定结果与对受试者测定的一个或多个变量组合，所述变量选自人口统计信息(例如，体重、性别、年龄、种族)、病史(例如，家族病史、手术类型、预先存在的疾病，诸如动脉瘤、充血性心力衰竭、子痫前期、子痫、糖尿病、高血压、冠状动脉疾

病、蛋白尿、肾功能不全或败血症；毒素暴露类型，诸如接触NSAID、环孢菌素、他克莫司、氨基糖苷类、膦甲酸、乙二醇、血红蛋白、肌红蛋白、异环磷酰胺、重金属、甲氨蝶呤、不透射线的造影剂或链脲佐菌素)、临床变量(例如，血压、体温、呼吸率)、危险评分(APACHE评分、PREDICT评分、UA/NSTEMI的TIMI危险评分、Framingham危险评分)、肾小球滤过率、估计的肾小球滤过率、尿产率、血清或血浆肌酸酐浓度、尿肌酸酐浓度、钠排泄分数、尿钠浓度、尿肌酸酐与血清或血浆肌酸酐之比、尿比重、尿渗透压、尿液尿素氮与血浆尿素氮之比、血浆BUN与肌酸酐之比、以尿钠/(尿肌酸酐/血浆肌酸酐)计算的肾衰竭指数、血清或血浆中性粒细胞明胶酶(NGAL)浓度、尿NGAL浓度、血清或血浆胱抑素C浓度、血清或血浆心肌肌钙蛋白浓度、血清或血浆BNP浓度、血清或血浆NTproBNP浓度和血清或血浆proBNP浓度。可与一种或多种肾损伤标志物测定结果组合的其他肾功能的测定如下文和Harrison's Principles of Internal Medicine，第17版，McGraw Hill，New York，第1741-1830页，以及Current Medical Diagnosis&Treatment 2008，第47版，McGraw Hill，New York，第785-815页所述，上述每个文献全文据此以引用的方式并入。

[0064] 当测定超过一种标志物时，单个标志物可在同时获得的样品中进行测定，或者可以从不同时间(例如，较早或较晚)获得的样品进行测定。也可以对相同或不同的体液样品测定单个标志物。例如，可以在血清或血浆样品中测定一种肾损伤标志物，并在尿样中测定另一种肾损伤标志物。此外，指定可能性可以将单个肾损伤标志物测定结果与一个或多个另外的变量的时间变化相组合。

[0065] 在各种相关方面，本发明还涉及用于进行本文所述方法的装置和试剂盒。合适的试剂盒包括足以进行所述肾损伤标志物中的至少一者的测定的试剂以及进行所述阈值比较的说明书。

[0066] 在某些实施方案中，进行此类测定的试剂提供于测定装置中，并且此类测定装置可包括在此类试剂盒中。优选的试剂可包括一种或多种固相抗体，该固相抗体包括检测与固相载体结合的预期生物标志物靶标的抗体。在夹心免疫测定的情况下，此类试剂还可以包括一种或多种以可检测方式标记的抗体，以可检测方式标记的抗体包括检测预期生物标志物靶标的抗体，所述预期生物标志物靶标与可检测的标记结合。可作为测定装置的一部分提供的另外任选要素在下文中描述。

[0067] 可检测的标记可包括自身可检测的分子(例如，荧光部分、电化学标记、ecl(电化学发光)标记、金属螯合物、胶体金属颗粒等)以及可通过产生可检测的反应产物(例如，酶，诸如辣根过氧化物酶、碱性磷酸酶等)或通过使用自身可被检测的特异性结合分子(例如，与第二抗体结合的标记抗体、生物素、地高辛、麦芽糖、寡聚组氨酸、2,4-二硝基苯、苯基砷酸盐、ssDNA、dsDNA等)而被间接检测的分子。

[0068] 可利用本领域熟知的各种光学、声学和电化学方法来进行由信号发生元件产生信号。检测模式的例子包括荧光、放射化学检测、反射、吸收、电流分析法、电导、阻抗、干涉法、椭圆光度法等。在这些方法的某些中，使固相抗体连接至转换器(例如，衍射光栅、电化学传感器等)以产生信号，而在其他方法中，由在空间上与固相抗体分开的转换器(例如，使用激发光源和光检测器的荧光计)产生信号。该列表并非意味着进行限制。也可使用基于抗体的生物传感器来确定分析物的存在或数量，其任选地可不再需要标记的分子。

具体实施方式

[0069] 本发明涉及通过测定一种或多种肾损伤标志物对罹患肾功能损伤、肾功能衰弱和/或急性肾衰竭或具有罹患上述疾病危险的受试者进行诊断、鉴别诊断、危险分级、监测、分类和确定治疗方案的方法及组合物。在各种实施方案中，将一种或多种标志物的测量浓度与受试者的肾状态关联，所述标志物选自卵泡抑素相关蛋白3、Basigin、组织蛋白酶B和腱生蛋白或一种或多种与其相关的标志物，以及任选地本领域已知的一种或多种另外肾损伤标志物。

[0070] 出于本文档的目的，应用以下定义：

[0071] 如本文所用，“肾功能损伤”是肾功能的度量发生急剧的(在14天内、优选7天内、更优选72小时内，还更优选48小时内)可测量的下降。此类损伤可例如通过肾小球滤过率或估计GFR的减小、排尿量的减少、血清肌酸酐的增加、血清胱抑素C的增加、对肾替代疗法的需求等进行鉴定。“肾功能的改善”是肾功能的度量发生急剧的(在14天内，优选7天内，更优选72小时内，还更优选48小时内)可测量的升高。用于测量和/或估计GFR的优选方法在下文中描述。

[0072] 如本文所用，“肾功能衰弱”是通过大于或等于0.1mg/dL(≥8.8μmol/L)的血清肌酸酐的绝对增加、大于或等于20％(基线的1.2倍)的血清肌酸酐的百分比增加或排尿量的减少(文献记载的少尿为小于0.5ml/kg/小时)鉴定的肾功能的急剧(在14天内，优选7天内，更优选72小时内，还更优选48小时内)下降。

[0073] 如本文所用，“急性肾衰竭”或“ARF”是通过大于或等于0.3mg/dl(≥26.4μmol/l)的血清肌酸酐的绝对增加、大于或等于50％(基线的1.5倍)的血清肌酸酐的百分比增加或排尿量的减少(文献记载的少尿为小于0.5ml/kg/小时达至少6小时)鉴定的肾功能的急剧(在14天内，优选7天内，更优选72小时内，还更优选48小时内)下降。该术语与“急性肾损伤”或“AKI”同义。

[0074] 就这一点而言，技术人员将会理解，从免疫测定获得的信号是在一种或多种抗体与靶标生物分子(即，分析物)和包含与抗体结合的必要表位的多肽之间形成复合物的直接结果。虽然此类测定可检测全长生物标志物，并且测定结果可表示为所关注生物标志物的浓度，但来自测定的信号实际上是样品中存在的所有此类“免疫反应性”多肽的结果。也可通过除免疫测定之外的方法来测定生物标志物的表达，包括蛋白质测量(例如，斑点印迹法、蛋白质印迹法、色谱法、质谱法等)和核酸测量(mRNA量化)。该列表并非意味着进行限制。

[0075] 如本文所用，术语“卵泡抑素相关蛋白3”是指衍生自卵泡抑素相关蛋白3前体的生物样品中存在的一种或多种多肽(人前体Swiss-Prot登录号095633(SEQ ID NO:1))：

[0076]
```
          10         20         30         40         50
MRPGAPGPLW PLPWGALAWA VGFVSSMGSG NPAPGGVCWL QQGQEATCSL
          60         70         80         90        100
VLQTDVTRAE CCASGNIDTA WSNLTHPGNK INLLGFLGLV HCLPCKDSCD
         110        120        130        140        150
GVECGPGKAC RMLGGRPRCE CAPDCSGLPA RLQVCGSDGA TYRDECELRA
         160        170        180        190        200
ARCRGHPDLS VMYRGRCRKS CEHVVCPRPQ SCVVDQTGSA HCVVCRAAPC
         210        220        230        240        250
PVPSSPGQEL CGNNNVTYIS SCHMRQATCF LGRSIGVRHA GSCAGTPEEP
         260
PGGESAEEEE NFV
```

[0077] 在卵泡抑素相关蛋白3中已鉴定以下结构域：

残基	长度	结构域 ID
1-26	26	信号序列

[0078]

27-263	237	卵泡抑素相关蛋白 3
1-26		卵泡抑素相关蛋白 3 同种型 2 中缺乏

[0079] 如本文所用，术语“组织蛋白酶B”是指衍生自组织蛋白酶B前体的生物样品中存在的一种或多种多肽(人前体Swiss-Prot登录号P07858(SEQ ID NO:2))：

[0080]
```
          10         20         30         40         50
MWQLWASLCC LLVLANARSR PSFHPLSDEL VNYVNKRNTT WQAGHNFYNV
          60         70         80         90        100
DMSYLKRLCG TFLGGPKPPQ RVMFTEDLKL PASFDAREQW PQCPTIKEIR
         110        120        130        140        150
DQGSCGSCWA FGAVEAISDR ICIHTNAHVS VEVSAEDLLT CCGSMCGDGC
         160        170        180        190        200
NGGYPAEAWN FWTRKGLVSG GLYESHVGCR PYSIPPCEHH VNGSRPPCTG
         210        220        230        240        250
EGDTPKCSKI CEPGYSPTYK QDKHYGYNSY SVSNSEKDIM AEIYKNGPVE
         260        270        280        290        300
GAFSVYSDFL LYKSGVYQHV TGEMMGGHAI RILGWGVENG TPYWLVANSW
         310        320        330
NTDWGDNGFF KILRGQDHCG IESEVVAGIP RTDQYWEKI
```

[0081] 在组织蛋白酶B中已鉴定以下结构域：

残基	长度	结构域ID
1-17	17	信号序列
18-79	62	活化肽
80-333	254	组织蛋白酶B
80-126-	47	组织蛋白酶B轻链
129-333	205	组织蛋白酶B重链
334-339	6	前肽

[0082]

[0083] 如本文所用,术语“腱生蛋白”是指衍生自腱生蛋白前体的生物样品中存在的一种或多种多肽(人前体Swiss-Prot登录号P24821(SEQ ID NO:3)):

[0084]

```
          10         20         30         40         50
MGAMTQLLAG VFLAFLALAT EGGVLKKVIR HKRQSGVNAT LPEENQPVVF
          60         70         80         90        100
NHVYNIKLPV GSQCSVDLES ASGEKDLAPP SEPSESFQEH TVDGENQIVF
         110        120        130        140        150
THRTNIPRRA CGCAAAPDVK ELLSRLEELE NLVSSLREQC TAGAGCCLQP
         160        170        180        190        200
ATGRLDTRPF CSGRGNFSTE GCGCVCEPGW KGPNCSEPEC PGNCHLRGRC
         210        220        230        240        250
IDGQCICDDG FTGEDCSQLA CPSDCNDQGK CVNGVCICFE GYAGADCSRE
```

```
          260        270        280        290        300
ICPVPCSEEH GICVDGLCVC HDGFAGDDCN KPLCLNNCYN RGRCVENECV
          310        320        330        340        350
CDEGFTGEDC SELICPNDCF DRGRCINGTC YCEEGFTGED CGKPTCPHAC
          360        370        380        390        400
HTQGRCEEGQ CVCDEGFAGV DCSEKRCPAD CHNRGRCVDG RCECDDGFTG
          410        420        430        440        450
ADCGELKCPN GCSGHGRCVN GQCVCDEGYT GEDCSQLRCP NDCHSRGRCV
          460        470        480        490        500
EGKCVCEQGF KGYDCSDMSC PNDCHQHGRC VNGMCVCDDG YTGEDCRDRQ
          510        520        530        540        550
CPRDCSNRGL CVDGQCVCED GFTGPDCAEL SCPNDCHGQG RCVNGQCVCH
          560        570        580        590        600
EGFMGKDCKE QRCPSDCHGQ GRCVDGQCIC HEGFIGLDCG QHSCPSDCNN
          610        620        630        640        650
LGQCVSGRCI CNEGYSGEDC SEVSPPKDLV VIEVTEETVN LANDNEMRVT
          660        670        680        690        700
EYLVVYTPTH EGGLEMQFRV PGDQTSTIIQ ELEPGVEYFI RVFAILENKK
          710        720        730        740        750
SIPVSARVAT YLPAPEGLKF KSIKETSVEV EWDPLDIAFE TWEIIFRNMN
          760        770        780        790        800
KEDEGEITKS LRRPETSYRQ TGLAPGQEYE ISLHIVKNNT RGPGLKRVTT
          810        820        830        840        850
TRLDAPSQIE VKDVTDTTAL ITWFKPLAEI DGIELTYGIK DVPGDRTTID
          860        870        880        890        900
[0085] LTEDENQYSI GNLKPDTEYE VSLISRRGDM SSNPAKETFT TGLDAPRNLR
          910        920        930        940        950
RVSQTDNSIT LEWRNGKAAI DSYRIKYAPI SGGDHAEVDV PKSQQATTKT
          960        970        980        990       1000
TLIGLRPGTE YGIGVSAVKE DKESNPATIN AATELDTPKD LQVSETAETS
         1010       1020       1030       1040       1050
LTLLWKTPLA KFDRYRLNYS LPTGQWVGVQ LPRNTTSYVL RGLEPGQEYN
         1060       1070       1080       1090       1100
VLLTAEKGRH KSKPARVKAS TEQAPELENL TVTEVGWDGL RLNWTAADQA
         1110       1120       1130       1140       1150
YEHFIIQVQE ANKVEAARNL TVPGSLRAVD IPGLKAATPY TVSIYGVIQG
         1160       1170       1180       1190       1200
YRTPVLSAEA SIGETPNLGE VVVAEVGWDA LKLNWTAPEG AYEYFFIQVQ
         1210       1220       1230       1240       1250
EADTVEAAQN LIVPGGLRST DLPGLKAATH YTITIRGVTQ DFSTTPLSVE
         1260       1270       1280       1290       1300
VLTEEVPDMG NLTVTEVSWD ALRLNWTTPD GTYDQFTIQV QEADQVEEAH
         1310       1320       1330       1340       1350
NLTVPGSLRS MEIPGLRAGT PYTVTLHGEV RGHSTRPLAV EVVTEDLPQL
         1360       1370       1380       1390       1400
GDLAVSEVGW DGLRLNWTAA DNAYEHFVIQ VQEVNKVEAA QNLTLPGSLR
         1410       1420       1430       1440       1450
AVDIPGLEAA TPYRVSIYGV IRGYRTPVLS AEASTAKEPE IGNLNVSDIT
         1460       1470       1480       1490       1500
PESFNLSWMA TDGIFETFTI EIIDSNRLLE TVEYNISGAE RTAHISGLPP
         1510       1520       1530       1540       1550
```

```
STDFIVYLSG LAPSIRTKTI SATATTEALP LLENLTISDI NPYGFTVSWM
      1560       1570       1580       1590       1600
ASENAFDSFL VTVVDSGKLL DPQEFTLSGT QRKLELRGLI TGIGYEVMVS
      1610       1620       1630       1640       1650
GFTQQHQTKP LRAEIVTEAE PEVDNLLVSD ATPDGFRLSW TADEGVFDNF
      1660       1670       1680       1690       1700
VLKIRDTKKQ SEPLEITLLA PERTRDITGL REATEYEIEL YGISKGRRSQ
      1710       1720       1730       1740       1750
TVSAIATTAM GSPKEVIFSD IIENSATVSW RAPTAQVESF RITYVPITGG
      1760       1770       1780       1790       1800
TPSMVTVDGT KTQTRLVKLI PGVEYLVSII AMKGFEESEP VSGSFTTALD
      1810       1820       1830       1840       1850
GPSGLVTANI TDSEALARWQ PAIATVDSYV ISYTGEKVPE ITRTVSGNTV
      1860       1870       1880       1890       1900
EYALTDLEPA TEYTLRIFAE KGPQKSSTIT AKFTTDLDSP RDLTATEVQS
      1910       1920       1930       1940       1950
ETALLTWRPP RASVTGYLLV YESVDGTVKE VIVGPDTTSY SLADLSPSTH
      1960       1970       1980       1990       2000
YTAKIQALNG PLRSNMIQTI FTTIGLLYPF PKDCSQAMLN GDTTSGLYTI
      2010       2020       2030       2040       2050
YLNGDKAEAL EVFCDMTSDG GGWIVFLRRK NGRENFYQNW KAYAAGFGDR
      2060       2070       2080       2090       2100
REEFWLGLDN LNKITAQGQY ELRVDLRDHG ETAFAVYDKF SVGDAKTRYK
      2110       2120       2130       2140       2150
LKVEGYSGTA GDSMAYHNGR SFSTFDKDTD SAITNCALSY KGAFWYRNCH
      2160       2170       2180       2190       2200
RVNLMGRYGD NNHSQGVNWF HWKGHEHSIQ FAEMKLRPSN FRNLEGRRKR

A
```

[0086]

[0087] 在腱生蛋白中已鉴定以下结构域：

残基	长度	结构域 ID
1-22	22	信号序列
23-2201	2179	腱生蛋白

[0088]

1072-1435	腱生蛋白同种型 2 中缺乏
1527-1617	腱生蛋白同种型 2 中缺乏
1072-1435	腱生蛋白同种型 3 中缺乏

1527-1617 腱生蛋白同种型 4 中缺乏

[0089] 1072-1617 腱生蛋白同种型 5 中缺乏

1072-1708 腱生蛋白同种型 6 中缺乏

[0090] 如本文所用，术语“Basigin”是指衍生自Basigin前体的生物样品中存在的一种或多种多肽(人前体Swiss-Prot登录号P35613(SEQ ID NO:4))：

[0091]
```
          10         20         30         40         50
MAAALFVLLG FALLGTHGAS GAAGFVQAPL SQQRWVGGSV ELHCEAVGSP
          60         70         80         90        100
VPEIQWWFEG QGPNDTCSQL WDGARLDRVH IHATYRQHAA STISIDTLVE
         110        120        130        140        150
EDTGTYECRA SNDPDRNHLT RAPRVKWVRA QAVVLVLEPG TVFTTVEDLG
         160        170        180        190        200
SKILLTCSLN DSATEVTGHR WLKGGVVLKE DALPGQKTEF KVDSDDQWGE
         210        220        230        240        250
YSCVFLPEPM GTANIQLHGP PRVKAVKSSE HINEGETAML VCKSESVPPV
         260        270        280        290        300
TDWAWYKITD SEDKALMNGS ESRFFVSSSQ GRSELHIENL NMEADPGQYR
         310        320        330        340        350
CNGTSSKGSD QAIITLRVRS HLAALWPFLG IVAEVLVLVT IIFIYEKRRK
         360        370        380
PEDVLDDDDA GSAPLKSSGQ HQNDKGKNVR QRNSS
```

[0092] 在Basigin中已鉴定以下结构域：

残基	长度	结构域 ID
1-21	21	信号序列
22-385	364	Basigin

[0093]

24-139	Basigin 同种型 2 中缺乏
1-209	Basigin 同种型 3 中缺乏
12-191	Basigin 同种型 4 中缺乏

[0094]

1-11 →Basigin 同种型 4 中的 MKQSDASPQER (SEQ ID NO:5)

[0095] 如本文所用，术语“将信号与分析物的存在或数量关联”反映的是这种理解。通常通过使用由已知浓度的所关注的分析物计算的标准曲线将测定信号与分析物的存在或量

关联。如该术语在本文中所用，如果测定可产生指示生理相关浓度的分析物的存在或量的可检测信号，则该测定“被设定为检测”分析物。因为抗体表位有大约8个氨基酸，所以被设定为检测所关注的标志物的免疫测定也检测与标志物序列相关的多肽，只要这些多肽含有结合至测定所用的一种或多种抗体必需的表位。

[0096] 如本文所用，关于生物标志物的术语“相关标志物”(诸如本文所述的肾损伤标志物之一)是指特定标志物或其生物合成母体的一种或多种片段、变体等，其可作为标志物本身的替代物或单独的生物标志物进行检测。该术语也指衍生自生物标志物前体与另外的物质(诸如结合蛋白、受体、肝素、脂质、糖等)复合的生物样品中存在的一种或多种多肽。

[0097] 如本文所用的术语“阳向”标志物是指相对于未罹患疾病或病症的受试者来说，在罹患该疾病或病症的受试者中确定为升高的标志物。如本文所用的术语“阴向”标志物是指相对于未罹患疾病或病症的受试者来说，在罹患该疾病或病症的受试者中确定为降低的标志物。

[0098] 如本文所用，术语“受试者”指人或非人生物体。因此，本文所述的方法和组合物适用于人和兽医疾病。此外，虽然受试者优选地为活生物体，但本文所述的发明也可用于死后分析。优选的受试者是人，最优选的是“患者”，本文中所用的“患者”是指接受疾病或病症的医疗护理的活人。这包括未患有所确定的疾病而正进行病理体征研究的人。

[0099] 优选地，测定样品中的分析物。这种样品可得自受试者，或可得自旨在提供给受试者的生物材料。例如，样品可得自正在评价可能移植到受试者的肾，并且分析物测定用于评价肾的预先存在的损害。优选的样品是体液样品。

[0100] 如本文所用的术语“体液样品”是指出于诊断、预后、分类或评价所关注的受试者(诸如患者或移植供体)的目的而获取的体液样品。在某些实施方案中，此类样品可出于确定进行中的病症的后果或治疗方案对病症的影响的目的而获取。优选的体液样品包括血液、血清、血浆、脑脊液、尿液、唾液、痰和胸腔积液。此外，本领域的技术人员将意识到，某些体液样品在分馏或纯化步骤后(例如，将全血分离为血清或血浆组分)更易于分析。

[0101] 如本文所用，术语“诊断”是指技术人员可估计和/或确定患者是否罹患给定疾病或病症的机率(“可能性”)的方法。就本发明而言，“诊断”包括使用对本发明的肾损伤标志物的测定的结果，最优选为免疫测定的结果，任选地连同其他临床特征一起，以实现由此获取和测定样品的受试者的急性肾损伤或ARF的诊断(即，是否出现)。此类诊断得以“确定”并不意味着诊断是100％准确的。许多生物标志物可指示多种病症。熟练的临床医生不使用产生信息真空的生物标志物，而是将测试结果与其他临床标识物一起用于达成诊断。因此，在预定诊断阈值的一侧上的测定生物标志物水平，相对于在预定诊断阈值的另一侧上的测定水平，表示受试者出现疾病的可能性更大。

[0102] 类似地，预后危险表示出现给定过程或后果的概率(“可能性”)。预后指标水平或预后指标水平的变化(其又与发病概率的增加有关，例如肾功能恶化、日后ARF或死亡))被认为是“指示”患者出现不利后果的“可能性增加”。

[0103] 标志物测定

[0104] 通常，免疫测定涉及使含有或怀疑含有所关注的生物标志物的样品与至少一种特异性结合生物标志物的抗体接触。然后产生指示通过样品中的多肽与抗体结合所形成的复合物的存在或量的信号。然后将信号与样品中生物标志物的存在或量关联。检测和分析生

物标志物的多种方法和装置是技术人员熟知的。参见例如美国专利6,143,576、6,113,855、6,019,944、5,985,579、5,947,124、5,939,272、5,922,615、5,885,527、5,851,776、5,824,799、5,679,526、5,525,524和5,480,792以及The Immunoassay Handbook,David Wild编,Stockton Press,New York,1994,上述每个文献全文包括所有的表格、附图和权利要求据此以引用的方式并入。

[0105] 本领域中已知的测定装置和方法可在各种夹心、竞争或非竞争性测定形式中利用标记的分子产生与所关注的生物标志物的存在或量相关的信号。合适的测定形式还包括色谱法、质谱法和蛋白质“印迹”法。另外,可使用某些方法和装置(诸如生物传感器和光学免疫测定)来确定分析物的存在或量,无需标记的分子。参见例如美国专利5,631,171和5,955,377,每个文献全文包括所有的表格、附图和权利要求据此以引用的方式并入。本领域技术人员还认识到,自动仪表装置(包括但不限于Beckman ACCESS®、Abbott AXSYM®、Roche ELECSYS®、Dade BehringSTRATUS®系统)属于能够进行免疫测定的免疫测定分析仪。但可利用任何合适的免疫测定,例如酶联免疫测定(ELISA)、放射免疫测定(RIA)、竞争结合测定等等。

[0106] 可将抗体或其他多肽固定在多种固相载体上以用于测定。可用于固定特异性结合成员的固相包括在固相结合测定中开发和/或用作固相的那些。合适固相的例子包括膜过滤器、基于纤维素的纸材、珠粒(包括聚合、乳胶和顺磁性颗粒)、玻璃、硅片、微粒、纳米粒子、TentaGel、AgroGel、PEGA凝胶、SPOCC凝胶和多孔板。可以通过将抗体或多种抗体以阵列的形式涂覆在固相载体上制备测定条。然后可将该测定条浸入试样中,然后通过洗涤和检测步骤快速处理,以产生可测量的信号,如染色斑点。抗体或其他多肽可通过直接缀合至测定装置表面或通过间接结合而结合至测定装置的特定区域。在后一种情况的例子中,可将抗体或其他多肽固定在颗粒或其他固相载体上,并且该固相载体固定至装置表面。

[0107] 生物测定需要检测方法,并且量化结果的最常用的方法之一是将可检测的标记物缀合至对所研究的生物系统中的一种组分具有亲和力的蛋白质或核酸。可检测的标记物可包括自身可检测的分子(例如,荧光部分、电化学标记、金属螯合物等)以及可通过产生可检测的反应产物(例如,酶,诸如辣根过氧化物酶、碱性磷酸酶等)或通过自身可检测的特异性结合分子(例如,生物素、地高辛、麦芽糖、寡聚组氨酸、2,4-二硝基苯、苯基砷酸盐、ssDNA、dsDNA等)而被间接检测的分子。

[0108] 固相和可检测的标记缀合物的制备通常包括使用化学交联剂。交联试剂含有至少两个反应性基团,并且通常分为同官能交联剂(含有相同的反应性基团)和异官能交联剂(含有不相同的反应性基团)。通过胺、巯基偶合或非特异性反应的同双官能交联剂可从多个商业来源获得。马来酰亚胺、烷基和芳基卤化物、α-卤代酰基和吡啶基二硫化物是硫醇反应性基团。马来酰亚胺、烷基和芳基卤化物和α-卤代酰基与巯基反应形成硫醚键,而吡啶基二硫化物与巯基反应生成混合二硫化物。吡啶基二硫化物产物是可裂解的。亚氨酸酯也非常适用于蛋白质-蛋白质交联。许多异双官能交联剂(各自结合了用于成功缀合的不同属性)可商购获得。

[0109] 在某些方面,本发明提供用于分析所述肾损伤标志物的试剂盒。该试剂盒包含用于分析至少一种试样的试剂,所述试剂包括至少一种肾损伤标志物的抗体。该试剂盒还可包括进行本文所述的一种或多种诊断和/或预后关联的装置和说明书。优选的试剂盒将包

括用于对分析物进行夹心测定的抗体对，或对分析物进行竞争性测定的标记的物质。优选地，抗体对包含与固相缀合的第一抗体和与可检测的标记缀合的第二抗体，其中第一和第二抗体各自结合肾损伤标志物。最优选地，每个抗体是单克隆抗体。使用试剂盒和进行关联的说明可以是标签的形式，它是指在制造、运输、销售或使用期间的任何时间附属于或者随附于试剂盒的任何书面或记录材料。例如，术语标签涵盖了广告传单和小册子、包装材料、说明书、录音带或录像带、计算机磁盘以及直接印在试剂盒上的字迹。

[0110] 抗体

[0111] 如本文所用，术语“抗体”是指衍生自、仿效或基本上由免疫球蛋白基因或多个免疫球蛋白基因或其片段编码的肽或多肽，它能够特异性结合抗原或表位。参见例如Fundamental Immunology，第3版，W.E.Paul编，Raven Press，N.Y.(1993)；Wilson(1994)；J.Immunol.Methods 175:267-273；Yarmush(1992)J.Biochem.Biophys.Methods 25:85-97。术语抗体包括抗原结合部分，即保留结合抗原能力的“抗原结合位点”(例如，片段、子序列、互补决定区(CDR))，包括(i)Fab片段，即由VL、VH、CL和CH1结构域组成的单价片段；(ii)F(ab')2片段，即包含在铰链区通过二硫桥连接的两个Fab片段的二价片段；(iii)由VH和CH1结构域组成的Fd片段；(iv)由单臂抗体的VL和VH域组成的Fv片段；(v)dAb片段(Ward等人，(1989)Nature 341:544-546)，它由VH域组成；以及(vi)分离的互补决定区(CDR)。单链抗体也以引用的方式包括在术语“抗体”中。

[0112] 本文所述的免疫测定中所用的抗体优先地与本发明的肾损伤标志物特异性结合。术语“特异性结合”并非旨在表明抗体排他性地结合其预期的靶标，因为如上所述，抗体与展示抗体结合表位的任何多肽结合。相反，如果抗体对其预期的靶标的亲和力，与其对不展示适当表位的非靶标分子的亲和力相比大约5倍，则抗体“特异性结合”。优选地，抗体对靶标分子的亲和力比其对非靶标分子亲和力大至少约5倍，优选为10倍，更优选为25倍，甚至更优选为50倍，最优选为100倍或更多。在优选的实施方案中，优选的抗体的结合亲和力为至少约$10^{7}M^{-1}$，优选在约$10^{8}M^{-1}$至约$10^{9}M^{-1}$之间，在约$10^{9}M^{-1}$至约$10^{10}M^{-1}$之间，或在约$10^{10}M^{-1}$至约$10^{12}M^{-1}$之间。

[0113] 根据$K_d=k_{off}/k_{on}$计算亲和力(k_{off}是解离速率常数，K_{on}是缔合速率常数，K_d是平衡常数)。可通过测量不同浓度(c)下标记的配体的结合分数(r)来确定平衡时的亲和力。利用Scatchard公式：r/c=K(n-r)对数据进行作图：其中r=平衡时结合配体的摩尔数/受体的摩尔数；c=平衡时游离配体浓度；K=平衡缔合常数；n=配体结合位点数/受体分子。通过作图分析，将r/c绘于Y-轴上，将r绘于X-轴上，由此制得Scatchard图。通过Scatchard分析测定抗体亲和力是本领域熟知的。参见例如van Erp等人，J.Immunoassay 12:425-43，1991；Nelson和Griswold，Comput.Methods Programs Biomed.27:65-8，1988。

[0114] 术语“表位”是指能够与抗体特异性结合的抗原决定簇。表位通常由分子的化学活性表面基团组成，诸如氨基酸或糖侧链，并且通常具有特定的三维结构特征以及特定的电荷特征。构象和非构象表位的区别在于在存在变性溶剂的情况下与前者而非后者的结合丧失。

[0115] 许多出版物讨论了利用噬菌体展示技术制备和筛选用于与选定分析物结合的多肽库。参见例如Cwirla等人，Proc.Natl.Acad.Sci.USA 87，6378-82，1990；Devlin等人，Science 249，404-6，1990，Scott和Smith，Science 249，386-88，1990；以及Ladner等人，美

国专利No.5,571,698。噬菌体展示法的基本概念是建立编码待筛选多肽的DNA与多肽之间的物理关联。这种物理关联由噬菌体颗粒提供，该噬菌体颗粒将多肽显示为包围编码多肽的噬菌体基因组的衣壳的一部分。多肽与其基因物质间的物理关联的建立允许同时进行大量带有不同多肽的噬菌体的群集筛选。展示对靶标具有亲和力的多肽的噬菌体与靶标结合，并且这些噬菌体通过对靶标的亲和力的筛选得以富集。由这些噬菌体展示的多肽的身份可由其各自的基因组来确定。采用这些方法，可通过常规的手段大量合成鉴定为对所需靶标具有结合亲和力的多肽。参见例如美国专利No.6,057,098，该专利全文包括所有表格、附图和权利要求据此并入本文。

[0116] 然后可以对由这些方法产生的抗体进行选择，其方式是首先筛选对所关注的纯化多肽的亲和力和特异性，并且如有需要，将抗体的亲和力和特异性的结果与期望从结合排除的多肽相比较。筛选程序可涉及将纯化的多肽固定在微量滴定板的单独孔中。然后将含有潜在抗体或抗体组的溶液置于各自的微量滴定孔中并孵育约30分钟至2小时。然后洗涤微量滴定孔并将标记的二抗(例如，如果产生的抗体是小鼠抗体，则为与碱性磷酸酶缀合的抗小鼠抗体)添加至孔中并孵育约30分钟，然后洗涤。将底物加入孔中，在固定多肽的抗体存在之处出现颜色反应。

[0117] 然后，在选定的测定设计中可以进一步分析这样鉴定的抗体的亲和力和特异性。在针对靶标蛋白的免疫测定的开发中，将纯化的靶标蛋白用作标准物来判断使用已选定抗体的免疫测定的灵敏度和特异性。因为各种抗体的结合亲和力可能会有所不同；某些抗体对(例如，在夹心测定中)可能会在空间上彼此干扰等，所以抗体的测定性能可为比抗体的绝对亲和力和特异性更重要的度量。

[0118] 测定关联

[0119] 如本文所用，关于生物标志物使用的术语“关联”是指将患者的生物标志物的存在或量与已知罹患或已知有罹患给定病症危险的人或已知不患有给定病症的人的生物标志物的存在或量进行比较。通常，采取的形式是将生物标志物浓度形式的测定结果与选择表示疾病是否发生或一些日后结局的可能性的预定阈值进行比较。

[0120] 选择诊断阈值涉及(除别的以外)考虑疾病的概率、不同测试阈值下真假诊断的分布以及基于诊断对治疗(或治疗失败)结局的估计。例如，当考虑施用高度有效且危险水平低的特定疗法时，需要进行的测试很少，因为临床医师可接受很大的诊断不确定性。在另一个方面，在治疗选项有效性不高且危险较大的情况下，临床医师往往需要更高程度的诊断确定性。因此，选择诊断阈值时涉及成本/效益分析。

[0121] 可以多种方式确定合适的阈值。例如，利用心肌肌钙蛋白诊断急性心肌梗塞的一个建议性诊断阈值是可见于正常群体中的浓度的第97.5百分位。另一个方法可为查看相同患者的系列样品，其中先前的“基线”结果用于监测生物标志物水平的时间变化。

[0122] 也可采用群体研究来选择判定阈值。源自二战期间开发用于雷达图像分析和ROC分析的信号检测理论领域的接收器操作特征(Reciever Operating Characteristic，“ROC”)常用于选择能最好地区分“患病”亚群与“未患病”亚群的阈值。当人测试为阳性但实际上未患病时，这种情况下出现的是假阳性。在另一个方面，当人测试为阴性时，表明其是健康的，而实际上却是患病的，则出现的是假阴性。为了绘制ROC曲线，随着判定阈值的连续变化，确定真阳性率(TPR)和假阳性率(FPR)。因为TPR相当于灵敏度，FPR等于1-特异性，所

以有时ROC图称为灵敏度与(1-特异性)的关系图。理想的测试具有的ROC曲线下面积为1.0;随机测试具有的面积为0.5。选择阈值以提供可接受的特异性和灵敏度水平。

[0123] 在该语境下,“患病”意指具有一种特征的群体(存在疾病或病症或出现一些结局),并且“未患病”意指缺乏该特征的群体。虽然单个判定阈值是此类方法的最简单应用,但可使用多个判定阈值。例如,小于第一阈值,可以相对高的置信度制定不存在疾病,并且大于第二阈值,也可以相对高的置信度指定存在疾病。在两个阈值之间可视为不确定。这实质上仅是示例性的。

[0124] 除阈值比较外,用于将测定结果与患者分类(是否出现疾病、结局的可能性等)关联的其他方法包括决策树、规则集、贝叶斯(Bayesian)方法和神经网络方法。这些方法可产生代表受试者归属多个分类中的一个分类的程度的概率值。

[0125] 测试精度的度量可以如Fischer等人,Intensive Care Med.29:1043-51,2003所述获得,并且用于确定给定生物标志物的有效性。这些度量包括灵敏度和特异性、预测值、概率比、诊断比值比和ROC曲线面积。ROC图的曲线下面积(“AUC”)等于分类器分级随机选择的阳性例高于随机选择的阴性例的概率。ROC曲线下面积可认为等同于Mann-Whitney U测试(如果所述组是连续数据组,则其测试在所考虑的两组中得到的分数之间的中值差)或等同于Wilcoxon分级测试。

[0126] 如上文所讨论,合适的测试可显示这些不同度量的一个或多个以下结果:特异性大于0.5,优选为至少0.6,更优选为至少0.7,还更优选为至少0.8,甚至更优选为至少0.9,并且最优选为至少0.95,相应的灵敏度大于0.2,优选为大于0.3,更优选为大于0.4,还更优选为至少0.5,甚至更优选为0.6,再更优选为大于0.7,还更优选为大于0.8,更优选为大于0.9,并且最优选为大于0.95;灵敏度大于0.5,优选为至少0.6,更优选为至少0.7,还更优选为至少0.8,甚至更优选为至少0.9,最优选为至少0.95,相应的特异性大于0.2,优选为大于0.3,更优选为大于0.4,还更优选为至少0.5,甚至更优选为0.6,再更优选为大于0.7,还更优选为大于0.8,更优选为大于0.9,并且最优选为大于0.95;至少75%灵敏度与至少75%特异性组合;ROC曲线面积大于0.5,优选为至少0.6,更优选为0.7,还更优选为至少0.8,甚至更优选为至少0.9,并且最优选为至少0.95;比值比不等于1,优选为至少约2或更大或约0.5或更小,更优选为至少约3或更大或约0.33或更小,还更优选为至少约4或更大或约0.25或更小,甚至更优选为至少约5或更大或约0.2或更小,并且最优选为至少约10或更大或约0.1或更小;阳性概率比(以公式灵敏度/(1-特异性)计算)大于1,至少为2,更优选为至少3,还更优选为至少5,最优选为至少10;以及或阴性概率比(以公式(1-灵敏度)/特异性计算)小于1,小于或等于0.5,更优选为小于或等于0.3,并且最优选为小于或等于0.1。

[0127] 另外的临床标识物可与本发明的肾损伤标志物测定结果相组合。这些包括与肾状态相关的其他生物标志物。例子包括如下(列举的是常见生物标志物名称,接着是该生物标志物或其母体的Swiss-Prot登录号):肌动蛋白(P68133);腺苷脱氨酶结合蛋白(DPP4,P27487);α-1-酸糖蛋白1(P02763);α-1-微球蛋白(P02760);白蛋白(P02768);血管紧张素原酶(肾素,P00797);巢蛋白-1(P07355);β-葡糖醛酸酶(P08236);B-2-微球蛋白(P61769);β-半乳糖苷酶(P16278);BMP-7(P18075);脑利钠肽(proBNP、BNP-32、NTproBNP;P16860);钙结合蛋白β(S100-β,P04271);碳酸酐酶9(Q16790);酪蛋白激酶2(P68400);簇蛋白(P10909);补体C3(P01024);富含半胱氨酸的蛋白(CYR61,O00622);细胞色素C(P99999);表

皮生长因子(EGF,P01133);内皮素-1(P05305);外排体胎球蛋白-A(P02765);心脏脂肪酸结合蛋白(FABP3,P05413);肝脏脂肪酸结合蛋白(P07148);铁蛋白(轻链,P02792;重链,P02794);果糖-1,6-二磷酸酶(P09467);GRO-α(CXCL1,P09341);生长激素(P01241);肝细胞生长因子(P14210);胰岛素样生长因子I(P05019);免疫球蛋白G;免疫球蛋白轻链(k和λ);干扰素γ(P01308);溶菌酶(P61626);白介素-1α(P01583);白介素-2(P60568);白介素-4(P05112);白介素-9(P15248);白介素-12p40(P29460);白介素-13(P35225);白介素-16(Q14005);L1细胞粘附分子(P32004);乳酸脱氢酶(P00338);亮氨酸氨基肽酶(P28838);甲基多巴A-α亚基(Q16819);甲基多巴A-β亚基(Q16820);中期因子(P21741);MIP2-α(CXCL2,P19875);MMP-2(P08253);MMP-9(P14780);神经生长因子-1(O95631);中性内肽酶(P08473);骨桥蛋白(O14788);肾乳头抗原1(RPA1);肾乳头抗原2(RPA2);视黄醇结合蛋白(P09455);核糖核酸酶;S100钙结合蛋白A6(P06703);血清淀粉样蛋白P成分(P02743);钠/氢离子交换剂同种型(NHE3,P48764);精脒/精胺N1-乙酰转移酶(P21673);TGF-β1(P01137);转铁蛋白(P02787);三叶因子3(TFF3,Q07654);Toll样蛋白4(O00206);总蛋白;肾小管间质肾炎抗原(Q9UJW2);尿调蛋白(Tamm-Horsfall蛋白,P07911)。

[0128] 出于危险分级的目的,脂联素(Q15848);碱性磷酸酶(P05186);氨基肽酶N(P15144);钙结合蛋白D28k(P05937);胱抑素C(P01034);8个亚基的F1FO ATP酶(P03928);γ-谷氨酰转移酶(P19440);GSTa(α-谷胱甘肽-S-转移酶,P08263);GSTpi(谷胱甘肽-S-转移酶P;GST类别-pi;P09211);IGFBP-1(P08833);IGFBP-2(P18065);IGFBP-6(P24592);整合膜蛋白1(Itm1,P46977);白介素-6(P05231);白介素-8(P10145);白介素-18(Q14116);IP-10(10kDa干扰素-γ-诱导蛋白,P02778);IRPR(IFRD1,O00458);异戊酰基-CoA脱氢酶(IVD,P26440);I-TAC/CXCL11(O14625);角蛋白19(P08727);Kim-1(甲型肝炎病毒细胞受体1,O43656);L-精氨酸:甘氨酸脒基转移酶(P50440);瘦蛋白(P41159);载脂蛋白2(NGAL,P80188);MCP-1(P13500);MIG(γ-干扰素-诱导单核因子Q07325);MIP-1a(P10147);MIP-3a(P78556);MIP-1β(P13236);MIP-1d(Q16663);NAG(N-乙酰基-β-D-氨基葡糖苷酶,P54802);有机离子转运蛋白(OCT2,O15244);保骨素(O14788);P8蛋白(O60356);纤溶酶原激活物抑制剂1(PAI-1,P05121);ProANP(1-98)(P01160);蛋白磷酸酶1-β(PPI-β,P62140);Rab GDI-β(P50395);肾激肽释放酶(P06870);整合膜蛋白的RT1.B-1(α)链(Q5Y7A8);可溶性肿瘤坏死因子受体超家族成员1A(sTNFR-I,P19438);可溶性肿瘤坏死因子受体超家族成员1B(sTNFR-II,P20333);金属蛋白酶组织抑制剂3(TIMP-3,P35625);uPAR(Q03405)可与本发明的肾损伤标志物测定结果组合。

[0129] 可与本发明的肾损伤标志物测定结果组合的其他临床标识物包括人口统计信息(例如,体重、性别、年龄、种族)、病史(例如,家族病史、手术类型、预先存在的疾病,诸如动脉瘤、充血性心力衰竭、子痫前期、子痫、糖尿病、高血压、冠状动脉疾病、蛋白尿、肾功能不全或败血症)、毒素暴露类型(诸如NSAID、环孢菌素、他克莫司、氨基糖苷类、膦甲酸、乙二醇、血红蛋白、肌红蛋白、异环磷酰胺、重金属、甲氨蝶呤、不透射线的造影剂或链脲佐菌素)、临床变量(例如,血压、温度、呼吸率)、危险评分(APACHE评分、PREDICT评分、UA/NSTEMI的TIMI危险评分、Framingham危险评分)、尿总蛋白测量值、肾小球滤过率、估计肾小球滤过率、尿产率、血清或血浆肌酸酐浓度、肾乳头抗原1(RPA1)测量值、肾乳头抗原2(RPA2)测量值、尿肌酸酐浓度、钠排泄分数、尿钠浓度、尿肌酸酐与血清或血浆肌酸酐之比、尿比重、尿

渗透压、尿液尿素氮与血浆尿素氮之比、血浆BUN与肌酸酐之比和/或以尿钠/(尿肌酸酐/血浆肌酸酐)计算的肾衰竭指数。可与肾损伤标志物测定结果组合的其他肾功能度量在下文和Harrison's Principles of Internal Medicine,第17版,McGraw Hill,New York,第1741-1830页和Current Medical Diagnosis&Treatment 2008,第47版,McGraw Hill,New York,第785-815页中有所描述,上述每个参考文献全文据此以引用的方式并入。

[0130] 以这种方式组合测定结果/临床标识物可包括采用多变量逻辑回归、对数线性建模、神经网络分析、n-of-m分析、决策树分析等。该列表并非意味着进行限制。

[0131] 急性肾衰竭的诊断

[0132] 如上文所述,本文所用的术语"急性肾(或肾脏)损伤"和"急性肾(或肾脏)衰竭"部分是以血清肌酸酐相对于基线值的变化定义的。大多数ARF定义具有共同的要素,包括使用血清肌酸酐以及通常地排尿量。患者可表现为肾功能障碍,而没有可用于该比较的肾功能基线度量。在这种情况下,可通过假设患者最初具有正常的GFR来估计血清肌酸酐基线值。肾小球滤过率(GFR)是每单位时间从肾(肾脏)小球毛细血管过滤进入波曼(Bowman)囊的流体体积。肾小球滤过率(GFR)可通过测定在血液中具有稳定水平并且自由过滤但不被肾脏再吸收或分泌的任意化学物质进行计算。GFR单位通常是ml/min:

[0133] $$GFR = \frac{\text{尿浓度} \times \text{尿流率}}{\text{血浆浓度}}$$

[0134] 通过将GFR归一化为身体表面积,可假设每1.73m^{2}的GFR为大约75-100ml/min。因此,所测定的比率是源自可计算血液量的尿液中物质的量。

[0135] 可采用多种不同的技术来计算或估计肾小球滤过率(GFR或eGFR)。然而,在临床实践中,使用肌酸酐清除率来度量GFR。肌酸酐是由身体自然产生的(肌酸酐是可见于肌肉中的肌酸的代谢物)。它可通过肾小球自由过滤,但极少量也由肾小管主动分泌,使得肌酸酐清除率比实际GFR高估10-20%。考虑到测定肌酸酐清除率的容易性,这种误差幅度是可接受的。

[0136] 如果肌酸酐的尿浓度(U_{Cr})、尿流率(V)和肌酸酐的血浆浓度(P_{Cr})值是已知的,则可计算肌酸酐清除率(CCr)。因为尿液浓度和尿流率的乘积为肌酸酐的排泄率,所以也可认为肌酸酐清除率为其排泄率($U_{Cr} \times V$)除以其血浆浓度。这在数学上通常表示为:

[0137] $$C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$$

[0138] 通常收集24小时的尿液,从早上的空膀胱到第二天早上的膀胱内容物,然后进行比较血液测试:

[0139] $$C_{Cr} = \frac{U_{Cr} \times \text{24小时体积}}{P_{Cr} \times 24 \times 60\text{分钟}}$$

[0140] 为了比较身材不同的人之间的结果,通常对CCr进行身体表面积(BSA)校正,并与平均身材的人相比表示为ml/min/1.73m2。虽然大多数成年人的BSA接近1.7(1.6-1.9),但极胖或极瘦患者应将其CCr按其实际BSA进行校正:

[0141] $$C_{Cr-校正}=\frac{C_{Cr}\times 1.73}{BSA}$$

[0142] 因为随着肾小球滤过率(GFR)的下降,肌酸酐分泌增加,从而导致血清肌酸酐升高变少,所以肌酸酐清除率测量值的精确度有限(即使在完成收集时)。因此,肌酸酐排泄比滤过负荷大得多,导致可能过高地估计GFR(多达两倍差异)。然而,出于临床目的,确定肾功能是否稳定或变坏或变好是重要的。这通常是通过单独监测血清肌酸酐而确定的。与肌酸酐清除率类似,在ARF的非稳定态条件下,血清肌酸酐并不准确地反映GFR。然而,血清肌酸酐从基线的变化程度将反映GFR的变化。血清肌酸酐可容易和方便地测量,并且对肾功能是特异性的。

[0143] 为了确定以mL/kg/h计的排尿量,按小时收集尿液并测量即可。在例如仅得到累积的24小时排尿量而未提供患者体重的情况下,对RIFLE排尿量标准的微小修改已有所描述。例如,Bagshaw等人,Nephrol.Dial.Transplant.23:1203-1210,2008假设患者平均体重为70kg,根据以下标准指定患者的RIFLE分类:<35mL/h(危险)、<21mL/h(损伤)或<4mL/h(衰竭)。

[0144] 选择治疗方案

[0145] 一旦获得诊断结果,临床医师即可容易地选择与诊断相容的治疗方案,诸如开始肾替代疗法、取消递送已知伤肾的化合物、肾移植、延迟或避免已知伤肾的程序、修改利尿剂的施用、开始目标指导性治疗等。技术人员可意识到与本文所述的诊断方法相关讨论的多种疾病的适当治疗。参见例如Merck Manual of Diagnosis and Therapy,第17版Merck Research Laboratories,Whitehouse Station,NJ,1999。此外,由于本文所述的方法和组合物提供了预后信息,本发明的标志物可用于监测治疗过程。例如,预后状态的改善或恶化可表明特定疗法是否有效。

[0146] 本领域技术人员很容易理解,本发明非常适合实现所提到的目标和得到所提到的结果和优点以及其中所固有的优点。本文提供的实例代表优选的实施方案,它们是示例性的,并不旨在限制本发明的范围。

[0147] 实施例1:造影剂诱发的肾病样品收集

[0148] 此样品收集研究的目的是在接受血管内造影介质之前和之后收集患者的血浆和尿液样品以及临床数据。招募大约250名经受放射照影/血管造影步骤(涉及血管内施用碘化造影介质)的成人。为了进入该项研究,每个患者必须满足以下所有纳入标准,并且不满足以下所有排除标准:

[0149] 纳入标准

[0150] 18岁或以上的男性和女性;

[0151] 经受涉及血管内施用造影介质的放射造影/血管造影程序(诸如CT扫描或冠状动脉介入治疗);

[0152] 预期在造影剂施用后住院至少48小时。

[0153] 能够且愿意提供参与研究的书面同意书并遵守所有的研究程序。

[0154] 排除标准

[0155] 肾移植接受者;

[0156] 在造影程序前肾功能急性恶化；

[0157] 已接受透析(急性或慢性)或在招募时急需透析；

[0158] 预期经历大手术(诸如涉及心肺旁路)或在施用造影剂后48小时内经历造影介质对肾有进一步伤害的重大危险的另外成像程序；

[0159] 在之前30天内参与了实验疗法的介入性临床研究；

[0160] 已知感染人类免疫缺陷病毒(HIV)或肝炎病毒。

[0161] 在第一次造影剂施用之前(且在任何前置步骤水合之后)，立即收集每个患者的EDTA抗凝结血样(10mL)和尿样(10mL)。然后在指数对比程序期间最后一次施用造影介质之后，在4(±0.5)、8(±1)、24(±2)、48(±2)和72(±2)小时收集血样和尿样。通过直接静脉穿刺或通过其他可用的静脉通路(诸如现有的股鞘、中央静脉管、外周静脉管或肝素锁)收集血液。将这些研究血样在临床地点处理成血浆，冷冻并运送到Astute Medical,Inc.,San Diego,CA。将研究尿样冷冻并运送到Astute Medical,Inc。

[0162] 在第一次造影剂施用之前(在任何前置步骤水合之后)和最后一次造影剂施用后的4(±0.5)、8(±1)、24(±2)和48(±2)和72(±2)小时(理想地，在获得研究样品的同时)立即在现场评估血清肌酸酐。此外，就另外的血清和尿肌酸酐测量值、对透析的需求、住院状态和不利临床结局(包括死亡)来评价每个患者第30天的状态。

[0163] 在造影剂施用之前，根据以下评估来指定每个患者的危险：收缩压<80mmHg＝5分；动脉内气囊泵＝5分；充血性心力衰竭(III-IV级或肺水肿史)＝5分；年龄>75岁＝4分；血细胞比容水平<39％(男)，<35％(女)＝3分；糖尿病＝3分；每100mL造影介质体积＝1分；血清肌酸酐水平>1.5g/dL＝4分或估计GFR 40-60mL/min/1.73m^2＝2分，20-40mL/min/1.73m^2＝4分，<20mL/min/1.73m^2＝6分。指定的危险如下：CIN和透析危险：总共5分或更少＝CIN危险-7.5％，透析危险-0.04％；总共6-10分＝CIN危险-14％，透析危险-0.12％；总共11-16分＝CIN危险-26.1％，透析危险-1.09％；总共>16分＝CIN危险-57.3％，透析危险-12.8％。

[0164] 实施例2：心脏手术样品收集

[0165] 此样品收集研究的目的是在经受心血管手术(已知对肾功能具有潜在危害性的程序)之前和之后收集患者血浆和尿液样品以及临床数据。招募大约900名经受此类手术的成人。为了进入该项研究，每个患者必须满足以下所有纳入标准，并且不满足以下所有排除标准：

[0166] 纳入标准

[0167] 18岁或以上的男性和女性；

[0168] 经受心血管手术；

[0169] 肾替代危险分数的Toronto/Ottawa预测危险指数为至少2(Wijeysundera等人，JAMA 297:1801-9,2007)；并且

[0170] 能够且愿意提供参与研究的书面同意书并遵守所有的研究步骤。

[0171] 排除标准

[0172] 已知怀孕；

[0173] 之前肾移植；

[0174] 在招募前肾功能急性恶化(例如，任何类别的RIFLE标准)；

[0175] 已接受透析(急性或慢性)或在招募时急需透析；

[0176] 目前被招募到另一个临床研究或预期在7天的心脏手术(涉及AKI的药物输注或治疗干预)内将招募到另一个临床研究；

[0177] 已知感染人类免疫缺陷病毒(HIV)或肝炎病毒。

[0178] 在第一次切割之前3小时内(且在任何前置步骤水合之后)，收集每个患者的EDTA抗凝结血样(10mL)、全血(3mL)和尿样(35mL)。然后在该程序后的3(±0.5)、6(±0.5)、12(±1)、24(±2)和48(±2)小时收集血样和尿样，若受试者仍住院，则在第3至7天每天收集。通过直接静脉穿刺或通过其他可用的静脉通路(诸如现有的股鞘、中央静脉管、外周静脉管或肝素锁)收集血液。将这些研究血样冷冻并运送到Astute Medical,Inc.,San Diego,CA。将研究尿样冷冻并运送到Astute Medical,Inc。

[0179] 实施例3:急性患病受试者样品收集

[0180] 该研究的目的是收集急性患病患者的样品。招募大约900名预期在ICU中至少48小时的成人。为了进入该项研究，每个患者必须满足以下所有纳入标准，并且不满足以下所有排除标准：

[0181] 纳入标准

[0182] 18岁或以上的男性和女性；

[0183] 研究群体1:具有以下至少一者的大约300名患者：

[0184] 休克(SBP<90mmHg和/或需要血管加压支持以维持MAP>60mmHg和/或文献记载的SBP下降至少40mmHg)；和

[0185] 败血病；

[0186] 研究群体2:具有以下至少一者的大约300名患者：

[0187] 在招募的24小时内，根据计算机化医嘱录入(CPOE)服用IV抗生素；

[0188] 在招募的24小时内暴露至造影介质；

[0189] 腹内压增加，伴随着急性失偿性心力衰竭;和

[0190] 严重创伤是ICU住院的主要原因且可能在招募后入住ICU 48小时；

[0191] 研究群体3:大约300名患者

[0192] 预期住院期间配备急性护理设备(ICU或ED)，具有已知的急性肾损伤的危险因素(例如，败血症、低血压/休克(休克＝收缩BP<90mmHg和/或需要血管加压支持以维持MAP>60mmHg和/或文献记载的SBP下降>40mmHg)、大创伤、出血或大手术)；和/或预期招募后入住ICU至少24小时。

[0193] 排除标准

[0194] 已知怀孕；

[0195] 入收容院的个体；

[0196] 之前肾移植；

[0197] 招募前已知肾功能急性恶化(例如，任何类别的RIFLE标准)；

[0198] 在招募前5天内接受透析(急性或慢性)或招募时急需透析；

[0199] 已知感染人类免疫缺陷病毒(HIV)或肝炎病毒；

[0200] 仅满足上述SBP<90mmHg的纳入标准，并且按照主治医师或首席研究员的意见不具有休克。

[0201] 在提供知情同意书后，收集每个患者的EDTA抗凝结血样(10mL)和尿样(25-30mL)。

然后在造影剂施用(如适用)后4(±0.5)和8(±1)小时;在招募后12(±1)、24(±2)和48(±2)小时收集血样和尿样,此后在受试者住院期间,每天进行收集,直到第7天至第14天。通过直接静脉穿刺或通过其他可用的静脉通路(诸如现有的股鞘、中央静脉管、外周静脉管或肝素锁)收集血液。将这些研究血样在临床地点处理成血浆,冷冻并运送到Astute Medical,Inc.,San Diego,CA。将研究尿样冷冻并运送到Astute Medical,Inc。

[0202] 实施例4.免疫测定形式

[0203] 利用标准夹心酶免疫测定技术来测定分析物。将结合分析物的第一抗体固定在96孔聚苯乙烯微孔板的孔中。用移液管将分析物标准和试样转移至合适的孔中,并且通过固定的抗体结合任何存在的分析物。在洗掉任何未结合的物质后,将结合分析物的辣根过氧化物酶缀合的二抗加入孔中,从而与分析物(如果存在)和一抗形成夹心复合物。在洗涤以移除任何未结合的抗体-酶试剂后,将包含四甲基联苯胺和过氧化氢的底物溶液加入孔中。按照与样品中所存在的分析物的量成比例地产生颜色。停止发色并在540nm或570nm下测定颜色强度。通过与由分析物标准确定的标准曲线进行比较来指定试样的分析物浓度。本文报告的卵泡抑素相关蛋白3、Basigin和腱生蛋白的单位为pg/mL;组织蛋白酶B的单位为ng/mL。

[0204] 实施例5.表面上健康的供体和慢性疾病患者的样品

[0205] 来自不患有已知的慢性或急性疾病的供体(“表面上健康的供体”)的人尿样购自两个供应商(Golden West Biologicals,Inc.,27625 Commerce Center Dr.,Temecula,CA 92590和Virginia Medical Research,Inc.,915First Colonial Rd.,Virginia Beach,VA 23454)。在低于-20℃下运输尿样并冷冻储藏。供应商提供个体供体的人口统计信息,包括性别、种族(黑人/白人)、吸烟状况和年龄。

[0206] 来自患有各种慢性疾病的供体(“慢性疾病患者”)的人尿样购自Virginia Medical Research,Inc.,915First Colonial Rd.,Virginia Beach,VA 23454,所述慢性疾病包括充血性心力衰竭、冠状动脉疾病、慢性肾病、慢性阻塞性肺疾病、糖尿病和高血压。在低于-20℃下运输尿样并冷冻储藏。供应商提供每个个体供体的病例报告,包括年龄、性别、种族(黑人/白人)、吸烟状况和酒精饮用、身高、体重、慢性疾病诊断、目前药物治疗和先前的手术。

[0207] 实施例6.使用卵泡抑素相关蛋白3评价进入ICU的患者的肾状态:从RIFLE I和F恢复至RIFLE 0

[0208] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定测定招募样品中的卵泡抑素相关蛋白3。

[0209] 在从样品收集之后起12、24、48或72小时期间或在样品收集后7天内的任何时间,通过基于血清肌酸酐、排尿量,或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为代表“恢复”和“未恢复”群体。“恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是无损伤(RIFLE 0)的那些患者。“未恢复”表示在24、48或72小时的时间段内最大RIFLE阶段具有损伤危险(R)、损伤(I)或衰竭(F)的那些患者。如果患者在招募的9天内死亡或被置于肾替代疗法(RRT),则患者视为“未恢复”。

[0210] 使用接收器操作特征(ROC)分析确定区分“恢复”和“未恢复”组的能力。

[0211] 表6.1:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后12小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0212] sCr或UO

[0213]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	36900	64700	36400	64500	36400	64500
平均值	43900	86000	44100	85700	44100	85700
标准偏差	21100	118000	22600	118000	22600	118000
p(t-检验)		0.29		0.32		0.32
最小值	24900	10500	24900	10500	24900	10500
最大值	89300	1230000	89300	1230000	89300	1230000
n(患者)	9	141	8	142	8	142

[0214] 仅sCr

[0215]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	39100	65900	37800	65800	37800	65800
平均值	83200	83500	85400	83200	85400	83200
标准偏差	154000	110000	158000	109000	158000	109000
p(t-检验)		0.99		0.94		0.94
最小值	10500	15100	10500	15100	10500	15100
最大值	689000	1230000	689000	1230000	689000	1230000
n(患者)	18	132	17	133	17	133

[0216]

[0217] 仅UO

[0218]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	47500	77400	47700	74000	47500	73900
平均值	58600	102000	59000	100000	58700	99200
标准偏差	42400	145000	42900	143000	43700	141000
p(t-检验)		0.023		0.031		0.037
最小值	15100	10500	15100	10500	15100	10500
最大值	265000	1230000	265000	1230000	265000	1230000
n(患者)	63	86	60	89	57	92

[0219]

恢复期持续时间(小时)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.74	0.68	0.70	0.74	0.68	0.69	0.74	0.68	0.70
SE	0.070	0.060	0.042	0.075	0.062	0.043	0.075	0.062	0.043
p 值	5.3E-4	0.0025	1.2E-6	0.0013	0.0036	4.9E-6	0.0013	0.0036	4.4E-6
n 恢复组	9	18	63	8	17	60	8	17	57
n 未恢	141	132	86	142	133	89	142	133	92

[0220]

复组									
截止四分位2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	77%	79%	86%	77%	79%	85%	77%	79%	85%
特异性	67%	56%	40%	75%	59%	40%	75%	59%	40%
截止四分位3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	52%	53%	64%	51%	53%	63%	51%	53%	63%
特异性	78%	72%	68%	75%	71%	68%	75%	71%	70%
截止四分位4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	27%	27%	36%	27%	26%	36%	27%	26%	36%
特异性	100%	83%	89%	100%	82%	90%	100%	82%	91%
OR四分位2	6.81	4.64	4.06	10.3	5.36	3.90	10.3	5.36	3.77
p值	0.0091	0.0031	5.3E-4	0.0055	0.0018	6.6E-4	0.0055	0.0018	8.2E-4
95% CI的下限	1.61	1.68	1.84	1.98	1.87	1.78	1.98	1.87	1.73
95% CI的上限	28.8	12.9	8.95	53.6	15.3	8.53	53.6	15.3	8.20
OR四分位3	3.76	2.94	3.81	3.17	2.67	3.66	3.17	2.67	4.01
p值	0.11	0.052	1.4E-4	0.17	0.080	2.4E-4	0.17	0.080	1.2E-4
95% CI的下限	0.754	0.990	1.91	0.619	0.890	1.83	0.619	0.890	1.98
95% CI的上限	18.7	8.70	7.60	16.3	7.99	7.33	16.3	7.99	8.15
OR四分位4	7.07	1.80	4.51	6.26	1.67	5.05	6.26	1.67	5.82
p值	0.18	0.37	0.0010	0.21	0.44	8.1E-4	0.21	0.44	6.5E-4
95% CI的下限	0.402	0.492	1.83	0.353	0.452	1.96	0.353	0.452	2.11
95% CI的上限	124	6.61	11.1	111	6.15	13.0	111	6.15	16.0

[0221] 表6.2:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0222] sCr或UO

[0223]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	35900	68300	36000	67200	36100	66600
平均值	49400	89000	51500	87800	52800	87400
标准偏差	52400	122000	56500	120000	58000	120000
p（t-检验）		0.14		0.21		0.25
最小值	10500	15100	10500	15100	10500	15100
最大值	265000	1230000	265000	1230000	265000	1230000
n（患者）	21	129	18	132	17	133

[0224] 仅sCr

[0225]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	37400	68400	37400	68100	37800	67900
平均值	74800	85400	77500	84700	79400	84300
标准偏差	130000	112000	134000	111000	137000	111000
p（t-检验）		0.66		0.77		0.85
最小值	10500	15100	10500	15100	10500	15100
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	28	122	26	124	25	125

[0226] 仅UO

[0227]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	49100	81200	49500	74000	48800	74000
平均值	59200	108000	59800	105000	59400	104000
标准偏差	39700	155000	40600	151000	41000	149000
p（t-检验）		0.011		0.021		0.022

[0228]

最小值	10500	21500	10500	21500	10500	21500
最大值	265000	1230000	265000	1230000	265000	1230000
n（患者）	71	74	66	79	64	81

[0229]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.78	0.72	0.71	0.76	0.71	0.69	0.75	0.70	0.70
SE	0.046	0.048	0.043	0.051	0.050	0.043	0.054	0.051	0.043
p 值	1.0E-9	2.7E-6	7.2E-7	3.0E-7	1.6E-5	1.2E-5	3.6E-6	8.3E-5	5.2E-6
n 恢复组	21	28	71	18	26	66	17	25	64
n 未恢复组	129	122	74	132	124	79	133	125	81
截止四分位 2	40800	40800	41800	40800	40800	41800	40800	40800	41800
灵敏度	81%	82%	86%	80%	81%	85%	80%	81%	85%
特异性	67%	57%	37%	67%	58%	36%	65%	56%	38%
截止四分位 3	63600	63600	64300	63600	63600	64300	63600	63600	64300
灵敏度	56%	57%	65%	55%	56%	63%	54%	55%	63%
特异性	86%	79%	65%	83%	77%	65%	82%	76%	66%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	29%	28%	38%	28%	27%	37%	28%	27%	37%
特异性	95%	86%	87%	94%	85%	88%	94%	84%	89%
OR 四分位 2	8.75	6.06	3.70	8.15	5.99	3.19	7.20	5.36	3.45
p 值	2.6E-5	5.9E-5	0.0018	1.2E-4	9.7E-5	0.0041	3.4E-4	2.8E-4	0.0023
95% CI 的下限	3.19	2.52	1.62	2.80	2.43	1.44	2.44	2.16	1.56
95% CI 的上限	24.0	14.6	8.42	23.8	14.7	7.05	21.2	13.3	7.64
OR 四分位 3	7.58	4.77	3.40	6.00	4.18	3.22	5.51	3.90	3.25

[0230]

	p 值	0.0018	0.0016	4.4E-4	0.0063	0.0042	7.7E-4	0.0097	0.0066	7.6E-4
	95% CI 的下限	2.13	1.81	1.72	1.66	1.57	1.63	1.51	1.46	1.64
	95% CI 的上限	27.0	12.6	6.72	21.7	11.1	6.38	20.1	10.4	6.44
	OR 四分位 4	8.04	2.32	4.19	6.62	2.08	4.20	6.17	1.96	4.79
	p 值	0.046	0.14	8.5E-4	0.071	0.21	0.0012	0.083	0.25	7.0E-4
	95% CI 的下限	1.04	0.749	1.81	0.850	0.667	1.76	0.789	0.628	1.94
	95% CI 的上限	62.1	7.18	9.74	51.5	6.47	10.0	48.2	6.13	11.8

[0231] 表6.3:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0232] sCr或UO

[0233]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	42000	68700	43700	68400	43600	68600
平均值	56500	91300	57900	90400	56600	89900
标准偏差	49700	127000	51100	126000	53200	124000
p(t-检验)		0.13		0.17		0.18
最小值	10500	15100	10500	15100	10500	15100
最大值	265000	1230000	265000	1230000	265000	1230000
n(患者)	32	117	30	119	27	122

[0234] 仅sCr

[0235]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组

中值	42700	69300	43600	68700	43600	68700
平均值	74500	87400	75700	86900	75700	86900
标准偏差	113000	117000	114000	117000	114000	117000
p(t-检验)		0.56		0.61		0.61
最小值	10500	15100	10500	15100	10500	15100
最大值	689000	1230000	689000	1230000	689000	1230000
n(患者)	38	110	37	111	37	111

[0236]

[0237] 仅UO

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	54200	73800	55100	72700	55100	72700
平均值	62900	109000	62900	107000	63200	103000
标准偏差	33800	161000	34300	158000	35100	152000
p(t-检验)		0.026		0.034		0.056
最小值	15100	23300	15100	23300	15100	23300
最大值	181000	1230000	181000	1230000	181000	1230000
n(患者)	64	69	61	72	55	78

[0238]

恢复期持续时间(小时)	24			48			72		
	sCr或UO	仅sCr	仅UO	sCr或UO	仅sCr	仅UO	sCr或UO	仅sCr	仅UO
AUC	0.71	0.68	0.66	0.69	0.67	0.66	0.71	0.67	0.64
SE	0.047	0.047	0.047	0.049	0.048	0.047	0.049	0.048	0.048
p值	1.1E-5	1.7E-4	5.5E-4	1.1E-4	5.5E-4	7.7E-4	1.8E-5	5.5E-4	0.0026
n恢复组	32	38	64	30	37	61	27	37	55
n未恢复组	117	110	69	119	111	72	122	111	78
截止四分位2	41800	41500	43900	41800	41500	43900	41800	41500	43900

[0239]

[0240]

灵敏度	82%	82%	83%	81%	81%	82%	80%	81%	79%
特异性	50%	45%	33%	47%	43%	33%	48%	43%	31%
截止四分位3	63900	64100	66600	63900	64100	66600	63900	64100	66600
灵敏度	58%	58%	61%	57%	58%	60%	57%	58%	59%
特异性	78%	74%	61%	77%	73%	61%	81%	73%	62%
截止四分位4	91300	91400	93500	91300	91400	93500	91300	91400	93500
灵敏度	30%	28%	35%	29%	28%	35%	29%	28%	32%
特异性	91%	84%	84%	90%	84%	85%	89%	84%	84%
OR四分位2	4.57	3.64	2.32	3.65	3.27	2.21	3.79	3.27	1.73
p值	3.8E-4	0.0016	0.042	0.0028	0.0040	0.053	0.0029	0.0040	0.17
95% CI的下限	1.98	1.63	1.03	1.56	1.46	0.991	1.58	1.46	0.784
95% CI的上限	10.6	8.13	5.23	8.54	7.31	4.95	9.11	7.31	3.83
OR四分位3	4.96	3.90	2.43	4.38	3.68	2.29	5.92	3.68	2.33
p值	6.1E-4	0.0011	0.013	0.0017	0.0018	0.020	7.6E-4	0.0018	0.019
95% CI的下限	1.98	1.72	1.21	1.74	1.62	1.14	2.10	1.62	1.15
95% CI的上限	12.4	8.80	4.87	11.0	8.33	4.59	16.7	8.33	4.72
OR四分位4	4.13	2.09	2.88	3.75	2.00	3.07	3.22	2.00	2.41
p值	0.027	0.13	0.013	0.039	0.16	0.010	0.070	0.16	0.044
95% CI的下限	1.18	0.797	1.25	1.07	0.761	1.30	0.910	0.761	1.02
95% CI的上限	14.4	5.50	6.65	13.2	5.27	7.25	11.4	5.27	5.69

[0241] 表6.4:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0242] sCr或UO

[0243]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	44700	70200	43900	70500	43600	70500
平均值	59300	94800	58100	93500	58000	92900
标准偏差	46200	133000	48800	130000	50200	129000
p（t-检验）		0.11		0.13		0.14
最小值	10500	15100	10500	15100	10500	15100
最大值	265000	1230000	265000	1230000	265000	1230000
n（患者）	38	106	33	111	31	113

[0244] 仅sCr

[0245]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	45400	70500	45400	70500	45400	70500
平均值	73600	90800	73600	90800	74300	90100
标准偏差	104000	123000	104000	123000	106000	122000
p（t-检验）		0.42		0.42		0.46
最小值	10500	15100	10500	15100	10500	15100
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	45	99	45	99	43	101

[0246] 仅UO

[0247]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	60900	73800	60900	71700	50700	74200
平均值	66000	111000	67200	105000	62000	105000
标准偏差	35600	165000	37000	157000	35000	151000
p（t-检验）		0.042		0.091		0.059
最小值	15100	23300	15100	23300	15100	23300
最大值	181000	1230000	181000	1230000	181000	1230000

[0248]

n（患者）	60	65	52	73	47	79

[0249]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.68	0.67	0.64	0.70	0.67	0.61	0.70	0.67	0.67
SE	0.047	0.046	0.049	0.048	0.046	0.050	0.048	0.047	0.048
p 值	1.4E-4	3.7E-4	0.0035	3.4E-5	3.7E-4	0.022	2.4E-5	3.6E-4	4.1E-4
n 恢复组	38	45	60	33	45	52	31	43	47
n 未恢复组	106	99	65	111	99	73	113	101	79
截止四分位 2	41800	41800	45200	41800	41800	45200	41800	41800	44800
灵敏度	82%	83%	83%	81%	83%	79%	81%	83%	81%
特异性	45%	42%	33%	45%	42%	31%	48%	44%	36%
截止四分位 3	65200	65200	68200	65200	65200	68200	65200	65200	68000
灵敏度	57%	58%	58%	57%	58%	56%	57%	57%	58%
特异性	68%	67%	58%	73%	67%	58%	74%	67%	64%
截止四分位 4	92300	92300	95500	92300	92300	95500	92300	92300	95100
灵敏度	31%	30%	35%	30%	30%	32%	29%	30%	32%
特异性	92%	87%	85%	91%	87%	83%	90%	86%	85%
OR 四分位 2	3.71	3.52	2.45	3.57	3.52	1.72	4.11	3.91	2.42
p 值	0.0015	0.0018	0.037	0.0028	0.0018	0.19	0.0011	7.9E-4	0.035
95% CI 的下限	1.65	1.60	1.06	1.55	1.60	0.758	1.76	1.76	1.07
95% CI 的上限	8.33	7.76	5.70	8.22	7.76	3.89	9.60	8.67	5.48
OR 四分位 3	2.83	2.71	1.97	3.50	2.71	1.75	3.76	2.79	2.46
p 值	0.0094	0.0079	0.062	0.0040	0.0079	0.13	0.0034	0.0072	0.018
95% CI 的下限	1.29	1.30	0.967	1.49	1.30	0.852	1.55	1.32	1.17
95% CI	6.19	5.67	4.02	8.21	5.67	3.58	9.11	5.91	5.18

[0250]

的上限									
OR 四分位 4	5.27	2.83	3.10	4.23	2.83	2.20	3.85	2.61	2.65
p 值	0.0091	0.034	0.011	0.024	0.034	0.077	0.036	0.051	0.041
95% CI 的下限	1.51	1.08	1.30	1.21	1.08	0.919	1.09	0.995	1.04
95% CI 的上限	18.4	7.38	7.42	14.8	7.38	5.26	13.5	6.82	6.72

[0251] 表6.5:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0252] sCr或UO

[0253]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	48400	73800	48200	73900	48200	73900
平均值	68600	101000	60800	109000	60800	109000
标准偏差	80100	145000	39500	160000	39500	160000
p(t-检验)		0.087		0.0096		0.0096
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	265000	1230000	265000	1230000
n(患者)	81	69	80	70	80	70

[0254] 仅sCr

[0255]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	45400	70900	45400	70900	45400	70900
平均值	68200	95700	67500	95600	67500	95600
标准偏差	87400	133000	88200	131000	88200	131000

[0256]

p(t-检验)		0.15		0.14		0.14
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n(患者)	67	83	65	85	65	85

[0257] 仅UO

[0258]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	50700	72700	50300	77200	49800	81200
平均值	70300	107000	63200	118000	62000	118000
标准偏差	76000	162000	40800	177000	40100	174000
p（t-检验）		0.059		0.0048		0.0037
最小值	10500	21500	10500	21500	10500	21500
最大值	689000	1230000	265000	1230000	265000	1230000
n（患者）	95	54	93	56	91	58

[0259]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.67	0.69	0.67	0.69	0.70	0.69	0.69	0.70	0.71
SE	0.044	0.043	0.047	0.044	0.042	0.046	0.044	0.042	0.045
p 值	8.3E-5	8.4E-6	2.7E-4	1.8E-5	3.3E-6	3.0E-5	1.8E-5	3.3E-6	3.6E-6
n 恢复组	81	67	95	80	65	93	80	65	91
n 未恢复组	69	83	54	70	85	56	70	85	58
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	86%	86%	89%	86%	86%	89%	86%	86%	90%
特异性	35%	39%	33%	35%	40%	33%	35%	40%	34%
截止四	63600	63600	63900	63600	63600	63900	63600	63600	63900

[0260]

分位 3									
灵敏度	62%	63%	65%	63%	62%	66%	63%	62%	67%
特异性	60%	66%	58%	61%	66%	59%	61%	66%	60%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	36%	34%	37%	37%	34%	39%	37%	34%	40%
特异性	84%	85%	81%	85%	86%	83%	85%	86%	84%
OR 四分位 2	3.12	3.75	3.88	3.23	4.06	4.17	3.23	4.06	4.48
p 值	0.0061	9.6E-4	0.0052	0.0046	4.9E-4	0.0032	0.0046	4.9E-4	0.0020
95% CI 的下限	1.38	1.71	1.50	1.43	1.85	1.61	1.43	1.85	1.73
95% CI 的上限	7.02	8.22	10.0	7.28	8.91	10.8	7.28	8.91	11.6
OR 四分位 3	2.53	3.21	2.53	2.67	3.24	2.82	2.67	3.24	3.14
p 值	0.0058	6.8E-4	0.0084	0.0035	6.5E-4	0.0033	0.0035	6.5E-4	0.0012
95% CI 的下限	1.31	1.64	1.27	1.38	1.65	1.41	1.38	1.65	1.57
95% CI 的上限	4.90	6.29	5.06	5.18	6.36	5.62	5.18	6.36	6.26
OR 四分位 4	2.97	2.90	2.52	3.35	3.22	3.11	3.35	3.22	3.33
p 值	0.0056	0.010	0.016	0.0025	0.0060	0.0034	0.0025	0.0060	0.0020
95% CI 的下限	1.38	1.29	1.18	1.53	1.40	1.46	1.53	1.40	1.55
95% CI 的上限	6.42	6.53	5.35	7.32	7.42	6.66	7.32	7.42	7.15

[0261] 实施例7.使用卵泡抑素相关蛋白3评价进入ICU的患者的肾状态:从RIFLE I和F恢复至RIFLE 0和R

[0262] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),并且此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的卵泡抑素相关蛋白3。

[0263] 在从样品收集之后起12、24、48或72小时期间或在样品收集后7天内的任何时间,通过基于血清肌酸酐、排尿量,或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“恢复”和“未恢复”群体。“恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是无损伤(RIFLE 0)或具有损伤危险(R)的那些患者。“未恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是损伤(I)或衰竭(F)的那些患者。如果患者在招募的9天内死亡或被置于肾替代疗法(RRT),则患者视为“未恢复”。

[0264] 使用接收器操作特征(ROC)分析确定区分“恢复”和“未恢复”组的能力。

[0265] 表7.1:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后12小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0266] sCr或UO

[0267]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	37600	70200	37100	70200	36900	70000
平均值	50400	92400	48900	92100	49000	91700
标准偏差	45400	126000	45900	125000	46700	125000
p(t-检验)		0.067		0.066		0.073
最小值	10500	20700	10500	20700	10500	20700
最大值	265000	1230000	265000	1230000	265000	1230000
n(患者)	32	118	30	120	29	121

[0268] 仅sCr

[0269]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	40400	70500	40400	70500	39100	70200
平均值	67200	89500	67200	89500	67800	89100
标准偏差	108000	118000	108000	118000	110000	117000
p(t-检验)		0.29		0.29		0.32
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n(患者)	41	109	41	109	40	110

[0270]

[0271] 仅UO

[0272]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	48200	81800	48200	81800	47900	81200
平均值	60200	108000	59900	107000	59800	107000
标准偏差	41300	156000	41500	154000	41800	154000
p（t-检验）		0.011		0.012		0.013
最小值	10500	21500	10500	21500	10500	21500
最大值	265000	1230000	265000	1230000	265000	1230000
n（患者）	76	73	74	75	73	76

[0273]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.76	0.74	0.70	0.78	0.74	0.71	0.78	0.74	0.71
SE	0.042	0.042	0.043	0.041	0.042	0.042	0.041	0.042	0.042
p 值	3.4E-10	8.9E-9	2.0E-6	5.3E-12	8.9E-9	1.2E-6	1.0E-11	1.8E-8	1.0E-6
n 恢复组	32	41	76	30	41	74	29	40	73
n 未恢复组	118	109	73	120	109	75	121	110	76
截止四	40800	40800	40400	40800	40800	40400	40800	40800	40400

[0274]

分位 2									
灵敏度	83%	84%	86%	83%	84%	87%	83%	85%	87%
特异性	56%	51%	36%	60%	51%	36%	62%	52%	37%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	59%	61%	67%	59%	61%	67%	59%	60%	67%
特异性	84%	78%	66%	87%	78%	66%	86%	78%	67%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	30%	30%	37%	30%	30%	37%	30%	30%	37%
特异性	91%	88%	86%	93%	88%	86%	93%	88%	86%
OR 四分位 2	6.30	5.68	3.47	7.50	5.68	3.73	8.26	6.05	3.87
p 值	2.1E-5	2.2E-5	0.0028	6.2E-6	2.2E-5	0.0016	3.3E-6	1.3E-5	0.0012
95% CI 的下限	2.70	2.55	1.54	3.13	2.55	1.65	3.39	2.70	1.71
95% CI 的上限	14.7	12.7	7.85	18.0	12.7	8.45	20.1	13.6	8.77
OR 四分位 3	7.88	5.46	3.93	9.42	5.46	3.92	8.88	5.17	4.16
p 值	7.6E-5	6.6E-5	8.2E-5	7.9E-5	6.6E-5	8.3E-5	1.3E-4	1.1E-4	4.3E-5
95% CI 的下限	2.83	2.37	1.99	3.09	2.37	1.99	2.91	2.24	2.10
95% CI 的上限	21.9	12.6	7.75	28.7	12.6	7.74	27.1	11.9	8.25
OR 四分位 4	4.08	3.13	3.47	6.00	3.13	3.81	5.72	3.00	3.68
p 值	0.028	0.029	0.0022	0.018	0.029	0.0013	0.022	0.035	0.0017
95% CI 的下限	1.16	1.13	1.56	1.36	1.13	1.69	1.29	1.08	1.63
95% CI 的上限	14.3	8.68	7.69	26.5	8.68	8.61	25.3	8.34	8.29

[0275] 表7.2:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0276] sCr或UO

[0277]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	40400	71700	38700	71700	38700	71700
平均值	49900	97800	48800	97400	48800	97400
标准偏差	39700	133000	39800	132000	39800	132000
p（t-检验）		0.019		0.019		0.019
最小值	10500	20700	10500	20700	10500	20700
最大值	265000	1230000	265000	1230000	265000	1230000
n（患者）	45	105	43	107	43	107

[0278] 仅sCr

[0279]

恢复期持续时间(小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	41800	71900	41800	71700	41800	71700
平均值	63300	93500	63700	93000	63700	93000
标准偏差	98400	122000	99400	121000	99400	121000
p（t-检验）		0.13		0.14		0.14
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	50	100	49	101	49	101

[0280] 仅UO

[0281]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	49100	81200	48400	81200	48400	81200
平均值	60500	113000	59900	112000	59900	112000
标准偏差	39600	164000	39800	161000	39800	161000
p（t-检验）		0.0069		0.0071		0.0071
最小值	10500	21500	10500	21500	10500	21500
最大值	265000	1230000	265000	1230000	265000	1230000

[0282]

n（患者）	79	66	77	68	77	68

[0283]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.78	0.76	0.71	0.79	0.76	0.72	0.79	0.76	0.72
SE	0.038	0.039	0.043	0.037	0.039	0.043	0.037	0.039	0.043
p 值	1.6E-13	8.2E-12	8.2E-7	5.6E-15	2.1E-11	2.2E-7	5.6E-15	2.1E-11	2.2E-7
n 恢复组	45	50	79	43	49	77	43	49	77
n 未恢复组	105	100	66	107	101	68	107	101	68
截止四分位 2	40800	40800	41800	40800	40800	41800	40800	40800	41800
灵敏度	86%	86%	89%	86%	86%	90%	86%	86%	90%
特异性	51%	48%	37%	53%	49%	38%	53%	49%	38%
截止四分位 3	63600	63600	64300	63600	63600	64300	63600	63600	64300
灵敏度	64%	65%	67%	64%	64%	68%	64%	64%	68%
特异性	82%	80%	63%	84%	80%	65%	84%	80%	65%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	33%	33%	38%	34%	33%	38%	34%	33%	38%
特异性	93%	90%	85%	95%	90%	86%	95%	90%	86%
OR 四分位 2	6.27	5.67	4.89	7.05	5.97	5.26	7.05	5.97	5.26
p 值	6.9E-6	1.7E-5	6.1E-4	2.3E-6	1.1E-5	3.4E-4	2.3E-6	1.1E-5	3.4E-4
95% CI 的下限	2.82	2.57	1.97	3.14	2.69	2.12	3.14	2.69	2.12
95% CI 的上限	14.0	12.5	12.1	15.9	13.2	13.1	15.9	13.2	13.1
OR 四分位 3	8.15	7.43	3.45	8.97	7.04	3.87	8.97	7.04	3.87
p 值	1.8E-6	1.1E-6	4.1E-4	1.8E-6	2.0E-6	1.2E-4	1.8E-6	2.0E-6	1.2E-4

[0284]

95% CI 的下限	3.44	3.32	1.74	3.64	3.15	1.94	3.64	3.15	1.94
95% CI 的上限	19.3	16.6	6.85	22.1	15.8	7.73	22.1	15.8	7.73
OR 四分位 4	7.00	4.43	3.40	10.4	4.27	3.71	10.4	4.27	3.71
p 值	0.0021	0.0040	0.0024	0.0019	0.0050	0.0014	0.0019	0.0050	0.0014
95% CI 的下限	2.03	1.61	1.54	2.38	1.55	1.66	2.38	1.55	1.66
95% CI 的上限	24.2	12.2	7.50	45.4	11.8	8.30	45.4	11.8	8.30

[0285] 表7.3:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0286] sCr或UO

[0287]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	43500	72000	43500	72000	43600	71900
平均值	55600	102000	55600	102000	56000	101000
标准偏差	40500	142000	40500	142000	40700	141000
p(t-检验)		0.017		0.017		0.020
最小值	10500	20700	10500	20700	10500	20700
最大值	265000	1230000	265000	1230000	265000	1230000
n(患者)	58	91	58	91	57	92

[0288] 仅sCr

[0289]

恢复期持	24	48	72

[0290]

续时间（小时）						
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	43900	71700	43900	71700	43900	71700
平均值	67700	95600	67700	95600	67700	95600
标准偏差	90500	130000	90500	130000	90500	130000
p（t-检验）		0.15		0.15		0.15
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	61	87	61	87	61	87

[0291] 仅UO

[0292]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	52000	81800	52000	81800	52000	81800
平均值	62100	116000	62100	116000	61900	114000
标准偏差	33300	169000	33300	169000	33100	167000
p（t-检验）		0.0094		0.0094		0.011
最小值	15100	24400	15100	24400	15100	24400
最大值	181000	1230000	181000	1230000	181000	1230000
n（患者）	72	61	72	61	70	63

[0293]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.74	0.71	0.70	0.74	0.71	0.70	0.73	0.71	0.69
SE	0.040	0.042	0.046	0.040	0.042	0.046	0.041	0.042	0.046
p 值	3.8E-9	1.2E-6	1.8E-5	3.8E-9	1.2E-6	1.8E-5	2.7E-8	1.2E-6	2.8E-5
n 恢复组	58	61	72	58	61	72	57	61	70
n 未恢复组	91	87	61	91	87	61	92	87	63

[0294]

截止四分位 2	41800	41500	43900	41800	41500	43900	41800	41500	43900
灵敏度	87%	86%	87%	87%	86%	87%	86%	86%	86%
特异性	43%	41%	35%	43%	41%	35%	42%	41%	34%
截止四分位 3	63900	64100	66600	63900	64100	66600	63900	64100	66600
灵敏度	64%	62%	66%	64%	62%	66%	63%	62%	65%
特异性	71%	67%	62%	71%	67%	62%	70%	67%	63%
截止四分位 4	91300	91400	93500	91300	91400	93500	91300	91400	93500
灵敏度	37%	34%	38%	37%	34%	38%	37%	34%	38%
特异性	93%	89%	85%	93%	89%	85%	93%	89%	86%
OR 四分位 2	4.99	4.34	3.52	4.99	4.34	3.52	4.42	4.34	3.13
p 值	8.1E-5	2.9E-4	0.0054	8.1E-5	2.9E-4	0.0054	2.2E-4	2.9E-4	0.0094
95% CI 的下限	2.24	1.96	1.45	2.24	1.96	1.45	2.01	1.96	1.32
95% CI 的上限	11.1	9.61	8.56	11.1	9.61	8.56	9.72	9.61	7.41
OR 四分位 3	4.24	3.35	3.17	4.24	3.35	3.17	4.01	3.35	3.15
p 值	6.5E-5	5.6E-4	0.0015	6.5E-5	5.6E-4	0.0015	1.2E-4	5.6E-4	0.0015
95% CI 的下限	2.09	1.69	1.56	2.09	1.69	1.56	1.98	1.69	1.55
95% CI 的上限	8.61	6.67	6.47	8.61	6.67	6.47	8.15	6.67	6.41
OR 四分位 4	8.05	4.06	3.36	8.05	4.06	3.36	7.77	4.06	3.69
p 值	2.0E-4	0.0024	0.0040	2.0E-4	0.0024	0.0040	2.6E-4	0.0024	0.0023
95% CI 的下限	2.68	1.65	1.47	2.68	1.65	1.47	2.58	1.65	1.59
95% CI 的上限	24.2	10.0	7.66	24.2	10.0	7.66	23.4	10.0	8.56

[0295] 表7.4:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0296] sCr或UO

[0297]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	44700	80700	44300	80900	44700	80700
平均值	67200	100000	57100	107000	56400	106000
标准偏差	88100	135000	40700	148000	40000	146000
p（t-检验）		0.090		0.011		0.013
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	265000	1230000	265000	1230000
n（患者）	65	79	62	82	59	85

[0298] 仅sCr

[0299]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	45400	74000	45400	74000	45600	73900
平均值	68500	100000	68500	100000	69000	99300
标准偏差	87100	137000	87100	137000	87600	136000
p（t-检验）		0.11		0.11		0.12
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	67	77	67	77	66	78

[0300] 仅UO

[0301]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	60900	80700	55400	81200	55200	81200
平均值	74300	108000	65100	115000	63700	115000
标准偏差	82100	160000	34900	171000	33900	168000
p（t-检验）		0.13		0.022		0.019

[0302]

最小值	15100	24400	15100	24400	15100	24400
最大值	689000	1230000	181000	1230000	181000	1230000
n（患者）	70	55	65	60	64	62

[0303]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.73	0.71	0.66	0.74	0.71	0.67	0.74	0.70	0.68
SE	0.041	0.042	0.050	0.040	0.042	0.048	0.040	0.043	0.048
p 值	1.8E-8	3.9E-7	0.0015	1.2E-9	3.9E-7	5.0E-4	2.3E-9	1.9E-6	2.1E-4
n 恢复组	65	67	70	62	67	65	59	66	64
n 未恢复组	79	77	55	82	77	60	85	78	62
截止四分位 2	41800	41800	45200	41800	41800	45200	41800	41800	44800
灵敏度	89%	88%	85%	88%	88%	85%	87%	87%	84%
特异性	42%	40%	33%	42%	40%	34%	42%	39%	34%
截止四分位 3	65200	65200	68200	65200	65200	68200	65200	65200	68000
灵敏度	65%	64%	62%	65%	64%	62%	64%	63%	61%
特异性	68%	66%	59%	69%	66%	60%	69%	65%	61%
截止四分位 4	92300	92300	95500	92300	92300	95500	92300	92300	95100
灵敏度	37%	35%	38%	38%	35%	38%	38%	35%	39%
特异性	89%	87%	84%	92%	87%	86%	93%	86%	88%
OR 四分位 2	5.53	5.10	2.88	5.20	5.10	2.90	4.95	4.42	2.72
p 值	8.3E-5	1.7E-4	0.022	1.0E-4	1.7E-4	0.017	1.3E-4	4.3E-4	0.021
95% CI 的下限	2.36	2.18	1.17	2.26	2.18	1.21	2.18	1.93	1.16
95% CI 的上限	12.9	11.9	7.07	11.9	11.9	6.96	11.2	10.1	6.38
OR 四分位 3	3.82	3.35	2.29	4.14	3.35	2.41	3.97	3.16	2.47
p 值	1.6E-4	5.5E-4	0.025	7.8E-5	5.5E-4	0.016	1.4E-4	9.7E-4	0.013

[0304]

95% CI 的下限	1.90	1.69	1.11	2.04	1.69	1.18	1.95	1.59	1.21
95% CI 的上限	7.65	6.64	4.71	8.37	6.64	4.95	8.06	6.26	5.06
OR 四分位 4	4.81	3.48	3.31	6.93	3.48	3.87	8.30	3.35	4.42
p 值	7.0E-4	0.0038	0.0053	1.9E-4	0.0038	0.0025	1.8E-4	0.0049	0.0012
95% CI 的下限	1.94	1.50	1.43	2.51	1.50	1.61	2.75	1.44	1.80
95% CI 的上限	11.9	8.09	7.70	19.2	8.09	9.28	25.1	7.80	10.9

[0305] 表7.5:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0306] sCr或UO

[0307]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	48400	74000	48200	77400	47900	80700
平均值	68400	105000	68000	105000	60800	115000
标准偏差	77400	153000	77700	151000	39700	167000
p(t-检验)		0.054		0.050		0.0044
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	265000	1230000
n(患者)	89	61	88	62	87	63

[0308] 仅sCr

[0309]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	47100	74000	47100	74000	47100	74000

[0310]

平均值	67300	101000	67300	101000	67300	101000
标准偏差	81300	142000	81300	142000	81300	142000
p（t-检验）		0.070		0.070		0.070
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	79	71	79	71	79	71

[0311] 仅UO

[0312]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	50500	73800	50500	73800	50100	80700
平均值	70000	110000	70000	110000	63100	121000
标准偏差	75100	166000	75100	166000	40800	181000
p（t-检验）		0.044		0.044		0.0031
最小值	10500	33600	10500	33600	10500	33600
最大值	689000	1230000	689000	1230000	265000	1230000
n（患者）	98	51	98	51	96	53

[0313]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.69	0.71	0.69	0.70	0.71	0.69	0.71	0.71	0.71
SE	0.045	0.043	0.048	0.044	0.043	0.048	0.044	0.043	0.046
p 值	1.8E-5	1.4E-6	9.0E-5	6.8E-6	1.4E-6	9.0E-5	1.1E-6	1.4E-6	8.1E-6
n 恢复组	89	79	98	88	79	98	87	79	96
n 未恢复组	61	71	51	62	71	51	63	71	53
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	89%	87%	90%	89%	87%	90%	89%	87%	91%
特异性	35%	37%	33%	35%	37%	33%	36%	37%	33%

[0314]

截止四分位3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	66%	68%	67%	66%	68%	67%	67%	68%	68%
特异性	61%	66%	58%	61%	66%	58%	62%	66%	59%
截止四分位4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	38%	37%	37%	39%	37%	37%	40%	37%	40%
特异性	83%	85%	81%	84%	85%	81%	85%	85%	82%
OR 四分位2	4.12	4.00	4.46	4.27	4.00	4.46	4.43	4.00	4.80
p 值	0.0020	0.0012	0.0039	0.0016	0.0012	0.0039	0.0012	0.0012	0.0024
95% CI 的下限	1.68	1.73	1.62	1.74	1.73	1.62	1.80	1.73	1.74
95% CI 的上限	10.1	9.21	12.3	10.5	9.21	12.3	10.9	9.21	13.2
OR 四分位3	2.94	4.02	2.78	3.10	4.02	2.78	3.27	4.02	3.10
p 值	0.0018	6.2E-5	0.0046	0.0011	6.2E-5	0.0046	6.3E-4	6.2E-5	0.0017
95% CI 的下限	1.49	2.04	1.37	1.57	2.04	1.37	1.66	2.04	1.53
95% CI 的上限	5.79	7.94	5.64	6.11	7.94	5.64	6.46	7.94	6.27
OR 四分位4	2.99	3.23	2.47	3.34	3.23	2.47	3.74	3.23	3.05
p 值	0.0047	0.0033	0.019	0.0021	0.0033	0.019	8.5E-4	0.0033	0.0040
95% CI 的下限	1.40	1.48	1.16	1.55	1.48	1.16	1.72	1.48	1.43
95% CI 的上限	6.38	7.05	5.26	7.18	7.05	5.26	8.14	7.05	6.52

[0315] 实施例8.使用Basigin评价进入ICU的患者的肾状态:从RIFLE I和F恢复至RIFLE 0

[0316] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的Basigin。

[0317] 在从样品收集之后起12、24、48或72小时期间或在样品收集后7天内的任何时间,通过基于血清肌酸酐、排尿量,或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“恢复”和“未恢复”群体。“恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是无损伤(RIFLE 0)的那些患者。“未恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是具有损伤危险(R)、损伤(I)或衰竭(F)的那些患者。如果患者在招募的9天内死

亡或被置于肾替代疗法(RRT),则患者视为“未恢复”。

[0318] 使用接收器操作特征(ROC)分析确定区分“恢复”和“未恢复”组的能力。

[0319] 表8.1:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后12小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0320] sCr或UO

[0321]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	4230	11600	4090	11500	4090	11500
平均值	4730	16600	4430	16500	4430	16500
标准偏差	1860	14100	1730	14100	1730	14100
p(t-检验)		0.013		0.017		0.017
最小值	1970	2640	1970	2640	1970	2640
最大值	7150	72100	7010	72100	7010	72100
n(患者)	9	141	8	142	8	142

[0322] 仅sCr

[0323]

恢复期持续时间(小时)	24		48		72	

[0324]

	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	4670	12000	4930	11800	4930	11800
平均值	9050	16800	9330	16700	9330	16700
标准偏差	11700	14000	12000	14000	12000	14000
p(t-检验)		0.027		0.040		0.040
最小值	1970	3040	1970	3040	1970	3040
最大值	42400	72100	42400	72100	42400	72100
n(患者)	18	132	17	133	17	133

[0325] 仅UO

[0326]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7550	14000	7740	13900	7550	13900
平均值	10700	19700	10700	19400	10500	19300
标准偏差	10100	15200	10200	15100	10000	15000
p（t-检验）		7.3E-5		1.4E-4		1.3E-4
最小值	1970	2640	1970	2640	1970	2640
最大值	60400	72100	60400	72100	60400	72100
n（患者）	63	86	60	89	57	92

[0327]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.89	0.79	0.73	0.91	0.78	0.72	0.91	0.78	0.73
SE	0.038	0.046	0.041	0.034	0.049	0.041	0.034	0.049	0.041
p 值	0	2.5E-10	1.7E-8	0	1.3E-8	5.6E-8	0	1.3E-8	3.9E-8
n 恢复组	9	18	63	8	17	60	8	17	57
n 未恢	141	132	86	142	133	89	142	133	92

[0328]

复组									
截止四分位2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	78%	80%	84%	78%	80%	83%	78%	80%	83%
特异性	78%	67%	37%	88%	65%	37%	88%	65%	37%
截止四分位3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	53%	55%	70%	53%	54%	69%	53%	54%	67%
特异性	100%	83%	76%	100%	82%	77%	100%	82%	77%
截止四分位4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	27%	27%	35%	27%	27%	35%	27%	27%	35%
特异性	100%	89%	87%	100%	88%	88%	100%	88%	89%
OR四分位2	12.4	8.15	2.96	25.1	7.20	2.86	25.1	7.20	2.77
p值	0.0023	1.2E-4	0.0057	0.0031	3.4E-4	0.0071	0.0031	3.4E-4	0.0087
95% CI的下限	2.45	2.80	1.37	2.97	2.44	1.33	2.97	2.44	1.29
95% CI的上限	62.8	23.8	6.38	212	21.2	6.13	212	21.2	5.94
OR四分位3	21.6	6.00	7.38	19.0	5.51	7.16	19.0	5.51	6.99
p值	0.035	0.0063	1.2E-7	0.044	0.0097	2.4E-7	0.044	0.0097	4.7E-7
95% CI的下限	1.23	1.66	3.52	1.08	1.51	3.39	1.08	1.51	3.28
95% CI的上限	378	21.7	15.5	336	20.1	15.1	336	20.1	14.9
OR四分位4	7.07	3.00	3.68	6.26	2.78	4.05	6.26	2.78	4.53
p值	0.18	0.16	0.0031	0.21	0.19	0.0024	0.21	0.19	0.0018
95% CI的下限	0.402	0.657	1.55	0.353	0.606	1.64	0.353	0.606	1.76
95% CI的上限	124	13.7	8.74	111	12.8	9.96	111	12.8	11.7

[0329] 表8.2:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0330] sCr或UO

[0331]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	4390	12400	4260	12300	4230	12300
平均值	4740	17700	4600	17400	4620	17300
标准偏差	1650	14200	1680	14200	1730	14200
p（t-检验）		5.7E-5		2.0E-4		3.3E-4
最小值	1970	3040	1970	3040	1970	3040
最大值	7920	72100	7920	72100	7920	72100
n（患者）	21	129	18	132	17	133

[0332] 仅sCr

[0333]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	4660	12800	4850	12600	4930	12400
平均值	7670	17700	7930	17500	8070	17400
标准偏差	9500	14200	9820	14100	10000	14100
p（t-检验）		4.7E-4		0.0012		0.0020
最小值	1970	3040	1970	3040	1970	3040
最大值	42400	72100	42400	72100	42400	72100
n（患者）	28	122	26	124	25	125

[0334] 仅UO

[0335]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7920	14300	8010	13900	7740	13900
平均值	11600	20500	11800	19800	11500	19800
标准偏差	10500	15700	10800	15500	10600	15400
p（t-检验）		1.0E-4		5.1E-4		3.1E-4

[0336]

最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	71	74	66	79	64	81

[0337]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.93	0.85	0.73	0.93	0.84	0.70	0.93	0.83	0.71
SE	0.022	0.033	0.042	0.022	0.035	0.043	0.023	0.037	0.042
p 值	0	0	6.7E-8	0	0	1.6E-6	0	0	3.3E-7
n 恢复组	21	28	71	18	26	66	17	25	64
n 未恢复组	129	122	74	132	124	79	133	125	81
截止四分位 2	6820	6820	6850	6820	6820	6850	6820	6820	6850
灵敏度	84%	85%	88%	83%	84%	86%	82%	83%	86%
特异性	81%	71%	38%	83%	69%	38%	82%	68%	39%
截止四分位 3	11000	11000	11200	11000	11000	11200	11000	11000	11200
灵敏度	58%	59%	73%	57%	58%	70%	56%	58%	69%
特异性	100%	89%	72%	100%	88%	71%	100%	88%	72%
截止四分位 4	19900	19900	21500	19900	19900	21500	19900	19900	21500
灵敏度	29%	30%	35%	29%	29%	34%	29%	29%	35%
特异性	100%	93%	85%	100%	92%	85%	100%	92%	86%
OR 四分位 2	21.9	14.4	4.43	23.7	11.7	3.77	21.2	10.5	4.08
p 值	3.4E-7	5.1E-8	5.6E-4	2.5E-6	5.2E-7	0.0013	6.1E-6	1.6E-6	6.7E-4
95% CI 的下限	6.68	5.53	1.90	6.34	4.48	1.68	5.65	4.02	1.81
95% CI 的上限	71.5	37.7	10.3	88.6	30.6	8.46	79.6	27.5	9.17
OR 四分位 3	59.6	12.0	6.88	48.6	10.6	5.67	45.2	9.96	5.72
p 值	0.0046	9.9E-5	2.1E-7	0.0072	2.2E-4	2.1E-6	0.0084	3.4E-4	2.1E-6

[0338]

95% CI 的下限	3.53	3.44	3.32	2.87	3.03	2.77	2.66	2.83	2.78
95% CI 的上限	1000	41.9	14.3	823	37.2	11.6	767	35.0	11.8
OR 四分位 4	18.1	5.44	2.95	15.1	4.91	2.91	14.1	4.65	3.23
p 值	0.045	0.026	0.0080	0.061	0.037	0.011	0.067	0.044	0.0063
95% CI 的下限	1.07	1.23	1.33	0.886	1.10	1.28	0.828	1.04	1.39
95% CI 的上限	306	24.1	6.58	256	21.9	6.59	241	20.8	7.48

[0339] 表8.3:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0340] sCr或UO

[0341]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	6250	12900	6250	12700	5550	12600
平均值	8350	18000	8490	17800	7790	17700
标准偏差	7550	14600	7770	14500	7410	14400
p(t-检验)		4.1E-4		9.0E-4		6.6E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	33400	72100	33400	72100	33400	72100
n(患者)	32	117	30	119	27	122

[0342] 仅sCr

[0343]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组

	中值	7010	13200	7010	13100	7010	13100
	平均值	10000	18100	10200	18000	10200	18000
	标准偏差	10000	14500	10100	14500	10100	14500
[0344]	p（t-检验）		0.0019		0.0031		0.0031
	最小值	1970	3580	1970	3580	1970	3580
	最大值	42400	72100	42400	72100	42400	72100
	n（患者）	38	110	37	111	37	111

[0345] 仅UO

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	9030	13900	9000	13900	9000	13600
[0346] 平均值	13300	20300	13200	20200	13400	19500
标准偏差	11300	16000	11300	15900	11700	15600
p（t-检验）		0.0045		0.0046		0.016
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	64	69	61	72	55	78

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.79	0.75	0.66	0.78	0.74	0.66	0.81	0.74	0.64
[0347] SE	0.039	0.041	0.047	0.041	0.042	0.047	0.039	0.042	0.048
p 值	1.1E-13	9.2E-10	6.0E-4	4.3E-12	1.1E-8	4.2E-4	8.9E-16	1.1E-8	0.0024
n 恢复组	32	38	64	30	37	61	27	37	55
n 未恢复组	117	110	69	119	111	72	122	111	78
截止四分位 2	6850	6960	7010	6850	6960	7010	6850	6960	7010

[0348]

灵敏度	83%	83%	84%	82%	82%	85%	83%	82%	82%
特异性	53%	47%	33%	53%	46%	34%	59%	46%	33%
截止四分位 3	11000	11100	11800	11000	11100	11800	11000	11100	11800
灵敏度	60%	60%	65%	59%	59%	64%	59%	59%	60%
特异性	84%	79%	66%	83%	78%	66%	89%	78%	64%
截止四分位 4	20100	20400	23200	20100	20400	23200	20100	20400	23200
灵敏度	30%	29%	33%	29%	29%	33%	30%	29%	32%
特异性	91%	87%	83%	90%	86%	84%	93%	86%	84%
OR 四分位 2	5.50	4.31	2.58	5.33	3.87	2.91	7.00	3.87	2.22
p 值	7.7E-5	3.8E-4	0.025	1.3E-4	0.0010	0.012	2.3E-5	0.0010	0.052
95% CI 的下限	2.36	1.92	1.12	2.26	1.72	1.27	2.84	1.72	0.992
95% CI 的上限	12.8	9.65	5.90	12.6	8.67	6.69	17.2	8.67	4.99
OR 四分位 3	8.04	5.62	3.58	7.14	5.32	3.37	11.5	5.32	2.65
p 值	6.5E-5	9.6E-5	4.7E-4	1.8E-4	1.7E-4	8.6E-4	1.3E-4	1.7E-4	0.0073
95% CI 的下限	2.89	2.36	1.75	2.56	2.23	1.65	3.29	2.23	1.30
95% CI 的上限	22.4	13.4	7.32	20.0	12.7	6.88	40.3	12.7	5.41
OR 四分位 4	4.13	2.71	2.41	3.75	2.59	2.55	5.23	2.59	2.41
p 值	0.027	0.057	0.036	0.039	0.069	0.028	0.030	0.069	0.044
95% CI 的下限	1.18	0.970	1.06	1.07	0.927	1.10	1.18	0.927	1.02
95% CI 的上限	14.4	7.56	5.47	13.2	7.25	5.89	23.3	7.25	5.69

[0349] 表8.4:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0350] sCr或UO

[0351]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7010	13600	6300	13400	6300	13100
平均值	9170	18700	8670	18400	8830	18200
标准偏差	8610	14800	8740	14600	8980	14600
p(t-检验)		2.7E-4		3.8E-4		8.7E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	40700	72100	40700	72100	40700	72100
n(患者)	38	106	33	111	31	113

[0352] 仅sCr

[0353]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7010	13700	7010	13700	7010	13600
平均值	10400	18800	10400	18800	10600	18600
标准偏差	10300	14800	10300	14800	10500	14800
p(t-检验)		6.9E-4		6.9E-4		0.0015
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	42400	72100	42400	72100
n(患者)	45	99	45	99	43	101

[0354] 仅UO

[0355]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	9380	15600	9380	13700	9000	13900
平均值	13300	21200	13700	20100	12400	20200
标准偏差	10700	16300	11200	15800	10600	15600

[0356]

p（t-检验）		0.0020		0.014		0.0031
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	60	65	52	73	47	79

[0357]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.78	0.76	0.67	0.80	0.76	0.64	0.79	0.75	0.68
SE	0.039	0.040	0.048	0.038	0.040	0.049	0.040	0.041	0.047
p 值	6.5E-13	5.8E-11	4.9E-4	1.1E-15	5.8E-11	0.0055	1.3E-13	1.7E-9	1.5E-4
n 恢复组	38	45	60	33	45	52	31	43	47
n 未恢复组	106	99	65	111	99	73	113	101	79
截止四分位 2	7010	7010	7530	7010	7010	7530	7010	7010	7250
灵敏度	83%	84%	85%	84%	84%	81%	83%	83%	82%
特异性	47%	44%	35%	55%	44%	33%	55%	44%	38%
截止四分位 3	11100	11100	12400	11100	11100	12400	11100	11100	12300
灵敏度	62%	64%	63%	61%	64%	59%	60%	62%	59%
特异性	84%	80%	63%	88%	80%	62%	87%	79%	66%
截止四分位 4	21600	21600	23800	21600	21600	23800	21600	21600	23600
灵敏度	30%	30%	35%	30%	30%	33%	29%	30%	34%
特异性	89%	87%	85%	91%	87%	85%	90%	86%	89%
OR 四分位 2	4.40	4.15	2.96	6.20	4.15	2.05	6.01	3.91	2.88
p 值	3.6E-4	4.5E-4	0.013	2.6E-5	4.5E-4	0.088	4.6E-5	7.9E-4	0.012
95% CI 的下限	1.95	1.87	1.26	2.65	1.87	0.900	2.54	1.76	1.26
95% CI 的上限	9.93	9.19	6.98	14.5	9.19	4.66	14.2	8.67	6.57
OR 四	8.80	7.00	2.95	11.5	7.00	2.29	10.2	6.26	2.85

[0358]

分位 3									
p 值	8.3E-6	5.3E-6	0.0036	1.7E-5	5.3E-6	0.025	4.5E-5	1.8E-5	0.0064
95% CI 的下限	3.38	3.03	1.43	3.77	3.03	1.11	3.34	2.71	1.34
95% CI 的上限	22.9	16.2	6.11	34.9	16.2	4.75	31.1	14.5	6.04
OR 四分位 4	3.68	2.83	3.10	4.23	2.83	2.69	3.85	2.61	4.36
p 值	0.022	0.034	0.011	0.024	0.034	0.031	0.036	0.051	0.0054
95% CI 的下限	1.20	1.08	1.30	1.21	1.08	1.10	1.09	0.995	1.55
95% CI 的上限	11.2	7.38	7.42	14.8	7.38	6.61	13.5	6.82	12.3

[0359] 表8.5:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0360] sCr或UO

[0361]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	8090	13900	8010	14000	8010	14000
平均值	12200	20100	11800	20500	11800	20500
标准偏差	11000	15800	10500	15900	10500	15900
p(t-检验)		4.2E-4		1.2E-4		1.2E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n(患者)	81	69	80	70	80	70

[0362] 仅sCr

[0363]

恢复期持续时间(小时)	24	48	72

[0364]

	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7530	13900	7500	13900	7500	13900
平均值	10800	19900	10500	19900	10500	19900
标准偏差	9540	15600	9400	15500	9400	15500
p（t-检验）		4.5E-5		2.9E-5		2.9E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	42400	72100	42400	72100
n（患者）	67	83	65	85	65	85

[0365] 仅UO

[0366]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	8740	16800	8720	17000	8440	16800
平均值	12500	21900	12000	22300	12000	22000
标准偏差	10600	17000	10200	16900	10300	16700
p（t-检验）		4.8E-5		7.5E-6		1.3E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	95	54	93	56	91	58

[0367]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.70	0.74	0.71	0.72	0.75	0.73	0.72	0.75	0.73
SE	0.043	0.040	0.046	0.042	0.039	0.044	0.042	0.039	0.044
p 值	2.3E-6	1.7E-9	5.3E-6	3.7E-7	2.0E-10	3.5E-7	3.7E-7	2.0E-10	2.1E-7
n 恢复组	81	67	95	80	65	93	80	65	91
n 未恢复组	69	83	54	70	85	56	70	85	58

[0368]

截止四分位2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	88%	88%	91%	89%	88%	91%	89%	88%	91%
特异性	37%	42%	34%	38%	43%	34%	38%	43%	35%
截止四分位3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	68%	67%	72%	69%	67%	73%	69%	67%	74%
特异性	65%	72%	62%	66%	72%	63%	66%	72%	65%
截止四分位4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	33%	35%	37%	34%	35%	39%	34%	35%	38%
特异性	81%	87%	81%	82%	88%	83%	82%	88%	82%
OR四分位2	4.49	5.24	4.98	4.65	5.68	5.35	4.65	5.68	5.75
p值	6.6E-4	7.5E-5	0.0019	4.9E-4	3.5E-5	0.0012	4.9E-4	3.5E-5	7.1E-4
95% CI的下限	1.89	2.31	1.81	1.96	2.49	1.94	1.96	2.49	2.09
95% CI的上限	10.6	11.9	13.7	11.0	12.9	14.7	11.0	12.9	15.8
OR四分位3	4.04	5.24	4.26	4.28	5.32	4.74	4.28	5.32	5.29
p值	6.0E-5	3.8E-6	9.0E-5	3.2E-5	3.6E-6	2.7E-5	3.2E-5	3.6E-6	7.5E-6
95% CI的下限	2.04	2.60	2.06	2.16	2.62	2.29	2.16	2.62	2.55
95% CI的上限	8.00	10.6	8.80	8.50	10.8	9.81	8.50	10.8	11.0
OR四分位4	2.20	3.46	2.52	2.46	3.89	3.11	2.46	3.89	2.86
p值	0.040	0.0036	0.016	0.020	0.0021	0.0034	0.020	0.0021	0.0064
95% CI的下限	1.04	1.50	1.18	1.15	1.64	1.46	1.15	1.64	1.34
95% CI的上限	4.66	7.97	5.35	5.25	9.22	6.66	5.25	9.22	6.11

[0369] 实施例9.使用Basigin评价进入ICU的患者的肾状态:从RIFLE I和F恢复至RIFLE 0和R

[0370] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的Basigin。

[0371] 在从样品收集之后起12、24、48或72小时期间或在样品收集后7天内的任何时间,

通过基于血清肌酸酐、排尿量，或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“恢复”和“未恢复”群体。“恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是无损伤(RIFLE 0)或具有损伤危险(R)的那些患者。“未恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是损伤(I)或衰竭(F)的那些患者。如果患者在招募的9天内死亡或被置于肾替代疗法(RRT)，则患者视为“未恢复”。

[0372] 使用接收器操作特征(ROC)分析确定区分“恢复”和“未恢复”组的能力。

[0373] 表9.1：“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较，其中恢复在样品收集后12小时开始，并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0374] sCr或UO

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	5080	13000	5080	12800	5060	12700
平均值	6710	18300	6620	18200	6660	18100
标准偏差	4750	14600	4790	14500	4870	14500
p(t-检验)		1.7E-5		3.3E-5		5.2E-5
最小值	1970	3040	1970	3040	1970	3040
最大值	25700	72100	25700	72100	25700	72100
n(患者)	32	118	30	120	29	121

[0375]

[0376] 仅sCr

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	5620	13600	5620	13600	5590	13500
平均值	8410	18700	8410	18700	8480	18500
标准偏差	8550	14600	8550	14600	8650	14600
p(t-检验)		4.0E-5		4.0E-5		6.5E-5
最小值	1970	3040	1970	3040	1970	3040
最大值	42400	72100	42400	72100	42400	72100
n(患者)	41	109	41	109	40	110

[0377]

[0378] 仅UO

[0379]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	8160	14100	8160	13900	8090	13900
平均值	11600	20400	11700	20100	11700	19900
标准偏差	10500	15700	10600	15700	10600	15600
p（t-检验）		8.3E-5		1.9E-4		2.6E-4
最小值	1970	3170	1970	3170	1970	3170
最大值	60400	72100	60400	72100	60400	72100
n（患者）	76	73	74	75	73	76

[0380]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.85	0.82	0.72	0.85	0.82	0.71	0.85	0.81	0.71
SE	0.032	0.034	0.042	0.033	0.034	0.042	0.033	0.035	0.042
p 值	0	0	1.6E-7	0	0	7.2E-7	0	0	9.7E-7

[0381]

n 恢复组	32	41	76	30	41	74	29	40	73
n 未恢复组	118	109	73	120	109	75	121	110	76
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	86%	88%	86%	85%	88%	85%	84%	87%	86%
特异性	66%	61%	36%	67%	61%	35%	66%	60%	36%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	60%	62%	71%	60%	62%	71%	60%	62%	70%
特异性	88%	83%	70%	90%	83%	70%	90%	82%	70%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	31%	32%	36%	31%	32%	35%	31%	32%	34%
特异性	97%	93%	84%	97%	93%	84%	97%	92%	84%
OR 四分位 2	11.3	11.5	3.47	11.3	11.5	3.15	10.2	10.3	3.27
p 值	9.6E-8	2.0E-8	0.0028	1.7E-7	2.0E-8	0.0048	5.5E-7	6.5E-8	0.0037
95% CI 的下限	4.65	4.91	1.54	4.56	4.91	1.42	4.11	4.42	1.47
95% CI 的上限	27.7	27.1	7.85	28.1	27.1	7.00	25.3	24.0	7.27
OR 四分位 3	10.6	8.06	5.71	13.5	8.06	5.69	12.7	7.63	5.34
p 值	3.2E-5	5.7E-6	1.3E-6	4.3E-5	5.7E-6	1.3E-6	6.5E-5	1.0E-5	2.7E-6
95% CI 的下限	3.48	3.27	2.82	3.88	3.27	2.82	3.65	3.10	2.65
95% CI 的上限	32.1	19.8	11.5	47.0	19.8	11.5	44.4	18.8	10.8
OR 四分位 4	14.2	5.99	2.95	12.9	5.99	2.74	12.3	5.76	2.64
p 值	0.010	0.0047	0.0066	0.014	0.0047	0.011	0.015	0.0058	0.015
95% CI 的下限	1.86	1.73	1.35	1.70	1.73	1.26	1.62	1.66	1.21
95% CI 的上限	108	20.8	6.44	98.5	20.8	5.98	94.1	20.0	5.76

[0382] 表9.2:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0383] sCr或UO

[0384]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	5750	13900	5750	13900	5750	13900
平均值	6890	19700	6810	19500	6810	19500
标准偏差	4220	14900	4250	14800	4250	14800
p(t-检验)		7.3E-8		1.5E-7		1.5E-7
最小值	1970	3580	1970	3580	1970	3580
最大值	25700	72100	25700	72100	25700	72100
n(患者)	45	105	43	107	43	107

[0385] 仅sCr

[0386]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	5980	14000	6200	13900	6200	13900
平均值	8130	19700	8180	19600	8180	19600
标准偏差	7800	14700	7870	14700	7870	14700
p(t-检验)		6.5E-7		1.2E-6		1.2E-6
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	42400	72100	42400	72100
n(患者)	50	100	49	101	49	101

[0387] 仅UO

[0388]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	8220	15000	8090	14300	8090	14300

[0389]

平均值	12000	21100	12100	20800	12100	20800
标准偏差	10700	16000	10800	15900	10800	15900
p(t-检验)		7.9E-5		1.5E-4		1.5E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n(患者)	79	66	77	68	77	68

[0390]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.86	0.85	0.72	0.86	0.84	0.72	0.86	0.84	0.72
SE	0.029	0.031	0.043	0.029	0.032	0.043	0.029	0.032	0.043
p 值	0	0	2.7E-7	0	0	3.6E-7	0	0	3.6E-7
n 恢复组	45	50	79	43	49	77	43	49	77
n 未恢复组	105	100	66	107	101	68	107	101	68
截止四分位 2	6820	6820	6850	6820	6820	6850	6820	6820	6850
灵敏度	90%	91%	89%	89%	90%	90%	89%	90%	90%
特异性	60%	58%	37%	60%	57%	38%	60%	57%	38%
截止四分位 3	11000	11000	11200	11000	11000	11200	11000	11000	11200
灵敏度	67%	68%	74%	66%	67%	74%	66%	67%	74%
特异性	89%	86%	68%	91%	86%	69%	91%	86%	69%
截止四分位 4	19900	19900	21500	19900	19900	21500	19900	19900	21500
灵敏度	35%	35%	36%	35%	35%	35%	35%	35%	35%
特异性	98%	94%	84%	98%	94%	83%	98%	94%	83%
OR 四分位 2	12.8	14.0	4.89	12.1	12.1	5.26	12.1	12.1	5.26
p 值	7.1E-9	5.4E-9	6.1E-4	1.2E-8	1.5E-8	3.4E-4	1.2E-8	1.5E-8	3.4E-4
95% CI 的下限	5.40	5.76	1.97	5.14	5.11	2.12	5.14	5.11	2.12
95% CI 的上限	30.4	33.9	12.1	28.5	28.8	13.1	28.5	28.8	13.1

[0391]

OR 四分位 3	16.0	13.1	6.23	19.2	12.4	6.13	19.2	12.4	6.13
p 值	8.5E-8	2.4E-8	8.3E-7	1.5E-7	4.6E-8	8.8E-7	1.5E-7	4.6E-8	8.8E-7
95% CI 的下限	5.80	5.29	3.01	6.37	5.02	2.98	6.37	5.02	2.98
95% CI 的上限	44.1	32.2	12.9	58.0	30.5	12.6	58.0	30.5	12.6
OR 四分位 4	23.9	8.44	2.90	22.2	8.13	2.69	22.2	8.13	2.69
p 值	0.0021	7.3E-4	0.0073	0.0027	9.0E-4	0.013	0.0027	9.0E-4	0.013
95% CI 的下限	3.17	2.45	1.33	2.94	2.36	1.24	2.94	2.36	1.24
95% CI 的上限	181	29.1	6.32	168	28.0	5.84	168	28.0	5.84

[0392] 表9.3:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0393] sCr或UO

[0394]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7010	14100	7010	14100	7010	14000
平均值	9750	19900	9750	19900	9810	19700
标准偏差	8860	15200	8860	15200	8930	15100
p(t-检验)		8.5E-6		8.5E-6		1.4E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	40700	72100	40700	72100	40700	72100
n(患者)	58	91	58	91	57	92

[0395] 仅sCr

[0396]

恢复期持续时间(小	24	48	72

[0397]

时）						
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7150	14100	7150	14100	7150	14100
平均值	10900	19700	10900	19700	10900	19700
标准偏差	10200	15100	10200	15100	10200	15100
p（t-检验）		1.2E-4		1.2E-4		1.2E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	42400	72100	42400	72100
n（患者）	61	87	61	87	61	87

[0398] 仅UO

[0399]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	8970	15600	8970	15600	8970	15600
平均值	13000	21600	13000	21600	13000	21400
标准偏差	11000	16400	11000	16400	11100	16300
p（t-检验）		4.6E-4		4.6E-4		5.9E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	72	61	72	61	70	63

[0400]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.79	0.76	0.70	0.79	0.76	0.70	0.78	0.76	0.70
SE	0.036	0.039	0.046	0.036	0.039	0.046	0.037	0.039	0.046
p 值	2.9E-15	2.6E-11	1.4E-5	2.9E-15	2.6E-11	1.4E-5	2.2E-14	2.6E-11	1.6E-5
n 恢复组	58	61	72	58	61	72	57	61	70

[0401]

n 未恢复组	91	87	61	91	87	61	92	87	63
截止四分位 2	6850	6960	7010	6850	6960	7010	6850	6960	7010
灵敏度	89%	89%	89%	89%	89%	89%	88%	89%	87%
特异性	47%	44%	35%	47%	44%	35%	46%	44%	34%
截止四分位 3	11000	11100	11800	11000	11100	11800	11000	11100	11800
灵敏度	69%	68%	69%	69%	68%	69%	68%	68%	68%
特异性	79%	75%	65%	79%	75%	65%	79%	75%	66%
截止四分位 4	20100	20400	23200	20100	20400	23200	20100	20400	23200
灵敏度	34%	33%	36%	34%	33%	36%	34%	33%	37%
特异性	88%	87%	83%	88%	87%	83%	88%	87%	84%
OR 四分位 2	7.05	6.11	4.10	7.05	6.11	4.10	6.18	6.11	3.59
p 值	4.6E-6	1.9E-5	0.0028	4.6E-6	1.9E-5	0.0028	1.3E-5	1.9E-5	0.0050
95% CI 的下限	3.06	2.67	1.63	3.06	2.67	1.63	2.73	2.67	1.47
95% CI 的上限	16.3	14.0	10.3	16.3	14.0	10.3	14.0	14.0	8.74
OR 四分位 3	8.62	6.46	4.16	8.62	6.46	4.16	8.15	6.46	4.12
p 值	5.2E-8	6.8E-7	1.2E-4	5.2E-8	6.8E-7	1.2E-4	1.1E-7	6.8E-7	1.3E-4
95% CI 的下限	3.97	3.09	2.01	3.97	3.09	2.01	3.76	3.09	2.00
95% CI 的上限	18.7	13.5	8.60	18.7	13.5	8.60	17.7	13.5	8.50
OR 四分位 4	3.76	3.31	2.82	3.76	3.31	2.82	3.63	3.31	3.08
p 值	0.0039	0.0068	0.012	0.0039	0.0068	0.012	0.0051	0.0068	0.0073
95% CI 的下限	1.53	1.39	1.25	1.53	1.39	1.25	1.47	1.39	1.35
95% CI 的上限	9.27	7.88	6.34	9.27	7.88	6.34	8.94	7.88	7.02

[0402] 表9.4:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量

(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0403] sCr或UO

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7530	14500	7520	15000	7530	14500
平均值	10800	20600	10200	20700	10000	20400
标准偏差	9670	15600	8860	15600	8680	15500
p（t-检验）		2.3E-5		5.0E-6		7.1E-6
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	40700	72100	40700	72100
n（患者）	65	79	62	82	59	85

[0404]

[0405] 仅sCr

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7550	14500	7550	14500	7630	14300
平均值	11300	20500	11300	20500	11400	20300
标准偏差	10100	15600	10100	15600	10200	15600
p（t-检验）		6.6E-5		6.6E-5		1.2E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	42400	72100	42400	72100
n（患者）	67	77	67	77	66	78

[0406]

[0407] 仅UO

[0408]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	9320	16700	9260	16800	9160	16800
平均值	13800	21900	13200	21900	13000	21800
标准偏差	11100	16800	10700	16500	10600	16400
p（t-检验）		0.0016		5.7E-4		4.3E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	70	55	65	60	64	62

[0409]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.76	0.75	0.68	0.78	0.75	0.69	0.77	0.74	0.69
SE	0.039	0.040	0.049	0.038	0.040	0.047	0.038	0.041	0.047
p 值	2.2E-11	7.0E-10	3.2E-4	2.7E-13	7.0E-10	5.9E-5	1.3E-12	5.1E-9	3.6E-5
n 恢复组	65	67	70	62	67	65	59	66	64
n 未恢复组	79	77	55	82	77	60	85	78	62
截止四分位 2	7010	7010	7530	7010	7010	7530	7010	7010	7250
灵敏度	89%	88%	87%	88%	88%	87%	86%	87%	85%
特异性	42%	40%	34%	42%	40%	35%	41%	39%	36%
截止四分位 3	11100	11100	12400	11100	11100	12400	11100	11100	12300
灵敏度	71%	70%	67%	71%	70%	67%	69%	69%	66%
特异性	75%	73%	63%	77%	73%	65%	78%	73%	66%
截止四分位 4	21600	21600	23800	21600	21600	23800	21600	21600	23600
灵敏度	34%	34%	36%	35%	34%	37%	35%	33%	37%

[0410]

特异性	86%	85%	83%	89%	85%	85%	90%	85%	86%
OR 四分位 2	5.53	5.10	3.58	5.20	5.10	3.56	4.17	4.42	3.30
p 值	8.3E-5	1.7E-4	0.0075	1.0E-4	1.7E-4	0.0058	4.8E-4	4.3E-4	0.0072
95% CI 的下限	2.36	2.18	1.41	2.26	2.18	1.45	1.87	1.93	1.38
95% CI 的上限	12.9	11.9	9.10	11.9	11.9	8.77	9.30	10.1	7.90
OR 四分位 3	7.46	6.39	3.48	8.29	6.39	3.65	8.03	6.00	3.73
p 值	1.2E-7	5.9E-7	0.0010	5.4E-8	5.9E-7	5.9E-4	1.1E-7	1.2E-6	4.6E-4
95% CI 的下限	3.54	3.09	1.65	3.87	3.09	1.74	3.72	2.91	1.78
95% CI 的上限	15.7	13.2	7.31	17.8	13.2	7.65	17.3	12.4	7.79
OR 四分位 4	3.23	2.91	2.76	4.30	2.91	3.18	4.82	2.80	3.60
p 值	0.0064	0.011	0.016	0.0016	0.011	0.0079	0.0012	0.014	0.0040
95% CI 的下限	1.39	1.28	1.20	1.73	1.28	1.36	1.86	1.23	1.51
95% CI 的上限	7.51	6.61	6.33	10.7	6.61	7.48	12.5	6.37	8.63

[0411] 表9.5:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0412] sCr或UO

[0413]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复	恢复组	未恢复	恢复组	未恢复

[0414]

		组		组		组
中值	8090	16700	8010	16800	7920	16900
平均值	12000	21400	11900	21500	11600	21800
标准偏差	10600	16300	10600	16100	10200	16200
p（t-检验）		3.4E-5		2.4E-5		5.0E-6
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	89	61	88	62	87	63

[0415] 仅sCr

[0416]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	7550	14100	7550	14100	7550	14100
平均值	11800	20400	11800	20400	11800	20400
标准偏差	11100	15400	11100	15400	11100	15400
p（t-检验）		1.3E-4		1.3E-4		1.3E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	79	71	79	71	79	71

[0417] 仅UO

[0418]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	8730	16900	8730	16900	8580	17200
平均值	12400	22600	12400	22600	12000	23000
标准偏差	10500	17200	10500	17200	10100	17000
p（t-检验）		1.4E-5		1.4E-5		1.9E-6
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	98	51	98	51	96	53

[0419]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.73	0.74	0.72	0.74	0.74	0.72	0.75	0.74	0.74
SE	0.043	0.041	0.046	0.042	0.041	0.046	0.042	0.041	0.044
p 值	8.5E-8	7.3E-9	9.3E-7	2.4E-8	7.3E-9	9.3E-7	2.4E-9	7.3E-9	4.5E-8
n 恢复组	89	79	98	88	79	98	87	79	96
n 未恢复组	61	71	51	62	71	51	63	71	53
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	92%	92%	92%	92%	92%	92%	92%	92%	92%
特异性	37%	41%	34%	38%	41%	34%	38%	41%	34%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	72%	72%	75%	73%	72%	75%	73%	72%	75%
特异性	65%	70%	62%	66%	70%	62%	67%	70%	64%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	36%	35%	39%	37%	35%	39%	38%	35%	42%
特异性	82%	84%	82%	83%	84%	82%	84%	84%	83%
OR 四分位 2	6.60	7.38	5.97	6.84	7.38	5.97	7.09	7.38	6.42
p 值	2.5E-4	3.7E-5	0.0015	1.9E-4	3.7E-5	0.0015	1.5E-4	3.7E-5	9.5E-4
95% CI 的下限	2.40	2.85	1.98	2.49	2.85	1.98	2.58	2.85	2.13
95% CI 的上限	18.1	19.1	18.0	18.8	19.1	18.0	19.5	19.1	19.3
OR 四分位 3	4.84	5.84	4.82	5.12	5.84	4.82	5.41	5.84	5.36
p 值	1.3E-5	9.3E-7	4.0E-5	6.8E-6	9.3E-7	4.0E-5	3.4E-6	9.3E-7	1.2E-5
95% CI 的下限	2.38	2.89	2.28	2.51	2.89	2.28	2.65	2.89	2.53
95% CI 的上限	9.85	11.8	10.2	10.4	11.8	10.2	11.0	11.8	11.4

[0420]

OR四分位4	2.57	2.76	2.87	2.87	2.76	2.87	3.21	2.76	3.55
p值	0.014	0.0097	0.0066	0.0064	0.0097	0.0066	0.0028	0.0097	0.0012
95% CI的下限	1.21	1.28	1.34	1.35	1.28	1.34	1.49	1.28	1.65
95% CI的上限	5.46	5.95	6.13	6.12	5.95	6.13	6.90	5.95	7.63

[0421] 实施例10.使用组织蛋白酶B评价进入ICU的患者的肾状态:从RIFLE I和F恢复至RIFLE 0

[0422] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的组织蛋白酶B。

[0423] 在从样品收集之后起12、24、48或72小时期间或在样品收集后7天内的任何时间,通过基于血清肌酸酐、排尿量,或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“恢复”和“未恢复”群体。“恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是无损伤(RIFLE 0)的那些患者。“未恢复”表示在24、48或72小时的时间段内最大RIFLE阶段具有损伤危险(R)、损伤(I)或衰竭(F)的那些患者。如果患者在招募的9天内死亡或被置于肾替代疗法(RRT),则患者视为“未恢复”。

[0424] 使用接收器操作特征(ROC)分析确定区分“恢复”和“未恢复”组的能力。

[0425] 表10.1:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后12小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0426] sCr或UO

[0427]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	0.826	3.83	0.678	3.81	0.678	3.81
平均值	1.93	12.6	2.01	12.5	2.01	12.5
标准偏差	2.20	20.8	2.34	20.7	2.34	20.7
p(t-检验)		0.13		0.16		0.16
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	5.56	111	5.56	111	5.56	111
n(患者)	9	139	8	140	8	140

[0428] 仅sCr

[0429]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	0.917	4.84	0.863	4.83	0.863	4.83
平均值	1.72	13.7	1.73	13.6	1.73	13.6
标准偏差	1.82	21.5	1.86	21.4	1.86	21.4
p（t-检验）		0.010		0.012		0.012
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	6.53	111	6.53	111	6.53	111
n（患者）	22	126	21	127	21	127

[0430] 仅UO

[0431]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.60	4.28	3.61	3.83	3.60	4.28
平均值	10.3	13.3	10.1	13.3	9.39	13.6
标准偏差	17.5	22.2	17.5	22.1	17.1	22.1
p（t-检验）		0.37		0.34		0.22

[0432]

最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	103	111	103	111	103	111
n（患者）	63	84	60	87	57	90

[0433]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.76	0.78	0.54	0.76	0.78	0.54	0.76	0.78	0.55
SE	0.068	0.045	0.048	0.071	0.046	0.048	0.071	0.046	0.048
p 值	1.3E-4	7.3E-10	0.42	2.8E-4	1.1E-9	0.37	2.8E-4	1.1E-9	0.27
n 恢复组	9	22	63	8	21	60	8	21	57
n 未恢复组	139	126	84	140	127	87	140	127	90
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	77%	80%	75%	77%	80%	76%	77%	80%	76%
特异性	56%	55%	25%	62%	57%	27%	62%	57%	26%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	52%	56%	52%	51%	56%	52%	51%	56%	52%
特异性	78%	86%	52%	75%	86%	52%	75%	86%	53%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	27%	29%	26%	26%	29%	26%	26%	29%	28%
特异性	100%	100%	76%	100%	100%	77%	100%	100%	79%
OR 四分位 2	4.18	4.85	1.02	5.62	5.44	1.14	5.62	5.44	1.10
p 值	0.041	0.0011	0.96	0.023	6.1E-4	0.73	0.023	6.1E-4	0.80
95% CI 的下限	1.06	1.88	0.481	1.27	2.06	0.538	1.27	2.06	0.516
95% CI 的上限	16.5	12.5	2.17	24.8	14.3	2.43	24.8	14.3	2.36
OR 四分位 3	3.76	8.18	1.21	3.18	7.61	1.15	3.18	7.61	1.21
p 值	0.11	0.0012	0.57	0.17	0.0018	0.69	0.17	0.0018	0.57

[0434]

95% CI 的下限	0.755	2.30	0.629	0.620	2.13	0.593	0.620	2.13	0.625
95% CI 的上限	18.7	29.0	2.33	16.3	27.1	2.21	16.3	27.1	2.36
OR 四分位 4	6.95	18.9	1.14	6.16	17.8	1.18	6.16	17.8	1.44
p 值	0.19	0.042	0.74	0.22	0.046	0.67	0.22	0.046	0.36
95% CI 的下限	0.395	1.11	0.533	0.347	1.05	0.550	0.347	1.05	0.657
95% CI 的上限	122	319	2.42	109	302	2.54	109	302	3.17

[0435] 表10.2:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0436] sCr或UO

[0437]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	1.35	4.83	2.06	4.73	1.75	4.77
平均值	2.15	13.7	2.40	13.3	2.26	13.3
标准偏差	1.90	21.6	2.00	21.4	1.95	21.3
p(t-检验)		0.011		0.028		0.031
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	6.09	111	6.09	111	6.09	111
n(患者)	23	125	19	129	18	130

[0438] 仅sCr

[0439]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	1.35	5.87	1.35	4.92	1.32	4.94

[0440]

平均值	2.21	14.7	2.27	14.5	2.18	14.4
标准偏差	2.04	22.2	2.09	22.1	2.06	22.0
p（t-检验）		0.0016		0.0026		0.0029
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	7.07	111	7.07	111	7.07	111
n（患者）	33	115	31	117	30	118

[0441] 仅UO

[0442]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.46	4.81	3.61	4.73	3.61	4.73
平均值	9.67	14.3	9.12	14.4	9.09	14.3
标准偏差	16.6	23.5	16.1	23.3	16.3	23.0
p（t-检验）		0.17		0.12		0.13
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	103	111	103	111	103	111
n（患者）	70	73	64	79	62	81

[0443]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.72	0.74	0.55	0.69	0.73	0.55	0.70	0.74	0.55
SE	0.051	0.044	0.048	0.058	0.046	0.048	0.058	0.045	0.048
p 值	9.9E-6	5.7E-8	0.30	0.0010	4.2E-7	0.32	4.0E-4	1.2E-7	0.30
n 恢复组	23	33	70	19	31	64	18	30	62
n 未恢复组	125	115	73	129	117	79	130	118	81
截止四分位 2	1.13	1.13	1.06	1.13	1.13	1.06	1.13	1.13	1.06
灵敏度	78%	80%	75%	77%	79%	76%	77%	80%	75%
特异性	39%	42%	26%	37%	42%	27%	39%	43%	26%
截止四分	3.63	3.63	3.80	3.63	3.63	3.80	3.63	3.63	3.80

[0444]

位 3									
灵敏度	55%	58%	53%	53%	57%	52%	54%	58%	52%
特异性	78%	79%	53%	74%	77%	52%	78%	80%	52%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	30%	32%	27%	29%	32%	28%	28%	31%	28%
特异性	100%	100%	77%	100%	100%	78%	100%	100%	79%
OR 四分位 2	2.23	2.95	1.06	1.92	2.80	1.14	2.12	3.00	1.06
p 值	0.094	0.010	0.88	0.21	0.017	0.73	0.15	0.011	0.88
95% CI 的下限	0.873	1.29	0.497	0.696	1.20	0.535	0.756	1.28	0.496
95% CI 的上限	5.68	6.74	2.25	5.33	6.50	2.44	5.95	7.01	2.27
OR 四分位 3	4.44	5.18	1.29	3.22	4.59	1.15	4.08	5.44	1.15
p 值	0.0055	4.1E-4	0.45	0.034	0.0011	0.68	0.018	5.9E-4	0.68
95% CI 的下限	1.55	2.08	0.667	1.10	1.83	0.594	1.28	2.07	0.593
95% CI 的上限	12.7	12.9	2.48	9.46	11.5	2.22	13.1	14.3	2.23
OR 四分位 4	19.9	32.0	1.27	15.8	29.3	1.38	14.8	28.1	1.49
p 值	0.038	0.016	0.53	0.056	0.019	0.41	0.062	0.021	0.31
95% CI 的下限	1.18	1.91	0.596	0.931	1.75	0.638	0.872	1.67	0.686
95% CI 的上限	336	537	2.72	269	493	2.98	253	471	3.26

[0445] 表10.3:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0446] sCr或UO

[0447]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复	恢复组	未恢复	恢复组	未恢复

[0448]

		组		组		组
中值	1.95	6.29	1.72	5.97	2.02	5.42
平均值	2.27	14.9	2.18	14.7	2.34	14.3
标准偏差	1.88	22.4	1.88	22.2	1.90	22.1
p（t-检验）		0.0013		0.0019		0.0041
最小值	0.0435	0.126	0.0435	0.126	0.208	0.0435
最大值	7.19	111	7.19	111	7.19	111
n（患者）	34	113	32	115	29	118

[0449] 仅sCr

[0450]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	1.50	6.80	1.44	6.67	1.44	6.67
平均值	2.33	16.0	2.26	15.9	2.26	15.9
标准偏差	2.05	23.0	2.04	22.9	2.04	22.9
p（t-检验）		1.9E-4		2.3E-4		2.3E-4
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	7.19	111	7.19	111	7.19	111
n（患者）	42	104	41	105	41	105

[0451] 仅UO

[0452]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.62	5.36	3.71	4.85	4.14	4.73
平均值	9.06	16.4	9.13	16.0	9.89	14.9
标准偏差	15.9	24.9	16.2	24.5	16.9	23.8
p（t-检验）		0.046		0.062		0.18
最小值	0.0435	0.126	0.0435	0.126	0.156	0.0435
最大值	103	111	103	111	103	111
n（患者）	65	66	62	69	56	75

[0453]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.72	0.74	0.59	0.73	0.75	0.59	0.70	0.75	0.54
SE	0.045	0.041	0.050	0.045	0.041	0.050	0.049	0.041	0.051
p 值	1.3E-6	3.9E-9	0.079	4.3E-7	1.2E-9	0.084	5.1E-5	1.2E-9	0.43
n 恢复组	34	42	65	32	41	62	29	41	56
n 未恢复组	113	104	66	115	105	69	118	105	75
截止四分位 2	1.13	1.12	1.16	1.13	1.12	1.16	1.13	1.12	1.16
灵敏度	79%	81%	80%	79%	81%	80%	78%	81%	76%
特异性	38%	40%	31%	41%	41%	31%	38%	41%	27%
截止四分位 3	3.62	3.63	4.38	3.62	3.63	4.38	3.62	3.63	4.38
灵敏度	58%	61%	55%	58%	61%	54%	57%	61%	51%
特异性	76%	76%	54%	78%	78%	53%	76%	78%	50%
截止四分位 4	13.1	13.3	14.2	13.1	13.3	14.2	13.1	13.3	14.2
灵敏度	33%	36%	29%	32%	35%	29%	31%	35%	27%
特异性	100%	100%	78%	100%	100%	79%	100%	100%	77%
OR 四分位 2	2.30	2.86	1.81	2.59	3.01	1.74	2.16	3.01	1.16
p 值	0.049	0.0089	0.15	0.026	0.0062	0.18	0.081	0.0062	0.72
95% CI 的下限	1.01	1.30	0.811	1.12	1.37	0.782	0.908	1.37	0.524
95% CI 的上限	5.24	6.27	4.05	5.99	6.63	3.85	5.15	6.63	2.56
OR 四分位 3	4.56	4.92	1.40	4.99	5.55	1.32	4.13	5.55	1.03
p 值	6.8E-4	1.2E-4	0.34	5.9E-4	6.0E-5	0.43	0.0027	6.0E-5	0.94
95% CI 的下限	1.90	2.18	0.704	1.99	2.40	0.662	1.64	2.40	0.514
95% CI 的上限	11.0	11.1	2.78	12.5	12.8	2.62	10.4	12.8	2.05
OR 四分位 4	33.8	47.2	1.47	31.1	45.4	1.54	27.1	45.4	1.20
p 值	0.014	0.0073	0.34	0.017	0.0079	0.29	0.022	0.0079	0.65

[0454]

95% CI 的下限	2.02	2.82	0.664	1.85	2.72	0.689	1.62	2.72	0.538
95% CI 的上限	567	790	3.26	521	760	3.43	456	760	2.69

[0455] 表10.4:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0456] sCr或UO

[0457]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	1.55	6.50	1.81	6.13	1.81	6.03
平均值	4.26	15.4	4.54	14.7	4.60	14.5
标准偏差	9.39	22.9	9.94	22.6	10.2	22.4
p(t-检验)		0.0033		0.0097		0.014
最小值	0.0435	0.126	0.208	0.0435	0.208	0.0435
最大值	57.5	111	57.5	111	57.5	111
n(患者)	41	101	36	106	34	108

[0458] 仅sCr

[0459]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	1.81	6.80	1.81	6.80	1.81	6.58
平均值	4.15	16.2	4.15	16.2	4.18	16.0
标准偏差	8.71	23.5	8.71	23.5	8.88	23.4
p(t-检验)		7.8E-4		7.8E-4		0.0012
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	57.5	111	57.5	111	57.5	111
n(患者)	48	94	48	94	46	96

[0460] 仅UO

[0461]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.61	5.87	3.85	4.81	4.14	4.77
平均值	9.26	16.7	9.70	15.5	10.2	14.9
标准偏差	16.1	25.3	16.6	24.4	17.0	23.8
p（t-检验）		0.056		0.14		0.23
最小值	0.0435	0.126	0.156	0.0435	0.156	0.0435
最大值	103	111	103	111	103	111
n（患者）	60	61	52	69	48	74

[0462]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.71	0.60	0.69	0.71	0.56	0.69	0.71	0.53
SE	0.044	0.043	0.051	0.047	0.043	0.052	0.048	0.044	0.053
p 值	1.3E-6	8.0E-7	0.043	6.2E-5	8.0E-7	0.26	9.7E-5	1.5E-6	0.58
n 恢复组	41	48	60	36	48	52	34	46	48
n 未恢复组	101	94	61	106	94	69	108	96	74
截止四分位 2	1.12	1.12	1.22	1.12	1.12	1.22	1.12	1.12	1.23
灵敏度	80%	81%	80%	79%	81%	77%	79%	80%	73%
特异性	39%	38%	30%	39%	38%	27%	38%	37%	23%
截止四分位 3	3.71	3.71	4.38	3.71	3.71	4.38	3.71	3.71	4.56
灵敏度	60%	63%	56%	58%	63%	52%	58%	62%	51%
特异性	76%	75%	55%	75%	75%	52%	76%	76%	52%
截止四分位 4	13.3	13.3	16.1	13.3	13.3	16.1	13.3	13.3	15.7
灵敏度	33%	35%	30%	31%	35%	28%	31%	34%	27%
特异性	93%	94%	78%	92%	94%	77%	91%	93%	77%

[0463]

OR 四分位 2	2.59	2.53	1.75	2.43	2.53	1.22	2.29	2.38	0.803
p 值	0.019	0.019	0.19	0.033	0.019	0.64	0.051	0.030	0.61
95% CI 的下限	1.17	1.16	0.756	1.07	1.16	0.532	0.997	1.09	0.344
95% CI 的上限	5.74	5.52	4.05	5.51	5.52	2.80	5.25	5.19	1.87
OR 四分位 3	4.73	5.06	1.54	4.23	5.06	1.18	4.55	5.30	1.15
p 值	1.9E-4	4.2E-5	0.24	8.6E-4	4.2E-5	0.66	7.4E-4	3.8E-5	0.71
95% CI 的下限	2.09	2.33	0.751	1.81	2.33	0.573	1.89	2.40	0.555
95% CI 的上限	10.7	11.0	3.15	9.87	11.0	2.42	11.0	11.7	2.37
OR 四分位 4	6.15	8.11	1.51	4.97	8.11	1.27	4.55	7.51	1.25
p 值	0.0043	9.6E-4	0.32	0.012	9.6E-4	0.58	0.018	0.0015	0.61
95% CI 的下限	1.77	2.34	0.663	1.42	2.34	0.550	1.30	2.16	0.534
95% CI 的上限	21.4	28.1	3.45	17.4	28.1	2.92	15.9	26.0	2.90

[0464] 表10.5:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0465] sCr或UO

[0466]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	2.42	6.53	2.46	6.52	2.46	6.52
平均值	8.34	16.7	8.43	16.5	8.43	16.5
标准偏差	15.4	24.8	15.4	24.6	15.4	24.6
p(t-检验)		0.012		0.016		0.016
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126

[0467]

最大值	103	111	103	111	103	111
n(患者)	85	63	84	64	84	64

[0468] 仅sCr

[0469]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	1.95	8.30	2.04	7.97	2.04	7.97
平均值	4.59	18.5	4.71	18.0	4.71	18.0
标准偏差	8.07	25.2	8.15	25.0	8.15	25.0
p(t-检验)		1.9E-5		4.5E-5		4.5E-5
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	57.5	111	57.5	111	57.5	111
n(患者)	70	78	68	80	68	80

[0470] 仅UO

[0471]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.05	6.20	3.05	5.36	3.05	5.36
平均值	8.92	17.6	9.06	17.0	9.16	16.6
标准偏差	15.1	26.7	15.2	26.3	15.4	26.0
p(t-检验)		0.013		0.021		0.032
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	103	111	103	111	103	111
n(患者)	95	52	93	54	91	56

[0472]

恢复期持续时间(小时)	24			48			72		
	sCr 或	仅 sCr	仅 UO	sCr 或	仅 sCr	仅 UO	sCr 或	仅 sCr	仅 UO

[0473]

	UO			UO			UO		
AUC	0.64	0.71	0.60	0.63	0.69	0.59	0.63	0.69	0.58
SE	0.047	0.042	0.050	0.047	0.043	0.049	0.047	0.043	0.049
p 值	0.0030	3.3E-7	0.053	0.0063	1.0E-5	0.082	0.0063	1.0E-5	0.093
n 恢复组	85	70	95	84	68	93	84	68	91
n 未恢复组	63	78	52	64	80	54	64	80	56
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	83%	83%	77%	81%	81%	76%	81%	81%	77%
特异性	31%	34%	26%	30%	32%	26%	30%	32%	26%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	62%	65%	60%	61%	64%	59%	61%	64%	59%
特异性	59%	67%	55%	58%	66%	55%	58%	66%	55%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	32%	40%	31%	31%	39%	30%	31%	39%	29%
特异性	80%	91%	78%	80%	91%	77%	80%	91%	77%
OR 四分位 2	2.08	2.61	1.19	1.84	2.07	1.10	1.84	2.07	1.18
p 值	0.071	0.015	0.67	0.13	0.059	0.82	0.13	0.059	0.67
95% CI 的下限	0.938	1.20	0.540	0.839	0.972	0.504	0.839	0.972	0.545
95% CI 的上限	4.62	5.65	2.62	4.02	4.42	2.39	4.02	4.42	2.57
OR 四分位 3	2.32	3.86	1.79	2.18	3.44	1.77	2.18	3.44	1.75
p 值	0.013	1.1E-4	0.098	0.021	3.6E-4	0.10	0.021	3.6E-4	0.10
95% CI 的下限	1.19	1.95	0.899	1.12	1.75	0.895	1.12	1.75	0.892
95% CI 的上限	4.52	7.64	3.54	4.24	6.78	3.48	4.24	6.78	3.43
OR 四分位 4	1.86	7.04	1.57	1.79	6.54	1.44	1.79	6.54	1.33
p 值	0.11	5.9E-5	0.25	0.13	1.1E-4	0.34	0.13	1.1E-4	0.46
95% CI 的下限	0.878	2.72	0.730	0.846	2.53	0.675	0.846	2.53	0.625
95% CI 的上限	3.94	18.2	3.36	3.79	16.9	3.09	3.79	16.9	2.84

[0474] 表10.6:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后12小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量

(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0475] sCr或UO

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	62.2	104	58.6	103	58.6	103
平均值	72.8	116	74.2	115	74.2	115
标准偏差	33.3	66.6	35.3	66.6	35.3	66.6
p（t-检验）		0.057		0.084		0.084
最小值	41.1	13.2	41.1	13.2	41.1	13.2
最大值	134	401	134	401	134	401
n（患者）	9	141	8	142	8	142

[0476]

[0477] 仅sCr

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	65.2	105	68.2	104	68.2	104
平均值	81.9	118	83.5	117	83.5	117
标准偏差	44.3	67.3	45.1	67.2	45.1	67.2
p（t-检验）		0.031		0.048		0.048
最小值	23.6	13.2	23.6	13.2	23.6	13.2
最大值	174	401	174	401	174	401
n（患者）	18	132	17	133	17	133

[0478]

[0479] 仅UO

[0480]

恢复期持续时间（小时）	24	48	72

[0481]

	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	91.4	115	92.8	114	94.2	112
平均值	98.4	125	98.1	124	99.5	122
标准偏差	51.1	73.2	50.5	73.0	51.2	72.4
p（t-检验）		0.015		0.018		0.038
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	246	401
n（患者）	63	86	60	89	57	92

[0482]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.66	0.60	0.71	0.65	0.60	0.71	0.65	0.58
SE	0.076	0.062	0.046	0.081	0.064	0.047	0.081	0.064	0.047
p 值	0.0049	0.0075	0.032	0.012	0.018	0.037	0.012	0.018	0.082
n 恢复组	9	18	63	8	17	60	8	17	57
n 未恢复组	141	132	86	142	133	89	142	133	92
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	77%	78%	80%	76%	77%	79%	76%	77%	78%
特异性	56%	50%	32%	50%	47%	30%	50%	47%	30%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	52%	52%	57%	51%	52%	56%	51%	52%	54%
特异性	78%	67%	59%	75%	65%	58%	75%	65%	56%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	27%	27%	30%	27%	27%	30%	27%	27%	29%
特异性	100%	89%	81%	100%	88%	82%	100%	88%	81%
OR 四分位 2	4.09	3.55	1.89	3.18	3.05	1.58	3.18	3.05	1.53
p 值	0.044	0.014	0.097	0.12	0.035	0.23	0.12	0.035	0.27
95% CI 的下限	1.04	1.29	0.891	0.754	1.08	0.746	0.754	1.08	0.720
95% CI 的	16.1	9.77	4.00	13.4	8.60	3.34	13.4	8.60	3.25

[0483]

上限									
OR 四分位 3	3.76	2.19	1.88	3.17	1.98	1.79	3.17	1.98	1.52
p 值	0.11	0.14	0.059	0.17	0.20	0.083	0.17	0.20	0.21
95% CI 的下限	0.754	0.776	0.975	0.619	0.691	0.925	0.619	0.691	0.784
95% CI 的上限	18.7	6.18	3.64	16.3	5.66	3.48	16.3	5.66	2.96
OR 四分位 4	7.07	3.00	1.84	6.26	2.78	1.94	6.26	2.78	1.74
p 值	0.18	0.16	0.12	0.21	0.19	0.10	0.21	0.19	0.17
95% CI 的下限	0.402	0.657	0.845	0.353	0.606	0.876	0.353	0.606	0.783
95% CI 的上限	124	13.7	4.01	111	12.8	4.30	111	12.8	3.85

[0484] 表10.7:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0485] sCr或UO

[0486]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	54.6	111	60.9	105	67.1	104
平均值	73.4	120	77.6	118	79.0	118
标准偏差	42.2	66.8	44.0	67.0	45.0	66.9
p(t-检验)		0.0025		0.014		0.022
最小值	23.6	13.2	23.6	13.2	23.6	13.2
最大值	170	401	170	401	170	401
n(患者)	21	129	18	132	17	133

[0487] 仅sCr

[0488]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	64.7	111	67.7	109	68.2	106
平均值	81.1	121	84.1	119	85.2	119
标准偏差	44.6	67.9	44.9	68.0	45.4	68.0
p（t-检验）		0.0039		0.012		0.019
最小值	23.6	13.2	23.6	13.2	23.6	13.2
最大值	174	401	174	401	174	401
n（患者）	28	122	26	124	25	125

[0489] 仅UO

[0490]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	88.6	120	90.0	118	90.0	113
平均值	96.7	131	97.1	129	97.5	128
标准偏差	52.3	73.9	52.2	73.4	52.9	72.8
p（t-检验）		0.0016		0.0039		0.0061
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	246	401
n（患者）	71	74	66	79	64	81

[0491]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.73	0.68	0.64	0.70	0.66	0.63	0.69	0.65	0.62
SE	0.052	0.051	0.046	0.059	0.054	0.046	0.061	0.056	0.046
p 值	8.7E-6	3.2E-4	0.0024	7.8E-4	0.0033	0.0061	0.0022	0.0071	0.0094
n 恢复组	21	28	71	18	26	66	17	25	64

[0492]

n 未恢复组	129	122	74	132	124	79	133	125	81
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	80%	80%	84%	78%	79%	81%	77%	78%	81%
特异性	57%	50%	34%	50%	46%	32%	47%	44%	33%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	53%	54%	59%	52%	53%	57%	52%	53%	56%
特异性	71%	68%	59%	67%	65%	58%	65%	64%	56%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	29%	29%	34%	28%	28%	33%	28%	28%	32%
特异性	95%	89%	83%	94%	88%	83%	94%	88%	83%
OR 四分位 2	5.28	4.08	2.64	3.55	3.23	1.99	3.05	2.85	2.15
p 值	7.3E-4	0.0014	0.016	0.014	0.0093	0.077	0.035	0.022	0.050
95% CI 的下限	2.01	1.72	1.20	1.29	1.33	0.927	1.08	1.16	0.999
95% CI 的上限	13.9	9.70	5.81	9.77	7.82	4.28	8.60	7.00	4.62
OR 四分位 3	2.88	2.49	2.12	2.19	2.15	1.80	1.98	1.99	1.61
p 值	0.040	0.040	0.026	0.14	0.089	0.082	0.20	0.13	0.16
95% CI 的下限	1.05	1.04	1.09	0.776	0.890	0.928	0.691	0.818	0.830
95% CI 的上限	7.88	5.94	4.12	6.18	5.19	3.48	5.66	4.84	3.11
OR 四分位 4	8.04	3.35	2.51	6.62	3.01	2.45	6.17	2.85	2.28
p 值	0.046	0.060	0.022	0.071	0.087	0.028	0.083	0.11	0.044
95% CI 的下限	1.04	0.951	1.14	0.850	0.851	1.10	0.789	0.803	1.02
95% CI 的上限	62.1	11.8	5.50	51.5	10.7	5.46	48.2	10.1	5.07

[0493] 表10.8:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0494] sCr或UO

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	76.1	106	76.1	106	84.0	105
平均值	90.2	120	90.3	120	91.9	119
标准偏差	51.3	68.1	52.3	67.8	54.0	67.5
p（t-检验）		0.022		0.029		0.057
最小值	23.6	13.2	23.6	13.2	23.6	13.2
最大值	246	401	246	401	246	401
n（患者）	32	117	30	119	27	122

[0495]

[0496] 仅sCr

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	86.1	109	87.0	106	87.0	106
平均值	95.9	121	97.0	120	97.0	120
标准偏差	51.8	69.1	52.1	69.1	52.1	69.1
p（t-检验）		0.047		0.067		0.067
最小值	23.6	13.2	23.6	13.2	23.6	13.2
最大值	246	401	246	401	246	401
n（患者）	38	110	37	111	37	111

[0497]

[0498] 仅UO

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	98.3	118	96.1	115	106	108
平均值	105	130	106	128	111	123
标准偏差	56.9	73.2	58.0	72.1	58.5	71.9
p（t-检验）		0.034		0.050		0.28
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	260	401	260	401	260	401
n（患者）	64	69	61	72	55	78

[0499]

[0500]

[0501]

恢复期持续时间(小时)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.64	0.60	0.60	0.64	0.60	0.59	0.62	0.60	0.54
SE	0.052	0.051	0.049	0.053	0.052	0.049	0.056	0.052	0.051
p 值	0.0073	0.041	0.046	0.0095	0.067	0.060	0.027	0.067	0.41
n 恢复组	32	38	64	30	37	61	27	37	55
n 未恢复组	117	110	69	119	111	72	122	111	78
截止四分位 2	66.7	66.8	69.2	66.7	66.8	69.2	66.7	66.8	69.2
灵敏度	79%	80%	81%	79%	79%	81%	79%	79%	76%
特异性	41%	39%	31%	40%	38%	31%	41%	38%	25%
截止四分位 3	101	101	106	101	101	106	101	101	106
灵敏度	53%	53%	54%	53%	52%	53%	52%	52%	50%
特异性	59%	58%	53%	60%	57%	52%	59%	57%	49%
截止四分位 4	142	143	148	142	143	148	142	143	148
灵敏度	29%	27%	33%	29%	27%	32%	28%	27%	29%
特异性	88%	82%	83%	87%	81%	82%	85%	81%	80%
OR 四分位 2	2.65	2.61	1.96	2.51	2.33	1.87	2.54	2.33	1.06
p 值	0.022	0.019	0.10	0.035	0.040	0.12	0.038	0.040	0.89
95% CI 的下限	1.15	1.17	0.878	1.07	1.04	0.845	1.05	1.04	0.478
95% CI 的上限	6.12	5.81	4.37	5.88	5.22	4.16	6.13	5.22	2.35
OR 四分位 3	1.65	1.53	1.31	1.69	1.44	1.23	1.61	1.44	0.964
p 值	0.22	0.26	0.44	0.21	0.34	0.55	0.27	0.34	0.92
95% CI 的下限	0.745	0.728	0.663	0.747	0.679	0.623	0.689	0.679	0.484

[0502]

95% CI 的上限	3.64	3.23	2.59	3.81	3.04	2.44	3.74	3.04	1.92
OR 四分位 4	2.87	1.66	2.41	2.60	1.59	2.13	2.22	1.59	1.67
p 值	0.066	0.28	0.036	0.096	0.33	0.070	0.17	0.33	0.22
95% CI 的下限	0.935	0.661	1.06	0.844	0.631	0.940	0.715	0.631	0.736
95% CI 的上限	8.80	4.17	5.47	8.01	4.00	4.84	6.90	4.00	3.80

[0503] 表10.9:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0504] sCr或UO

[0505]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	77.9	118	84.0	113	87.0	113
平均值	88.8	125	91.7	123	94.1	121
标准偏差	49.9	68.6	52.1	68.3	52.5	68.3
p(t-检验)		0.0033		0.018		0.041
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	246	401
n(患者)	38	106	33	111	31	113

[0506] 仅sCr

[0507]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	85.2	118	85.2	118	87.0	113
平均值	94.3	125	94.3	125	96.1	124
标准偏差	50.5	70.1	50.5	70.1	50.7	70.2

[0508]

p(t-检验)		0.0088		0.0088		0.021
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	246	401
n(患者)	45	99	45	99	43	101

[0509] 仅UO

[0510]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	109	118	119	104	111	113
平均值	111	131	119	124	116	125
标准偏差	57.6	73.3	57.6	72.9	58.8	71.0
p（t-检验）		0.091		0.67		0.46
最小值	24.0	13.2	24.0	13.2	24.0	13.2
最大值	260	401	260	401	260	401
n（患者）	60	65	52	73	47	79

[0511]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.67	0.63	0.58	0.64	0.63	0.50	0.62	0.61	0.53
SE	0.048	0.048	0.051	0.052	0.048	0.053	0.054	0.049	0.053
p 值	4.2E-4	0.0062	0.13	0.0068	0.0062	0.99	0.025	0.020	0.61
n 恢复组	38	45	60	33	45	52	31	43	47
n 未恢复组	106	99	65	111	99	73	113	101	79
截止四分位 2	67.0	67.0	75.7	67.0	67.0	75.7	67.0	67.0	75.8
灵敏度	81%	81%	83%	78%	81%	75%	78%	80%	76%
特异性	42%	38%	33%	36%	38%	25%	35%	37%	28%
截止四分位 3	103	103	113	103	103	113	103	103	112
灵敏度	55%	55%	52%	53%	55%	48%	52%	53%	51%

[0512]

特异性	63%	60%	52%	61%	60%	46%	58%	58%	51%
截止四分位 4	146	146	152	146	146	152	146	146	152
灵敏度	29%	28%	32%	28%	28%	29%	27%	28%	28%
特异性	87%	82%	82%	85%	82%	79%	84%	81%	79%
OR 四分位 2	3.13	2.56	2.45	2.07	2.56	1.02	1.94	2.40	1.21
p 值	0.0056	0.019	0.037	0.090	0.019	0.97	0.13	0.030	0.65
95% CI 的下限	1.40	1.17	1.06	0.893	1.17	0.447	0.820	1.09	0.531
95% CI 的上限	7.01	5.59	5.70	4.80	5.59	2.32	4.57	5.28	2.75
OR 四分位 3	2.07	1.80	1.17	1.75	1.80	0.789	1.51	1.60	1.07
p 值	0.061	0.11	0.66	0.17	0.11	0.52	0.31	0.20	0.85
95% CI 的下限	0.967	0.880	0.581	0.791	0.880	0.387	0.678	0.776	0.520
95% CI 的上限	4.44	3.68	2.37	3.85	3.68	1.61	3.38	3.28	2.20
OR 四分位 4	2.73	1.82	2.13	2.17	1.82	1.51	1.97	1.68	1.43
p 值	0.056	0.18	0.077	0.14	0.18	0.34	0.20	0.25	0.41
95% CI 的下限	0.974	0.756	0.922	0.769	0.756	0.652	0.693	0.694	0.608
95% CI 的上限	7.64	4.40	4.90	6.13	4.40	3.47	5.58	4.06	3.36

[0513] 表10.10:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0514] sCr或UO

[0515]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	91.4	113	90.0	115	90.0	115

[0516]

平均值	101	128	100.0	128	100.0	128
标准偏差	52.9	76.1	53.0	75.6	53.0	75.6
p（t-检验）		0.010		0.0078		0.0078
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	253	401	253	401	253	401
n（患者）	81	69	80	70	80	70

[0517] 仅sCr

[0518]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	87.0	118	85.2	119	85.2	119
平均值	94.1	129	92.9	129	92.9	129
标准偏差	49.4	73.3	49.6	72.5	49.6	72.5
p（t-检验）		0.0012		7.6E-4		7.6E-4
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	246	401
n（患者）	67	83	65	85	65	85

[0519] 仅UO

[0520]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	94.3	115	94.2	118	91.4	120
平均值	102	134	101	134	100	135
标准偏差	54.0	79.2	54.4	77.7	54.6	76.4
p（t-检验）		0.0034		0.0026		0.0017
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	260	401	260	401	260	401
n（患者）	95	54	93	56	91	58

[0521]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.60	0.64	0.62	0.61	0.65	0.63	0.61	0.65	0.64
SE	0.047	0.045	0.049	0.046	0.044	0.048	0.046	0.044	0.047
p 值	0.031	0.0020	0.016	0.020	7.6E-4	0.0091	0.020	7.6E-4	0.0039
n 恢复组	81	67	95	80	65	93	80	65	91
n 未恢复组	69	83	54	70	85	56	70	85	58
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	81%	84%	83%	81%	85%	84%	81%	85%	84%
特异性	31%	37%	29%	31%	38%	30%	31%	38%	31%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	57%	57%	57%	57%	58%	59%	57%	58%	60%
特异性	56%	58%	54%	56%	60%	55%	56%	60%	56%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	33%	33%	37%	34%	33%	38%	34%	33%	38%
特异性	81%	84%	81%	82%	85%	82%	82%	85%	82%
OR 四分位 2	1.92	3.21	2.09	1.99	3.46	2.25	1.99	3.46	2.42
p 值	0.094	0.0031	0.086	0.078	0.0017	0.058	0.078	0.0017	0.039
95% CI 的下限	0.894	1.48	0.901	0.927	1.60	0.972	0.927	1.60	1.05
95% CI 的上限	4.14	6.93	4.84	4.29	7.50	5.21	4.29	7.50	5.60
OR 四分位 3	1.62	1.82	1.56	1.71	2.04	1.74	1.71	2.04	1.94
p 值	0.14	0.072	0.19	0.10	0.033	0.10	0.10	0.033	0.052
95% CI 的下限	0.851	0.948	0.797	0.897	1.06	0.891	0.897	1.06	0.993
95% CI 的上限	3.10	3.49	3.06	3.28	3.94	3.41	3.28	3.94	3.79
OR 四分位 4	2.20	2.45	2.52	2.46	2.70	2.68	2.46	2.70	2.86
p 值	0.040	0.026	0.016	0.020	0.016	0.010	0.020	0.016	0.0064

[0522]

95% CI 的下限	1.04	1.11	1.18	1.15	1.20	1.26	1.15	1.20	1.34
95% CI 的上限	4.66	5.42	5.35	5.25	6.08	5.70	5.25	6.08	6.11

[0523] 实施例11.使用组织蛋白酶B评价进入ICU的患者的肾状态:从RIFLE I和F恢复至RIFLE 0和R

[0524] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的组织蛋白酶B。

[0525] 在从样品收集之后起12、24、48或72小时期间或在样品收集后7天内的任何时间,通过基于血清肌酸酐、排尿量,或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“恢复”和“未恢复”群体。“恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是无损伤(RIFLE 0)或具有损伤危险(R)的那些患者。“未恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是损伤(I)或衰竭(F)的那些患者。如果患者在招募的9天内死亡或被置于肾替代疗法(RRT),则患者视为“未恢复”。

[0526] 使用接收器操作特征(ROC)分析确定区分“恢复”和“未恢复”组的能力。

[0527] 表11.1:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后12小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0528] sCr或UO

[0529]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	2.04	5.92	2.13	5.39	2.06	4.92
平均值	2.93	14.6	3.03	14.4	2.98	14.3
标准偏差	3.31	22.4	3.38	22.2	3.42	22.2
p(t-检验)		0.0029		0.0047		0.0054
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	14.6	111	14.6	111	14.6	111
n(患者)	34	114	32	116	31	117

[0530] 仅sCr

[0531]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	1.57	6.58	1.57	6.58	1.55	6.50
平均值	2.86	16.0	2.86	16.0	2.82	15.9
标准偏差	3.18	23.2	3.18	23.2	3.20	23.1
p(t-检验)		2.0E-4		2.0E-4		2.4E-4
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	14.6	111	14.6	111	14.6	111
n(患者)	46	102	46	102	45	103

[0532] 仅UO

[0533]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.05	5.36	3.29	4.83	3.17	4.85
平均值	9.39	14.8	9.61	14.5	9.07	14.9
标准偏差	16.2	23.9	16.3	23.6	15.8	23.8
p(t-检验)		0.11		0.15		0.080
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	103	111	103	111	103	111

[0534]

n(患者)	77	70	75	72	74	73

[0535]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.69	0.72	0.57	0.68	0.72	0.56	0.68	0.72	0.57
SE	0.048	0.042	0.047	0.050	0.042	0.047	0.050	0.042	0.047
p 值	9.4E-5	2.0E-7	0.13	4.2E-4	2.0E-7	0.23	2.6E-4	1.0E-7	0.14
n 恢复组	34	46	77	32	46	75	31	45	74
n 未恢复组	114	102	70	116	102	72	117	103	73
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	76%	80%	76%	76%	80%	75%	76%	81%	75%
特异性	29%	37%	26%	28%	37%	25%	29%	38%	26%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	57%	60%	57%	56%	60%	56%	56%	60%	56%
特异性	74%	72%	56%	72%	72%	55%	74%	73%	55%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	31%	34%	27%	30%	34%	26%	30%	34%	27%
特异性	94%	96%	77%	94%	96%	76%	94%	96%	77%
OR 四分位 2	1.34	2.40	1.09	1.23	2.40	1.02	1.30	2.52	1.06
p 值	0.50	0.026	0.81	0.65	0.026	0.96	0.56	0.020	0.89
95% CI 的下限	0.571	1.11	0.518	0.510	1.11	0.483	0.537	1.16	0.501
95% CI 的上限	3.16	5.21	2.31	2.97	5.21	2.14	3.15	5.47	2.22
OR 四分位 3	3.68	3.78	1.69	3.26	3.78	1.51	3.72	4.16	1.59
p 值	0.0026	5.5E-4	0.12	0.0067	5.5E-4	0.22	0.0036	2.8E-4	0.16
95% CI 的下限	1.58	1.78	0.878	1.39	1.78	0.787	1.54	1.93	0.830
95% CI 的上限	8.60	8.03	3.24	7.65	8.03	2.89	9.00	8.98	3.05

[0536]

OR 四分位 4	7.09	11.5	1.22	6.48	11.5	1.14	6.19	11.1	1.27
p 值	0.0096	0.0012	0.60	0.014	0.0012	0.74	0.016	0.0014	0.54
95% CI 的下限	1.61	2.63	0.579	1.47	2.63	0.539	1.40	2.53	0.599
95% CI 的上限	31.2	50.2	2.57	28.6	50.2	2.39	27.4	48.4	2.67

[0537] 表11.2:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0538] sCr或UO

[0539]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	2.02	6.53	2.02	6.50	2.02	6.50
平均值	3.19	16.0	3.21	15.7	3.21	15.7
标准偏差	3.76	23.4	3.82	23.2	3.82	23.2
p(t-检验)		2.8E-4		4.5E-4		4.5E-4
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	17.5	111	17.5	111	17.5	111
n(患者)	47	101	45	103	45	103

[0540] 仅sCr

[0541]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	1.74	7.50	1.60	7.19	1.60	7.19
平均值	3.05	17.0	3.01	16.9	3.01	16.9
标准偏差	3.60	23.9	3.63	23.8	3.63	23.8
p(t-检验)		3.6E-5		4.4E-5		4.4E-5
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126

[0542]

最大值	17.5	111	17.5	111	17.5	111
n(患者)	54	94	53	95	53	95

[0543] 仅UO

[0544]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.04	5.87	3.04	5.87	3.04	5.87
平均值	8.93	16.0	8.51	16.3	8.51	16.3
标准偏差	15.7	24.9	15.2	24.9	15.2	24.9
p（t-检验）		0.039		0.023		0.023
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	103	111	103	111	103	111
n（患者）	80	63	78	65	78	65

[0545]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.70	0.73	0.59	0.70	0.74	0.59	0.70	0.74	0.59
SE	0.044	0.041	0.048	0.044	0.041	0.048	0.044	0.041	0.048
p 值	4.0E-6	1.3E-8	0.072	8.0E-6	7.1E-9	0.061	8.0E-6	7.1E-9	0.061
n 恢复组	47	54	80	45	53	78	45	53	78
n 未恢复组	101	94	63	103	95	65	103	95	65
截止四分位 2	1.13	1.13	1.06	1.13	1.13	1.06	1.13	1.13	1.06
灵敏度	79%	82%	79%	79%	82%	78%	79%	82%	78%
特异性	34%	37%	29%	33%	38%	28%	33%	38%	28%
截止四分位 3	3.63	3.63	3.80	3.63	3.63	3.80	3.63	3.63	3.80
灵敏度	60%	63%	57%	60%	63%	57%	60%	63%	57%
特异性	72%	72%	55%	73%	74%	55%	73%	74%	55%
截止四分	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1

[0546]

位 4									
灵敏度	34%	36%	30%	33%	36%	31%	33%	36%	31%
特异性	94%	94%	79%	93%	94%	79%	93%	94%	79%
OR 四分位 2	1.97	2.66	1.55	1.84	2.78	1.43	1.84	2.78	1.43
p 值	0.086	0.012	0.27	0.12	0.0087	0.36	0.12	0.0087	0.36
95% CI 的下限	0.909	1.24	0.712	0.845	1.30	0.663	0.845	1.30	0.663
95% CI 的上限	4.25	5.71	3.38	4.01	5.97	3.09	4.01	5.97	3.09
OR 四分位 3	3.99	4.38	1.63	4.16	4.78	1.62	4.16	4.78	1.62
p 值	3.2E-4	6.9E-5	0.15	2.8E-4	3.4E-5	0.15	2.8E-4	3.4E-5	0.15
95% CI 的下限	1.88	2.12	0.838	1.93	2.28	0.836	1.93	2.28	0.836
95% CI 的上限	8.47	9.07	3.17	8.98	10.0	3.15	8.98	10.0	3.15
OR 四分位 4	7.44	9.63	1.60	6.90	9.29	1.72	6.90	9.29	1.72
p 值	0.0015	3.4E-4	0.22	0.0023	4.2E-4	0.16	0.0023	4.2E-4	0.16
95% CI 的下限	2.15	2.79	0.749	1.99	2.69	0.804	1.99	2.69	0.804
95% CI 的上限	25.7	33.2	3.42	23.9	32.0	3.69	23.9	32.0	3.69

[0547] 表11.3:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0548] sCr或UO

[0549]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	2.10	6.53	2.10	6.53	2.13	6.52
平均值	5.53	16.4	5.53	16.4	5.61	16.2
标准偏差	10.1	24.2	10.1	24.2	10.1	24.1

[0550]

p（t-检验）		0.0012		0.0012		0.0017
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	57.5	111	57.5	111	57.5	111
n（患者）	60	87	60	87	59	88

[0551] 仅sCr

[0552]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	2.10	7.37	2.10	7.37	2.10	7.37
平均值	5.35	17.3	5.35	17.3	5.35	17.3
标准偏差	9.78	24.6	9.78	24.6	9.78	24.6
p（t-检验）		3.7E-4		3.7E-4		3.7E-4
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	57.5	111	57.5	111	57.5	111
n（患者）	64	82	64	82	64	82

[0553] 仅UO

[0554]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.61	6.53	3.61	6.53	3.61	5.87
平均值	9.24	17.3	9.24	17.3	9.42	16.9
标准偏差	15.8	26.0	15.8	26.0	16.0	25.7
p（t-检验）		0.029		0.029		0.045
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	103	111	103	111	103	111
n（患者）	74	57	74	57	72	59

[0555]

恢复期持续时间（小时）	24	48	72

[0556]

	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.67	0.69	0.60	0.67	0.69	0.60	0.67	0.69	0.59
SE	0.044	0.043	0.050	0.044	0.043	0.050	0.044	0.043	0.050
p 值	8.8E-5	6.9E-6	0.058	8.8E-5	6.9E-6	0.058	1.9E-4	6.9E-6	0.082
n 恢复组	60	64	74	60	64	74	59	64	72
n 未恢复组	87	82	57	87	82	57	88	82	59
截止四分位 2	1.13	1.12	1.16	1.13	1.12	1.16	1.13	1.12	1.16
灵敏度	80%	83%	79%	80%	83%	79%	80%	83%	78%
特异性	33%	36%	28%	33%	36%	28%	32%	36%	28%
截止四分位 3	3.62	3.63	4.38	3.62	3.63	4.38	3.62	3.63	4.38
灵敏度	63%	65%	56%	63%	65%	56%	62%	65%	56%
特异性	68%	69%	54%	68%	69%	54%	68%	69%	54%
截止四分位 4	13.1	13.3	14.2	13.1	13.3	14.2	13.1	13.3	14.2
灵敏度	33%	35%	30%	33%	35%	30%	33%	35%	29%
特异性	87%	88%	78%	87%	88%	78%	86%	88%	78%
OR 四分位 2	2.06	2.72	1.49	2.06	2.72	1.49	1.85	2.72	1.36
p 值	0.061	0.011	0.34	0.061	0.011	0.34	0.11	0.011	0.45
95% CI 的下限	0.968	1.26	0.659	0.968	1.26	0.659	0.870	1.26	0.610
95% CI 的上限	4.38	5.88	3.35	4.38	5.88	3.35	3.92	5.88	3.04
OR 四分位 3	3.71	4.02	1.51	3.71	4.02	1.51	3.51	4.02	1.50
p 值	2.3E-4	8.9E-5	0.25	2.3E-4	8.9E-5	0.25	4.1E-4	8.9E-5	0.25
95% CI 的下限	1.85	2.00	0.752	1.85	2.00	0.752	1.75	2.00	0.751
95% CI 的上限	7.45	8.06	3.02	7.45	8.06	3.02	7.04	8.06	3.00
OR 四分位 4	3.25	3.83	1.54	3.25	3.83	1.54	3.13	3.83	1.42
p 值	0.0078	0.0024	0.29	0.0078	0.0024	0.29	0.0099	0.0024	0.39
95% CI 的下限	1.36	1.61	0.697	1.36	1.61	0.697	1.32	1.61	0.642
95% CI 的上限	7.74	9.13	3.40	7.74	9.13	3.40	7.46	9.13	3.13

[0557] 表11.4:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量

(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0558] sCr或UO

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	2.17	7.97	2.20	6.94	2.17	7.00
平均值	5.61	18.2	5.77	17.5	5.70	17.2
标准偏差	9.71	25.6	9.89	25.3	10.0	24.9
p(t-检验)		2.1E-4		5.6E-4		8.4E-4
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	57.5	111	57.5	111	57.5	111
n(患者)	68	74	65	77	62	80

[0559]

[0560] 仅sCr

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	2.17	8.29	2.17	8.29	2.13	8.44
平均值	5.56	18.6	5.56	18.6	5.43	18.5
标准偏差	9.58	25.8	9.58	25.8	9.59	25.7
p(t-检验)		1.2E-4		1.2E-4		1.1E-4
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	57.5	111	57.5	111	57.5	111
n(患者)	70	72	70	72	69	73

[0561]

[0562] 仅UO

[0563]

恢复期持续时间(小时)	24	48	72

[0564]

	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.61	7.81	3.62	6.20	3.63	6.20
平均值	9.26	18.2	9.10	17.6	9.35	17.1
标准偏差	15.9	26.8	15.6	26.2	15.7	25.9
p（t-检验）		0.024		0.030		0.046
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	103	111	103	111	103	111
n（患者）	70	51	65	56	64	58

[0565]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.69	0.69	0.61	0.67	0.69	0.60	0.67	0.70	0.58
SE	0.044	0.044	0.052	0.045	0.044	0.052	0.045	0.044	0.052
p 值	2.5E-5	1.3E-5	0.032	1.3E-4	1.3E-5	0.062	1.3E-4	4.9E-6	0.12
n 恢复组	68	70	70	65	70	65	62	69	64
n 未恢复组	74	72	51	77	72	56	80	73	58
截止四分位 2	1.12	1.12	1.22	1.12	1.12	1.22	1.12	1.12	1.23
灵敏度	82%	83%	80%	81%	83%	79%	80%	84%	76%
特异性	34%	34%	29%	32%	34%	28%	32%	35%	27%
截止四分位 3	3.71	3.71	4.38	3.71	3.71	4.38	3.71	3.71	4.56
灵敏度	65%	65%	59%	64%	65%	57%	64%	66%	57%
特异性	66%	66%	56%	66%	66%	55%	68%	67%	56%
截止四分位 4	13.3	13.3	16.1	13.3	13.3	16.1	13.3	13.3	15.7
灵敏度	36%	38%	31%	35%	38%	30%	35%	38%	29%
特异性	87%	87%	79%	86%	87%	78%	87%	88%	78%
OR 四分位 2	2.40	2.61	1.64	1.97	2.61	1.40	1.90	2.71	1.14
p 值	0.028	0.018	0.26	0.083	0.018	0.43	0.098	0.014	0.76
95% CI 的下限	1.10	1.18	0.691	0.916	1.18	0.607	0.887	1.23	0.502

[0566]

95% CI 的上限	5.24	5.76	3.89	4.25	5.76	3.25	4.09	5.99	2.58
OR 四分位 3	3.61	3.60	1.80	3.42	3.60	1.66	3.69	3.84	1.70
p 值	2.8E-4	2.8E-4	0.12	5.0E-4	2.8E-4	0.17	2.6E-4	1.5E-4	0.15
95% CI 的下限	1.81	1.80	0.866	1.71	1.80	0.805	1.83	1.91	0.829
95% CI 的上限	7.22	7.20	3.73	6.84	7.20	3.40	7.44	7.70	3.48
OR 四分位 4	3.77	4.07	1.68	3.36	4.07	1.59	3.63	4.74	1.48
p 值	0.0021	0.0012	0.22	0.0050	0.0012	0.27	0.0038	4.9E-4	0.35
95% CI 的下限	1.62	1.74	0.737	1.44	1.74	0.699	1.52	1.98	0.653
95% CI 的上限	8.78	9.49	3.81	7.82	9.49	3.61	8.70	11.4	3.36

[0567] 表11.5:“恢复”和“未恢复”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0568] sCr或UO

[0569]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	2.46	7.97	2.42	7.81	2.46	7.17
平均值	8.00	18.4	8.04	18.1	8.12	17.8
标准偏差	14.8	25.8	14.9	25.7	15.0	25.5
p(t-检验)		0.0023		0.0030		0.0042
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	103	111	103	111	103	111
n(患者)	92	56	91	57	90	58

[0570] 仅sCr

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	2.22	8.53	2.22	8.53	2.22	8.53
平均值	5.57	19.8	5.57	19.8	5.57	19.8
标准偏差	9.15	26.7	9.15	26.7	9.15	26.7
p(t-检验)		1.3E-5		1.3E-5		1.3E-5
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	57.5	111	57.5	111	57.5	111
n(患者)	82	66	82	66	82	66

[0571]

[0572] 仅UO

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	3.03	7.97	3.03	7.97	3.03	7.17
平均值	8.64	18.9	8.64	18.9	8.76	18.2
标准偏差	14.9	27.4	14.9	27.4	15.0	27.0
p(t-检验)		0.0039		0.0039		0.0070
最小值	0.0435	0.126	0.0435	0.126	0.0435	0.126
最大值	103	111	103	111	103	111
n(患者)	99	48	99	48	97	50

[0573]

恢复期持续时间(小时)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.65	0.70	0.62	0.65	0.70	0.62	0.64	0.70	0.61
SE	0.048	0.044	0.050	0.047	0.044	0.050	0.047	0.044	0.050
p 值	0.0018	8.3E-6	0.016	0.0016	8.3E-6	0.016	0.0035	8.3E-6	0.028
n 恢复组	92	82	99	91	82	99	90	82	97
n 未恢复组	56	66	48	57	66	48	58	66	50

[0574]

[0575]

截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	82%	83%	79%	82%	83%	79%	81%	83%	78%
特异性	29%	32%	27%	30%	32%	27%	29%	32%	27%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	64%	67%	62%	65%	67%	62%	64%	67%	62%
特异性	59%	63%	56%	59%	63%	56%	59%	63%	56%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	36%	39%	33%	35%	39%	33%	34%	39%	32%
特异性	82%	87%	79%	81%	87%	79%	81%	87%	78%
OR 四分位 2	1.91	2.32	1.42	1.98	2.32	1.42	1.74	2.32	1.30
p 值	0.12	0.038	0.40	0.10	0.038	0.40	0.18	0.038	0.53
95% CI 的下限	0.843	1.05	0.624	0.876	1.05	0.624	0.781	1.05	0.580
95% CI 的上限	4.33	5.15	3.25	4.49	5.15	3.25	3.86	5.15	2.91
OR 四分位 3	2.56	3.47	2.08	2.70	3.47	2.08	2.52	3.47	2.05
p 值	0.0073	3.5E-4	0.042	0.0046	3.5E-4	0.042	0.0077	3.5E-4	0.044
95% CI 的下限	1.29	1.75	1.03	1.36	1.75	1.03	1.28	1.75	1.02
95% CI 的上限	5.08	6.85	4.22	5.36	6.85	4.22	4.98	6.85	4.12
OR 四分位 4	2.45	4.20	1.86	2.35	4.20	1.86	2.26	4.20	1.70
p 值	0.021	4.8E-4	0.11	0.027	4.8E-4	0.11	0.035	4.8E-4	0.17
95% CI 的下限	1.15	1.88	0.860	1.10	1.88	0.860	1.06	1.88	0.792
95% CI 的上限	5.24	9.38	4.01	5.02	9.38	4.01	4.81	9.38	3.66

[0576] 表11.6:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后12小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。sCr或UO

[0577]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	67.7	109	67.7	109	67.1	111
平均值	83.1	121	81.1	121	79.3	121
标准偏差	43.4	68.6	41.1	68.5	40.7	68.2
p（t-检验）		0.0032		0.0025		0.0018
最小值	31.3	13.2	31.3	13.2	31.3	13.2
最大值	174	401	170	401	170	401
n（患者）	32	118	30	120	29	121

[0578] 仅sCr

[0579]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	67.1	113	67.1	113	66.9	115
平均值	83.5	124	83.5	124	82.4	125
标准偏差	44.4	69.2	44.4	69.2	44.4	68.9
p（t-检验）		5.8E-4		5.8E-4		4.3E-4
最小值	23.6	13.2	23.6	13.2	23.6	13.2
最大值	182	401	182	401	182	401
n（患者）	41	109	41	109	40	110

[0580] 仅UO

[0581]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	94.2	113	94.2	113	94.2	112
平均值	102	126	101	126	101	125
标准偏差	53.7	75.0	53.4	74.6	53.8	74.2
p（t-检验）		0.023		0.023		0.025

[0582]

最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	253	401	253	401	253	401
n（患者）	76	73	74	75	73	76

[0583]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.68	0.69	0.59	0.69	0.69	0.59	0.70	0.69	0.59
SE	0.049	0.046	0.047	0.050	0.046	0.046	0.049	0.045	0.046
p 值	3.4E-4	4.2E-5	0.050	1.6E-4	4.2E-5	0.047	5.5E-5	1.7E-5	0.048
n 恢复组	32	41	76	30	41	74	29	40	73
n 未恢复组	118	109	73	120	109	75	121	110	76
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	81%	83%	81%	80%	83%	80%	80%	83%	80%
特异性	47%	46%	30%	47%	46%	30%	48%	48%	30%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	53%	56%	56%	53%	56%	56%	54%	56%	55%
特异性	62%	66%	55%	63%	66%	55%	66%	68%	55%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	30%	30%	32%	30%	30%	32%	30%	30%	32%
特异性	91%	88%	80%	93%	88%	81%	93%	88%	81%
OR 四分位 2	3.64	4.09	1.83	3.50	4.09	1.69	3.77	4.33	1.75
p 值	0.0023	4.6E-4	0.12	0.0037	4.6E-4	0.17	0.0023	2.9E-4	0.14
95% CI 的下限	1.59	1.86	0.854	1.50	1.86	0.796	1.61	1.96	0.825
95% CI 的上限	8.36	9.00	3.91	8.15	9.00	3.60	8.87	9.58	3.73
OR 四分位 3	1.91	2.45	1.58	1.97	2.45	1.58	2.21	2.68	1.50
p 值	0.11	0.019	0.16	0.11	0.019	0.16	0.067	0.011	0.22
95% CI 的	0.856	1.16	0.829	0.865	1.16	0.828	0.947	1.25	0.785

[0584]

下限									
95% CI 的上限	4.26	5.18	3.02	4.50	5.18	3.02	5.13	5.74	2.86
OR 四分位 4	4.08	3.13	1.87	6.00	3.13	2.02	5.72	3.00	1.95
p 值	0.028	0.029	0.10	0.018	0.029	0.070	0.022	0.035	0.085
95% CI 的下限	1.16	1.13	0.883	1.36	1.13	0.946	1.29	1.08	0.912
95% CI 的上限	14.3	8.68	3.96	26.5	8.68	4.30	25.3	8.34	4.15

[0585] 表11.7:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0586] sCr或UO

[0587]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	68.2	116	67.1	118	67.1	118
平均值	83.7	126	80.5	126	80.5	126
标准偏差	42.8	70.0	40.8	69.5	40.8	69.5
p(t-检验)		2.4E-4		7.8E-5		7.8E-5
最小值	23.6	13.2	23.6	13.2	23.6	13.2
最大值	174	401	171	401	171	401
n(患者)	45	105	43	107	43	107

[0588] 仅sCr

[0589]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	71.0	117	68.2	118	68.2	118
平均值	86.0	127	85.0	127	85.0	127

[0590]

标准偏差	44.4	70.6	44.4	70.3	44.4	70.3
p（t-检验）		2.6E-4		2.0E-4		2.0E-4
最小值	23.6	13.2	23.6	13.2	23.6	13.2
最大值	182	401	182	401	182	401
n（患者）	50	100	49	101	49	101

[0591] 仅UO

[0592]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	88.6	120	87.0	120	87.0	120
平均值	98.7	133	97.8	133	97.8	133
标准偏差	54.1	74.8	54.1	73.9	54.1	73.9
p（t-检验）		0.0018		0.0012		0.0012
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	253	401	253	401	253	401
n（患者）	79	66	77	68	77	68

[0593]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.69	0.68	0.64	0.71	0.69	0.65	0.71	0.69	0.65
SE	0.045	0.044	0.046	0.044	0.044	0.046	0.044	0.044	0.046
p 值	2.3E-5	5.2E-5	0.0028	1.4E-6	2.5E-5	0.0014	1.4E-6	2.5E-5	0.0014
n 恢复组	45	50	79	43	49	77	43	49	77
n 未恢复组	105	100	66	107	101	68	107	101	68
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	83%	84%	85%	83%	84%	85%	83%	84%	85%
特异性	44%	44%	33%	47%	45%	34%	47%	45%	34%

[0594]

截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	57%	58%	61%	58%	58%	60%	58%	58%	60%
特异性	67%	66%	58%	70%	67%	58%	70%	67%	58%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	31%	31%	35%	32%	31%	35%	32%	31%	35%
特异性	89%	86%	82%	91%	86%	83%	91%	86%	83%
OR 四分位 2	3.87	4.12	2.75	4.30	4.33	2.96	4.30	4.33	2.96
p 值	6.4E-4	3.3E-4	0.016	2.7E-4	2.1E-4	0.0096	2.7E-4	2.1E-4	0.0096
95% CI 的下限	1.78	1.90	1.21	1.96	1.99	1.30	1.96	1.99	1.30
95% CI 的上限	8.41	8.94	6.24	9.42	9.41	6.72	9.42	9.41	6.72
OR 四分位 3	2.67	2.68	2.14	3.18	2.90	2.14	3.18	2.90	2.14
p 值	0.0085	0.0063	0.025	0.0027	0.0036	0.025	0.0027	0.0036	0.025
95% CI 的下限	1.28	1.32	1.10	1.49	1.42	1.10	1.49	1.42	1.10
95% CI 的上限	5.54	5.44	4.17	6.77	5.93	4.15	6.77	5.93	4.15
OR 四分位 4	3.67	2.76	2.48	4.54	2.66	2.69	4.54	2.66	2.69
p 值	0.012	0.028	0.020	0.0074	0.034	0.013	0.0074	0.034	0.013
95% CI 的下限	1.33	1.12	1.15	1.50	1.07	1.24	1.50	1.07	1.24
95% CI 的上限	10.1	6.82	5.35	13.7	6.57	5.84	13.7	6.57	5.84

[0595] 表11.8:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0596] sCr或UO

[0597]

恢复期持续时间(小时)	24	48	72

	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	80.0	120	80.0	120	80.3	119
平均值	90.7	128	90.7	128	91.3	128
标准偏差	49.3	71.0	49.3	71.0	49.5	71.0
p（t-检验）		5.5E-4		5.5E-4		9.3E-4
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	246	401
n（患者）	58	91	58	91	57	92

[0598]

[0599] 仅sCr

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	85.2	119	85.2	119	85.2	119
平均值	95.4	127	95.4	127	95.4	127
标准偏差	50.6	72.1	50.6	72.1	50.6	72.1
p（t-检验）		0.0034		0.0034		0.0034
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	246	401
n（患者）	61	87	61	87	61	87

[0600]

[0601] 仅UO

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	94.2	129	94.2	129	94.2	122
平均值	103	136	103	136	104	134
标准偏差	56.0	74.2	56.0	74.2	56.5	73.8
p（t-检验）		0.0049		0.0049		0.0082
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	260	401	260	401	260	401
n（患者）	72	61	72	61	70	63

[0602]

[0603]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.67	0.63	0.64	0.67	0.63	0.64	0.66	0.63	0.63
SE	0.044	0.046	0.049	0.044	0.046	0.049	0.045	0.046	0.049
p 值	1.6E-4	0.0037	0.0051	1.6E-4	0.0037	0.0051	3.5E-4	0.0037	0.0086
n 恢复组	58	61	72	58	61	72	57	61	70
n 未恢复组	91	87	61	91	87	61	92	87	63
截止四分位 2	66.7	66.8	69.2	66.7	66.8	69.2	66.7	66.8	69.2
灵敏度	84%	83%	87%	84%	83%	87%	83%	83%	86%
特异性	38%	36%	35%	38%	36%	35%	37%	36%	34%
截止四分位 3	101	101	106	101	101	106	101	101	106
灵敏度	57%	56%	57%	57%	56%	57%	57%	56%	57%
特异性	60%	59%	56%	60%	59%	56%	60%	59%	56%
截止四分位 4	142	143	148	142	143	148	142	143	148
灵敏度	33%	30%	36%	33%	30%	36%	33%	30%	35%
特异性	86%	82%	83%	86%	82%	83%	86%	82%	83%
OR 四分位 2	3.10	2.71	3.52	3.10	2.71	3.52	2.77	2.71	3.13
p 值	0.0039	0.011	0.0054	0.0039	0.011	0.0054	0.0087	0.011	0.0094
95% CI 的下限	1.44	1.26	1.45	1.44	1.26	1.45	1.29	1.26	1.32
95% CI 的上限	6.67	5.81	8.56	6.67	5.81	8.56	5.94	5.81	7.41
OR 四分位 3	2.03	1.86	1.68	2.03	1.86	1.68	1.92	1.86	1.68
p 值	0.039	0.067	0.14	0.039	0.067	0.14	0.056	0.067	0.14
95% CI 的下限	1.04	0.957	0.846	1.04	0.957	0.846	0.983	0.957	0.844
95% CI 的上限	3.97	3.60	3.35	3.97	3.60	3.35	3.76	3.60	3.33

[0604]

OR 四分位 4	3.07	1.94	2.82	3.07	1.94	2.82	2.96	1.94	2.59
p 值	0.011	0.10	0.012	0.011	0.10	0.012	0.014	0.10	0.021
95% CI 的下限	1.29	0.872	1.25	1.29	0.872	1.25	1.25	0.872	1.15
95% CI 的上限	7.30	4.30	6.34	7.30	4.30	6.34	7.04	4.30	5.82

[0605] 表11.9:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0606] sCr或UO

[0607]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	88.6	122	87.8	120	88.6	119
平均值	96.6	131	96.1	130	96.1	129
标准偏差	49.0	74.1	49.3	73.2	50.4	72.3
p(t-检验)		0.0016		0.0019		0.0030
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	246	401
n(患者)	65	79	62	82	59	85

[0608] 仅sCr

[0609]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	91.4	122	91.4	122	92.9	120
平均值	97.8	131	97.8	131	98.0	130
标准偏差	49.1	74.8	49.1	74.8	49.5	74.5
p(t-检验)		0.0024		0.0024		0.0032
最小值	16.4	13.2	16.4	13.2	16.4	13.2

[0610]

最大值	246	401	246	401	246	401
n(患者)	67	77	67	77	66	78

[0611] 仅UO

[0612]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	103	122	106	118	103	118
平均值	110	136	111	133	111	132
标准偏差	55.0	77.5	56.3	75.3	56.8	74.4
p（t-检验）		0.034		0.069		0.077
最小值	24.0	13.2	24.0	13.2	24.0	13.2
最大值	260	401	260	401	260	401
n（患者）	70	55	65	60	64	62

[0613]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.64	0.63	0.59	0.64	0.63	0.58	0.63	0.62	0.58
SE	0.046	0.046	0.052	0.046	0.046	0.051	0.046	0.046	0.051
p 值	0.0031	0.0063	0.078	0.0027	0.0063	0.13	0.0036	0.0086	0.12
n 恢复组	65	67	70	62	67	65	59	66	64
n 未恢复组	79	77	55	82	77	60	85	78	62
截止四分位 2	67.0	67.0	75.7	67.0	67.0	75.7	67.0	67.0	75.8
灵敏度	82%	82%	84%	82%	82%	83%	82%	82%	82%
特异性	34%	33%	31%	34%	33%	32%	36%	33%	33%
截止四分位 3	103	103	113	103	103	113	103	103	112
灵敏度	56%	56%	55%	56%	56%	53%	55%	55%	53%
特异性	57%	57%	53%	58%	57%	52%	58%	56%	53%
截止四分	146	146	152	146	146	152	146	146	152

[0614]

位 4									
灵敏度	33%	32%	36%	33%	32%	33%	32%	32%	32%
特异性	85%	84%	83%	85%	84%	82%	85%	83%	81%
OR 四分位 2	2.38	2.20	2.34	2.29	2.20	2.39	2.58	2.29	2.26
p 值	0.028	0.045	0.056	0.035	0.045	0.046	0.016	0.036	0.055
95% CI 的下限	1.10	1.02	0.977	1.06	1.02	1.01	1.19	1.06	0.983
95% CI 的上限	5.15	4.76	5.62	4.93	4.76	5.61	5.58	4.95	5.22
OR 四分位 3	1.66	1.66	1.35	1.77	1.66	1.25	1.68	1.57	1.29
p 值	0.13	0.13	0.41	0.094	0.13	0.53	0.13	0.18	0.48
95% CI 的下限	0.857	0.856	0.662	0.908	0.856	0.621	0.860	0.810	0.640
95% CI 的上限	3.22	3.21	2.73	3.45	3.21	2.53	3.29	3.03	2.60
OR 四分位 4	2.70	2.45	2.76	2.89	2.45	2.21	2.59	2.36	2.06
p 值	0.018	0.029	0.016	0.014	0.029	0.060	0.027	0.036	0.085
95% CI 的下限	1.19	1.10	1.20	1.24	1.10	0.968	1.11	1.06	0.906
95% CI 的上限	6.13	5.47	6.33	6.72	5.47	5.04	6.01	5.27	4.70

[0615] 表11.10:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0616] sCr或UO

[0617]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	94.2	113	92.8	115	91.4	118
平均值	101	131	101	130	101	131
标准偏差	52.5	78.8	52.8	78.2	52.8	77.6

[0618]

p（t-检验）		0.0070		0.0068		0.0053
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	253	401	253	401	253	401
n（患者）	89	61	88	62	87	63

[0619] 仅sCr

[0620]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	91.4	118	91.4	118	91.4	118
平均值	96.8	132	96.8	132	96.8	132
标准偏差	48.9	76.9	48.9	76.9	48.9	76.9
p（t-检验）		0.0010		0.0010		0.0010
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	246	401
n（患者）	79	71	79	71	79	71

[0621] 仅UO

[0622]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	95.2	113	95.2	113	94.2	118
平均值	103	134	103	134	102	134
标准偏差	54.5	80.1	54.5	80.1	54.9	78.6
p（t-检验）		0.0051		0.0051		0.0040
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	260	401	260	401	260	401
n（患者）	98	51	98	51	96	53

[0623]

恢复期持续时间(小	24	48	72

[0624]

时）									
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.60	0.63	0.61	0.60	0.63	0.61	0.61	0.63	0.62
SE	0.048	0.046	0.050	0.047	0.046	0.050	0.047	0.046	0.049
p 值	0.033	0.0045	0.028	0.029	0.0045	0.028	0.019	0.0045	0.016
n 恢复组	89	79	98	88	79	98	87	79	96
n 未恢复组	61	71	51	62	71	51	63	71	53
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	82%	85%	84%	82%	85%	84%	83%	85%	85%
特异性	30%	34%	30%	31%	34%	30%	31%	34%	30%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	56%	56%	57%	56%	56%	57%	57%	56%	58%
特异性	54%	56%	53%	55%	56%	53%	55%	56%	54%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	34%	35%	35%	34%	35%	35%	35%	35%	36%
特异性	81%	84%	80%	81%	84%	80%	82%	84%	80%
OR 四分位 2	1.98	2.83	2.26	2.05	2.83	2.26	2.13	2.83	2.43
p 值	0.092	0.010	0.067	0.076	0.010	0.067	0.062	0.010	0.045
95% CI 的下限	0.895	1.28	0.946	0.928	1.28	0.946	0.962	1.28	1.02
95% CI 的上限	4.38	6.26	5.39	4.54	6.26	5.39	4.70	6.26	5.81
OR 四分位 3	1.47	1.62	1.49	1.56	1.62	1.49	1.64	1.62	1.67
p 值	0.25	0.14	0.25	0.19	0.14	0.25	0.14	0.14	0.14
95% CI 的下限	0.766	0.850	0.754	0.809	0.850	0.754	0.853	0.850	0.845
95% CI 的上限	2.84	3.09	2.95	2.99	3.09	2.95	3.16	3.09	3.28
OR 四分位 4	2.22	2.76	2.13	2.14	2.76	2.13	2.38	2.76	2.26
p 值	0.036	0.0097	0.050	0.046	0.0097	0.050	0.023	0.0097	0.033
95% CI 的下限	1.05	1.28	0.999	1.01	1.28	0.999	1.12	1.28	1.07

[0625]

95% CI 的上限	4.69	5.95	4.53	4.51	5.95	4.53	5.04	5.95	4.81

[0626] 实施例12.使用腱生蛋白评价进入ICU的患者的肾状态:从RIFLE I和F恢复至RIFLE 0

[0627] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的腱生蛋白。

[0628] 在从样品收集之后起12、24、48或72小时期间或在样品收集后7天内的任何时间,通过基于血清肌酸酐、排尿量,或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“恢复”和“未恢复”群体。“恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是无损伤(RIFLE 0)的那些患者。“未恢复”表示在24、48或72小时的时间段内最大RIFLE阶段具有损伤危险(R)、损伤(I)或衰竭(F)的那些患者。如果患者在招募的9天内死亡或被置于肾替代疗法(RRT),则患者视为“未恢复”。

[0629] 使用接收器操作特征(ROC)分析确定区分“恢复”和“未恢复”组的能力。

[0630] 表12.1:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后12小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0631] sCr或UO

[0632]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复	恢复组	未恢复	恢复组	未恢复

[0633]

		组		组		组
中值	24200	53600	23000	53700	23000	53700
平均值	30200	56900	26300	56900	26300	56900
标准偏差	14500	26100	9010	26000	9010	26000
p(t-检验)		0.0028		0.0011		0.0011
最小值	20500	15600	20500	15600	20500	15600
最大值	61600	141000	47900	141000	47900	141000
n(患者)	9	141	8	142	8	142

[0634] 仅sCr

[0635]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	36100	53700	35600	53800	35600	53800
平均值	44200	56800	43200	56800	43200	56800
标准偏差	27100	25900	27600	25800	27600	25800
p（t-检验）		0.057		0.044		0.044
最小值	20500	15600	20500	15600	20500	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	18	132	17	133	17	133

[0636] 仅UO

[0637]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	46800	57200	45600	58200	46800	55700
平均值	46100	61700	45900	61400	46100	60700
标准偏差	20600	28200	20300	28100	20700	27900
p（t-检验）		2.8E-4		3.3E-4		8.3E-4
最小值	17100	15600	17100	15600	17100	15600
最大值	97900	141000	97900	141000	97900	141000
n（患者）	63	86	60	89	57	92

[0638]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.85	0.67	0.67	0.91	0.69	0.67	0.91	0.69	0.66
SE	0.048	0.061	0.044	0.034	0.060	0.044	0.034	0.060	0.044
p 值	3.8E-13	0.0047	1.2E-4	0	0.0014	9.6E-5	0	0.0014	2.8E-4
n 恢复组	9	18	63	8	17	60	8	17	57
n 未恢复组	141	132	86	142	133	89	142	133	92
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	78%	77%	83%	78%	77%	82%	78%	77%	82%
特异性	78%	44%	35%	88%	47%	35%	88%	47%	35%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	52%	53%	59%	53%	53%	60%	53%	53%	59%
特异性	89%	72%	62%	100%	76%	63%	100%	76%	63%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	27%	27%	33%	27%	27%	33%	27%	27%	32%
特异性	100%	89%	84%	100%	88%	85%	100%	88%	84%
OR 四分位 2	12.4	2.72	2.54	25.1	3.05	2.46	25.1	3.05	2.38
p 值	0.0023	0.053	0.016	0.0031	0.035	0.020	0.0031	0.035	0.024
95% CI 的下限	2.45	0.986	1.19	2.97	1.08	1.15	2.97	1.08	1.12
95% CI 的上限	62.8	7.50	5.43	212	8.60	5.24	212	8.60	5.08
OR 四分位 3	8.84	2.94	2.37	19.0	3.72	2.54	19.0	3.72	2.44
p 值	0.042	0.052	0.011	0.044	0.028	0.0067	0.044	0.028	0.010
95% CI 的下限	1.08	0.990	1.22	1.08	1.15	1.30	1.08	1.15	1.23
95% CI 的上限	72.5	8.70	4.61	336	12.0	4.99	336	12.0	4.81

[0639]

OR 四分位 4	7.07	3.00	2.56	6.26	2.78	2.74	6.26	2.78	2.46
p 值	0.18	0.16	0.023	0.21	0.19	0.018	0.21	0.19	0.035
95% CI 的下限	0.402	0.657	1.14	0.353	0.606	1.19	0.353	0.606	1.06
95% CI 的上限	124	13.7	5.77	111	12.8	6.32	111	12.8	5.67

[0640] 表12.2:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0641] sCr或UO

[0642]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	29900	55100	26200	55100	25200	55100
平均值	33900	58800	31900	58500	30300	58500
标准偏差	13200	26200	12400	26100	10700	26000
p(t-检验)		3.7E-5		3.9E-5		2.0E-5
最小值	20500	15600	20500	15600	20500	15600
最大值	61600	141000	59100	141000	51700	141000
n(患者)	21	129	18	132	17	133

[0643] 仅sCr

[0644]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	36100	55100	35300	55100	35000	55100
平均值	40900	58600	40300	58400	39500	58400
标准偏差	23100	25900	23600	25800	23700	25700
p(t-检验)		0.0012		0.0012		8.6E-4

[0645]

最小值	20500	15600	20500	15600	20500	15600
最大值	123000	141000	123000	141000	123000	141000
n(患者)	28	122	26	124	25	125

[0646] 仅UO

[0647]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	44700	62700	44500	62000	44500	61600
平均值	46300	64800	46100	63900	46100	63400
标准偏差	19100	28900	19000	28700	19100	28500
p(t-检验)		1.2E-5		3.1E-5		5.1E-5
最小值	18800	15600	20500	15600	20500	15600
最大值	97900	141000	97900	141000	97900	141000
n(患者)	71	74	66	79	64	81

[0648]

恢复期持续时间(小时)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.81	0.73	0.70	0.84	0.74	0.69	0.86	0.75	0.69
SE	0.041	0.047	0.043	0.039	0.047	0.043	0.036	0.046	0.043
p 值	5.1E-14	1.3E-6	4.2E-6	0	3.1E-7	7.0E-6	0	4.4E-8	1.0E-5
n 恢复组	21	28	71	18	26	66	17	25	64
n 未恢复组	129	122	74	132	124	79	133	125	81
截止四分位 2	34800	34800	35000	34800	34800	35000	34800	34800	35000
灵敏度	79%	79%	84%	80%	79%	84%	80%	79%	83%
特异性	52%	43%	34%	61%	46%	35%	65%	48%	34%
截止四分位 3	52000	52000	52200	52000	52000	52200	52000	52000	52200

[0649]

灵敏度	57%	57%	65%	56%	56%	65%	56%	57%	64%
特异性	90%	79%	65%	94%	81%	67%	100%	84%	67%
截止四分位 4	70700	70700	70800	70700	70700	70800	70700	70700	70800
灵敏度	29%	30%	38%	29%	29%	37%	29%	29%	36%
特异性	100%	93%	87%	100%	92%	88%	100%	92%	88%
OR 四分位 2	4.16	2.77	2.64	6.11	3.23	2.72	7.20	3.51	2.51
p 值	0.0035	0.021	0.016	6.3E-4	0.0093	0.012	3.4E-4	0.0059	0.020
95% CI 的下限	1.60	1.17	1.20	2.16	1.33	1.24	2.44	1.44	1.16
95% CI 的上限	10.8	6.58	5.81	17.3	7.82	5.93	21.2	8.61	5.43
OR 四分位 3	12.4	4.77	3.40	21.7	5.44	3.64	45.2	6.90	3.67
p 值	9.9E-4	0.0016	4.4E-4	0.0032	0.0014	2.3E-4	0.0084	7.7E-4	2.3E-4
95% CI 的下限	2.77	1.81	1.72	2.80	1.93	1.83	2.66	2.24	1.84
95% CI 的上限	55.4	12.6	6.72	168	15.4	7.25	767	21.3	7.33
OR 四分位 4	18.1	5.44	4.19	15.1	4.91	4.20	14.1	4.65	3.90
p 值	0.045	0.026	8.5E-4	0.061	0.037	0.0012	0.067	0.044	0.0021
95% CI 的下限	1.07	1.23	1.81	0.886	1.10	1.76	0.828	1.04	1.64
95% CI 的上限	306	24.1	9.74	256	21.9	10.0	241	20.8	9.31

[0650] 表12.3:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0651] sCr或UO

[0652]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组

[0653]

中值	35000	55200	34900	55800	34700	56000
平均值	41700	59200	38500	59800	36800	59600
标准偏差	23300	25800	18300	26300	17100	26200
p（t-检验）		7.0E-4		4.8E-5		2.9E-5
最小值	20500	15600	20500	15600	20500	15600
最大值	123000	141000	90400	141000	90400	141000
n（患者）	32	117	30	119	27	122

[0654] 仅sCr

[0655]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	36900	55500	36600	55800	36600	55800
平均值	43500	59800	43100	59800	43100	59800
标准偏差	23000	26100	23200	26000	23200	26000
p（t-检验）		8.7E-4		7.1E-4		7.1E-4
最小值	20500	15600	20500	15600	20500	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	38	110	37	111	37	111

[0656] 仅UO

[0657]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	47800	61600	47700	61200	47700	59500
平均值	51200	63500	50200	63900	50500	62600
标准偏差	20900	29200	19100	29700	19200	29300
p（t-检验）		0.0063		0.0024		0.0079
最小值	20500	15600	20500	15600	20500	15600
最大值	123000	141000	97900	141000	97900	141000
n（患者）	64	69	61	72	55	78

[0658]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.73	0.70	0.63	0.76	0.71	0.63	0.79	0.71	0.62
SE	0.045	0.045	0.048	0.043	0.045	0.048	0.042	0.045	0.049
p 值	4.4E-7	7.4E-6	0.0095	6.9E-10	3.1E-6	0.0053	6.3E-12	3.1E-6	0.015
n 恢复组	32	38	64	30	37	61	27	37	55
n 未恢复组	117	110	69	119	111	72	122	111	78
截止四分位 2	35000	35000	37100	35000	35000	37100	35000	35000	37100
灵敏度	81%	81%	78%	82%	81%	78%	81%	81%	77%
特异性	47%	42%	28%	50%	43%	28%	52%	43%	27%
截止四分位 3	52200	52300	54300	52200	52300	54300	52200	52300	54300
灵敏度	58%	58%	58%	59%	59%	58%	59%	59%	58%
特异性	78%	74%	58%	83%	76%	59%	89%	76%	60%
截止四分位 4	70800	70900	71600	70800	70900	71600	70800	70900	71600
灵敏度	29%	29%	35%	29%	29%	35%	30%	29%	33%
特异性	88%	87%	84%	90%	86%	85%	93%	86%	85%
OR 四分位 2	3.81	3.08	1.41	4.41	3.27	1.35	4.64	3.27	1.25
p 值	0.0017	0.0058	0.40	6.5E-4	0.0040	0.45	6.4E-4	0.0040	0.58
95% CI 的下限	1.65	1.38	0.639	1.88	1.46	0.615	1.92	1.46	0.565
95% CI 的上限	8.78	6.86	3.10	10.3	7.31	2.98	11.2	7.31	2.76
OR 四分位 3	4.96	3.90	1.89	7.14	4.40	2.02	11.5	4.40	2.05
p 值	6.1E-4	0.0011	0.070	1.8E-4	5.6E-4	0.047	1.3E-4	5.6E-4	0.046
95% CI 的下限	1.98	1.72	0.949	2.56	1.90	1.01	3.29	1.90	1.01
95% CI 的上限	12.4	8.80	3.76	20.0	10.2	4.03	40.3	10.2	4.13

[0659]

OR 四分位 4	2.87	2.71	2.88	3.75	2.59	3.07	5.23	2.59	2.94
p 值	0.066	0.057	0.013	0.039	0.069	0.010	0.030	0.069	0.017
95% CI 的下限	0.935	0.970	1.25	1.07	0.927	1.30	1.18	0.927	1.21
95% CI 的上限	8.80	7.56	6.65	13.2	7.25	7.25	23.3	7.25	7.12

[0660] 表12.4:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0661] sCr或UO

[0662]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	37700	57200	37400	58200	37400	58200
平均值	42400	61000	41100	60600	40300	60400
标准偏差	18900	26900	18500	26600	17100	26700
p(t-检验)		1.3E-4		1.4E-4		1.2E-4
最小值	20500	15600	20500	15600	20500	15600
最大值	90400	141000	90400	141000	90400	141000
n(患者)	38	106	33	111	31	113

[0663] 仅sCr

[0664]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	38000	58200	38000	58200	38000	58200
平均值	44600	61300	44600	61300	44200	61200
标准偏差	22600	26300	22600	26300	22000	26400
p(t-检验)		3.1E-4		3.1E-4		3.2E-4

[0665]

最小值	18800	15600	18800	15600	18800	15600
最大值	123000	141000	123000	141000	123000	141000
n(患者)	45	99	45	99	43	101

[0666] 仅UO

[0667]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	51300	59900	51300	58900	48300	59100
平均值	52900	64300	53600	62500	51800	62900
标准偏差	19000	30800	19300	30000	18700	29100
p(t-检验)		0.015		0.062		0.021
最小值	20500	15600	20500	15600	20500	15600
最大值	97900	141000	97900	141000	97900	141000
n(患者)	60	65	52	73	47	79

[0668]

恢复期持续时间(小时)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.72	0.70	0.60	0.73	0.70	0.57	0.74	0.71	0.61
SE	0.045	0.044	0.051	0.045	0.044	0.052	0.045	0.044	0.051
p 值	8.7E-7	3.6E-6	0.058	1.6E-7	3.6E-6	0.17	6.1E-8	2.9E-6	0.039
n 恢复组	38	45	60	33	45	52	31	43	47
n 未恢复组	106	99	65	111	99	73	113	101	79
截止四分位 2	36300	36300	37600	36300	36300	37600	36300	36300	37700
灵敏度	81%	83%	77%	80%	83%	75%	80%	82%	76%
特异性	42%	42%	27%	42%	42%	25%	42%	42%	28%
截止四分位 3	52700	52700	55100	52700	52700	55100	52700	52700	55100
灵敏度	59%	61%	57%	59%	61%	55%	59%	60%	56%
特异性	76%	73%	57%	82%	73%	56%	84%	74%	60%

[0669]

截止四分位 4	70900	70900	74700	70900	70900	74700	70900	70900	74300
灵敏度	30%	30%	32%	30%	30%	30%	30%	31%	32%
特异性	89%	87%	82%	91%	87%	81%	94%	88%	85%
OR 四分位 2	3.13	3.52	1.21	2.98	3.52	1.02	2.83	3.32	1.21
p 值	0.0056	0.0018	0.64	0.010	0.0018	0.97	0.016	0.0030	0.65
95% CI 的下限	1.40	1.60	0.538	1.30	1.60	0.447	1.21	1.50	0.531
95% CI 的上限	7.01	7.76	2.73	6.86	7.76	2.32	6.60	7.33	2.75
OR 四分位 3	4.72	4.23	1.73	6.60	4.23	1.53	7.57	4.44	1.85
p 值	3.0E-4	2.6E-4	0.13	1.2E-4	2.6E-4	0.25	1.1E-4	2.3E-4	0.099
95% CI 的下限	2.03	1.95	0.851	2.52	1.95	0.747	2.71	2.01	0.891
95% CI 的上限	11.0	9.17	3.51	17.3	9.17	3.13	21.2	9.80	3.85
OR 四分位 4	3.68	2.83	2.13	4.23	2.83	1.81	6.24	3.37	2.65
p 值	0.022	0.034	0.077	0.024	0.034	0.17	0.016	0.020	0.041
95% CI 的下限	1.20	1.08	0.922	1.21	1.08	0.773	1.41	1.21	1.04
95% CI 的上限	11.2	7.38	4.90	14.8	7.38	4.25	27.6	9.37	6.72

[0670] 表12.5:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0671] sCr或UO

[0672]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	44300	62000	44100	62800	44100	62800

[0673]

平均值	47600	64300	47200	64500	47200	64500
标准偏差	20900	29100	20600	29000	20600	29000
p（t-检验）		7.7E-5		3.5E-5		3.5E-5
最小值	18800	15600	18800	15600	18800	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	81	69	80	70	80	70

[0674] 仅sCr

[0675]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	42800	59300	41000	59300	41000	59300
平均值	46100	62700	45600	62700	45600	62700
标准偏差	20900	27900	20800	27700	20800	27700
p（t-检验）		9.3E-5		5.1E-5		5.1E-5
最小值	18800	15600	18800	15600	18800	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	67	83	65	85	65	85

[0676] 仅UO

[0677]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	47500	63200	47400	64500	47000	64500
平均值	49000	65900	48500	66200	47900	66400
标准偏差	20700	31400	20600	30900	20400	30500
p（t-检验）		1.3E-4		4.8E-5		1.7E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	95	54	93	56	91	58

[0678]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.68	0.68	0.66	0.69	0.69	0.67	0.69	0.69	0.69
SE	0.044	0.043	0.048	0.044	0.043	0.047	0.044	0.043	0.046
p 值	6.3E-5	2.2E-5	8.7E-4	1.9E-5	6.0E-6	2.1E-4	1.9E-5	6.0E-6	4.4E-5
n 恢复组	81	67	95	80	65	93	80	65	91
n 未恢复组	69	83	54	70	85	56	70	85	58
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	80%	81%	78%	80%	81%	79%	80%	81%	79%
特异性	30%	33%	26%	30%	34%	27%	30%	34%	27%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	65%	63%	65%	66%	62%	66%	66%	62%	67%
特异性	63%	66%	58%	64%	66%	59%	64%	66%	60%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	38%	36%	41%	39%	36%	41%	39%	36%	41%
特异性	85%	88%	83%	86%	89%	84%	86%	89%	85%
OR 四分位 2	1.65	2.05	1.25	1.71	2.21	1.35	1.71	2.21	1.45
p 值	0.19	0.060	0.58	0.16	0.038	0.46	0.16	0.038	0.35
95% CI 的下限	0.777	0.970	0.569	0.805	1.04	0.614	0.805	1.04	0.663
95% CI 的上限	3.52	4.32	2.75	3.65	4.66	2.96	3.65	4.66	3.18
OR 四分位 3	3.19	3.21	2.53	3.37	3.24	2.82	3.37	3.24	3.14
p 值	7.0E-4	6.8E-4	0.0084	3.9E-4	6.5E-4	0.0033	3.9E-4	6.5E-4	0.0012
95% CI 的下限	1.63	1.64	1.27	1.72	1.65	1.41	1.72	1.65	1.57
95% CI 的上限	6.23	6.29	5.06	6.60	6.36	5.62	6.60	6.36	6.26
OR 四分位 4	3.48	4.17	3.39	3.94	4.76	3.62	3.94	4.76	3.88
p 值	0.0018	0.0012	0.0017	7.6E-4	6.8E-4	0.0010	7.6E-4	6.8E-4	5.8E-4

[0679]

95% CI的下限	1.59	1.76	1.58	1.77	1.93	1.68	1.77	1.93	1.79
95% CI的上限	7.61	9.90	7.29	8.75	11.7	7.81	8.75	11.7	8.41

[0680] 实施例13.使用腱生蛋白评价进入ICU的患者的肾状态:从RIFLE I和F恢复至RIFLE 0和R

[0681] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的腱生蛋白。

[0682] 在从样品收集之后起12、24、48或72小时期间或在样品收集后7天内的任何时间,通过基于血清肌酸酐、排尿量,或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“恢复”和“未恢复”群体。“恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是无损伤(RIFLE 0)或具有损伤危险(R)的那些患者。“未恢复”表示在24、48或72小时的时间段内最大RIFLE阶段是损伤(I)或衰竭(F)的那些患者。如果患者在招募的9天内死亡或被置于肾替代疗法(RRT),则患者视为“未恢复”。

[0683] 使用接收器操作特征(ROC)分析确定区分“恢复”和“未恢复”组的能力。

[0684] 表13.1:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后12小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0685] sCr或UO

[0686]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	36100	55200	35800	55200	36600	55100
平均值	41800	58900	41400	58800	41800	58500
标准偏差	22000	26200	22400	26100	22700	26100
p(t-检验)		9.4E-4		0.0010		0.0018
最小值	20500	15600	20500	15600	20500	15600
最大值	123000	141000	123000	141000	123000	141000
n(患者)	32	118	30	120	29	121

[0687] 仅sCr

[0688]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	37100	55800	37100	55800	37400	55500
平均值	43400	59700	43400	59700	43800	59400
标准偏差	21400	26600	21400	26600	21600	26700
p（t-检验）		6.0E-4		6.0E-4		0.0011
最小值	20500	15600	20500	15600	20500	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	41	109	41	109	40	110

[0689] 仅UO

[0690]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	45700	58900	45700	58900	44700	58600
平均值	47900	62700	47900	62300	47800	62200
标准偏差	21700	28600	21900	28400	22100	28200

[0691]

p（t-检验）		5.1E-4		6.9E-4		7.1E-4
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	76	73	74	75	73	76

[0692]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.70	0.66	0.72	0.70	0.66	0.71	0.69	0.66
SE	0.046	0.045	0.045	0.047	0.045	0.045	0.048	0.046	0.044
p 值	3.8E-6	1.4E-5	4.3E-4	1.9E-6	1.4E-5	4.8E-4	7.9E-6	4.3E-5	4.3E-4
n 恢复组	32	41	76	30	41	74	29	40	73
n 未恢复组	118	109	73	120	109	75	121	110	76
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	80%	81%	81%	80%	81%	81%	79%	80%	82%
特异性	44%	41%	30%	47%	41%	31%	45%	40%	32%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	56%	57%	62%	56%	57%	61%	55%	56%	62%
特异性	72%	68%	61%	73%	68%	61%	72%	68%	62%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	30%	31%	33%	29%	31%	32%	29%	31%	32%
特异性	91%	90%	82%	90%	90%	81%	90%	90%	81%
OR 四分位 2	3.05	2.97	1.83	3.50	2.97	1.96	3.12	2.67	2.04
p 值	0.0085	0.0064	0.12	0.0037	0.0064	0.082	0.0090	0.015	0.067
95% CI 的下限	1.33	1.36	0.854	1.50	1.36	0.918	1.33	1.21	0.951
95% CI 的上限	6.99	6.49	3.91	8.15	6.49	4.21	7.33	5.85	4.36
OR 四分位 3	3.24	2.84	2.46	3.48	2.84	2.46	3.26	2.68	2.60

[0693]

p 值	0.0068	0.0070	0.0073	0.0058	0.0070	0.0074	0.0093	0.011	0.0045
95% CI 的下限	1.38	1.33	1.28	1.43	1.33	1.27	1.34	1.25	1.35
95% CI 的上限	7.60	6.07	4.76	8.43	6.07	4.76	7.93	5.74	5.04
OR 四分位 4	4.08	4.19	2.17	3.71	4.19	2.02	3.53	4.03	1.95
p 值	0.028	0.011	0.045	0.041	0.011	0.070	0.050	0.014	0.085
95% CI 的下限	1.16	1.38	1.02	1.06	1.38	0.946	1.00	1.33	0.912
95% CI 的上限	14.3	12.7	4.63	13.0	12.7	4.30	12.4	12.2	4.15

[0694] 表13.2:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后24小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0695] sCr或UO

[0696]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	37100	58200	37400	56200	37400	56200
平均值	42900	60600	43400	60000	43400	60000
标准偏差	21400	26500	21800	26500	21800	26500
p(t-检验)		1.2E-4		3.7E-4		3.7E-4
最小值	18800	15600	18800	15600	18800	15600
最大值	123000	141000	123000	141000	123000	141000
n(患者)	45	105	43	107	43	107

[0697] 仅sCr

[0698]

恢复期持续时间(小时)	24	48	72

[0699]

	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	37300	57200	37400	56200	37400	56200
平均值	43900	61000	44200	60700	44200	60700
标准偏差	21800	26600	21900	26600	21900	26600
p（t-检验）		1.3E-4		2.5E-4		2.5E-4
最小值	18800	15600	18800	15600	18800	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	50	100	49	101	49	101

[0700] 仅UO

[0701]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	47000	62700	47000	62000	47000	62000
平均值	48500	64500	48600	64000	48600	64000
标准偏差	20800	29300	21000	29100	21000	29100
p（t-检验）		1.7E-4		3.3E-4		3.3E-4
最小值	18800	15600	18800	15600	18800	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	79	66	77	68	77	68

[0702]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.72	0.70	0.67	0.70	0.70	0.66	0.70	0.70	0.66
SE	0.043	0.043	0.045	0.044	0.043	0.045	0.044	0.043	0.045
p 值	4.2E-7	1.7E-6	1.8E-4	3.6E-6	5.8E-6	3.2E-4	3.6E-6	5.8E-6	3.2E-4
n 恢复组	45	50	79	43	49	77	43	49	77
n 未恢复组	105	100	66	107	101	68	107	101	68

[0703]

截止四分位 2	34800	34800	35000	34800	34800	35000	34800	34800	35000
灵敏度	81%	82%	82%	80%	81%	82%	80%	81%	82%
特异性	40%	40%	30%	40%	39%	31%	40%	39%	31%
截止四分位 3	52000	52000	52200	52000	52000	52200	52000	52000	52200
灵敏度	59%	59%	64%	58%	58%	63%	58%	58%	63%
特异性	71%	68%	61%	70%	67%	61%	70%	67%	61%
截止四分位 4	70700	70700	70800	70700	70700	70800	70700	70700	70800
灵敏度	31%	32%	36%	31%	32%	35%	31%	32%	35%
特异性	89%	88%	84%	88%	88%	83%	88%	88%	83%
OR 四分位 2	2.83	3.04	1.96	2.68	2.73	2.11	2.68	2.73	2.11
p 值	0.0080	0.0043	0.093	0.013	0.0096	0.063	0.013	0.0096	0.063
95% CI 的下限	1.31	1.42	0.893	1.23	1.28	0.961	1.23	1.28	0.961
95% CI 的上限	6.12	6.51	4.32	5.81	5.85	4.65	5.81	5.85	4.65
OR 四分位 3	3.55	3.06	2.71	3.18	2.90	2.69	3.18	2.90	2.69
p 值	9.8E-4	0.0022	0.0038	0.0027	0.0036	0.0039	0.0027	0.0036	0.0039
95% CI 的下限	1.67	1.50	1.38	1.49	1.42	1.37	1.49	1.42	1.37
95% CI 的上限	7.54	6.25	5.32	6.77	5.93	5.28	6.77	5.93	5.28
OR 四分位 4	3.67	3.45	2.90	3.39	3.32	2.69	3.39	3.32	2.69
p 值	0.012	0.011	0.0073	0.019	0.013	0.013	0.019	0.013	0.013
95% CI 的下限	1.33	1.33	1.33	1.22	1.28	1.24	1.22	1.28	1.24
95% CI 的上限	10.1	8.93	6.32	9.39	8.61	5.84	9.39	8.61	5.84

[0704] 表13.3:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后48小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0705] sCr或UO

[0706]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	41900	58900	41900	58900	41000	58600
平均值	45400	61900	45400	61900	45300	61800
标准偏差	21400	27100	21400	27100	21600	27000
p（t-检验）		1.5E-4		1.5E-4		1.4E-4
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	58	91	58	91	57	92

[0707] 仅sCr

[0708]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	42800	58900	42800	58900	42800	58900
平均值	46100	62300	46100	62300	46100	62300
标准偏差	21700	27300	21700	27300	21700	27300
p（t-检验）		1.8E-4		1.8E-4		1.8E-4
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	61	87	61	87	61	87

[0709] 仅UO

[0710]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	47800	62000	47800	62000	47600	62000

[0711]

平均值	51100	65300	51100	65300	50800	65100
标准偏差	20500	30000	20500	30000	20800	29500
p（t-检验）		0.0016		0.0016		0.0014
最小值	18800	15600	18800	15600	18800	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	72	61	72	61	70	63

[0712]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.69	0.68	0.64	0.69	0.68	0.64	0.69	0.68	0.64
SE	0.043	0.043	0.048	0.043	0.043	0.048	0.043	0.043	0.048
p 值	1.2E-5	2.7E-5	0.0041	1.2E-5	2.7E-5	0.0041	8.5E-6	2.7E-5	0.0027
n 恢复组	58	61	72	58	61	72	57	61	70
n 未恢复组	91	87	61	91	87	61	92	87	63
截止四分位 2	35000	35000	37100	35000	35000	37100	35000	35000	37100
灵敏度	81%	82%	79%	81%	82%	79%	82%	82%	79%
特异性	34%	34%	28%	34%	34%	28%	35%	34%	29%
截止四分位 3	52200	52300	54300	52200	52300	54300	52200	52300	54300
灵敏度	60%	60%	59%	60%	60%	59%	61%	60%	60%
特异性	66%	64%	57%	66%	64%	57%	67%	64%	59%
截止四分位 4	70800	70900	71600	70800	70900	71600	70800	70900	71600
灵敏度	34%	33%	38%	34%	33%	38%	34%	33%	37%
特异性	88%	87%	85%	88%	87%	85%	88%	87%	84%
OR 四分位 2	2.29	2.33	1.42	2.29	2.33	1.42	2.38	2.33	1.54
p 值	0.032	0.029	0.39	0.032	0.029	0.39	0.024	0.029	0.29
95% CI 的下限	1.08	1.09	0.638	1.08	1.09	0.638	1.12	1.09	0.691
95% CI 的上限	4.88	4.97	3.16	4.88	4.97	3.16	5.08	4.97	3.43

[0713]

OR 四分位 3	2.90	2.63	1.90	2.90	2.63	1.90	3.11	2.63	2.15
p 值	0.0023	0.0050	0.068	0.0023	0.0050	0.068	0.0013	0.0050	0.031
95% CI 的下限	1.46	1.34	0.954	1.46	1.34	0.954	1.56	1.34	1.07
95% CI 的上限	5.76	5.18	3.80	5.76	5.18	3.80	6.21	5.18	4.30
OR 四分位 4	3.76	3.31	3.36	3.76	3.31	3.36	3.63	3.31	3.08
p 值	0.0039	0.0068	0.0040	0.0039	0.0068	0.0040	0.0051	0.0068	0.0073
95% CI 的下限	1.53	1.39	1.47	1.53	1.39	1.47	1.47	1.39	1.35
95% CI 的上限	9.27	7.88	7.66	9.27	7.88	7.66	8.94	7.88	7.02

[0714] 表13.4:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后72小时开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0715] sCr或UO

[0716]

恢复期持续时间(小时)	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	44300	58900	43700	59100	43500	58200
平均值	47700	63000	46700	63200	46600	62700
标准偏差	21600	27800	21500	27400	22000	27100
p(t-检验)		3.9E-4		1.4E-4		2.3E-4
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n(患者)	65	79	62	82	59	85

[0717] 仅sCr

[0718]

恢复期持	24	48	72

[0719]

续时间（小时）						
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	44300	58900	44300	58900	44100	58600
平均值	47800	63400	47800	63400	47700	63200
标准偏差	21500	28000	21500	28000	21600	27800
p（t-检验）		3.0E-4		3.0E-4		3.2E-4
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	67	77	67	77	66	78

[0720] 仅UO

[0721]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	51300	62000	48300	61000	50000	59400
平均值	53100	66100	52700	65500	52900	64900
标准偏差	20800	30700	21100	29800	21200	29500
p（t-检验）		0.0057		0.0062		0.0097
最小值	18800	15600	18800	15600	18800	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	70	55	65	60	64	62

[0722]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.67	0.67	0.62	0.68	0.67	0.62	0.68	0.67	0.61
SE	0.045	0.045	0.051	0.044	0.045	0.050	0.044	0.045	0.050
p 值	2.1E-4	2.1E-4	0.020	2.6E-5	2.1E-4	0.014	3.7E-5	2.0E-4	0.022
n 恢复组	65	67	70	62	67	65	59	66	64
n 未恢复	79	77	55	82	77	60	85	78	62

[0723]

组									
截止四分位 2	36300	36300	37600	36300	36300	37600	36300	36300	37700
灵敏度	82%	83%	80%	83%	83%	80%	84%	83%	81%
特异性	34%	34%	29%	35%	34%	29%	37%	35%	31%
截止四分位 3	52700	52700	55100	52700	52700	55100	52700	52700	55100
灵敏度	59%	60%	60%	61%	60%	58%	60%	60%	56%
特异性	62%	61%	57%	65%	61%	57%	64%	62%	56%
截止四分位 4	70900	70900	74700	70900	70900	74700	70900	70900	74300
灵敏度	34%	35%	35%	34%	35%	33%	33%	35%	32%
特异性	86%	87%	81%	87%	87%	82%	86%	86%	81%
OR 四分位 2	2.38	2.57	1.60	2.67	2.57	1.65	3.02	2.67	1.89
p 值	0.028	0.018	0.27	0.013	0.018	0.23	0.0055	0.014	0.13
95% CI 的下限	1.10	1.18	0.691	1.23	1.18	0.722	1.38	1.22	0.832
95% CI 的上限	5.15	5.62	3.71	5.80	5.62	3.78	6.57	5.84	4.31
OR 四分位 3	2.35	2.34	2.00	2.84	2.34	1.85	2.71	2.49	1.67
p 值	0.013	0.013	0.058	0.0028	0.013	0.090	0.0044	0.0080	0.16
95% CI 的下限	1.20	1.20	0.976	1.43	1.20	0.909	1.37	1.27	0.824
95% CI 的上限	4.60	4.57	4.10	5.63	4.57	3.76	5.40	4.87	3.37
OR 四分位 4	3.23	3.48	2.31	3.50	3.48	2.21	3.13	3.35	2.06
p 值	0.0064	0.0038	0.045	0.0048	0.0038	0.060	0.010	0.0049	0.085
95% CI 的下限	1.39	1.50	1.02	1.46	1.50	0.968	1.31	1.44	0.906
95% CI 的上限	7.51	8.09	5.25	8.37	8.09	5.04	7.49	7.80	4.70

[0724] 表13.5:“恢复”和“未恢复”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中恢复在样品收集后7天内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0725] sCr或UO

[0726]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	46800	64300	45700	64500	44700	64600
平均值	48100	65800	47900	65700	47500	66000
标准偏差	20900	29800	20900	29500	20700	29400
p（t-检验）		3.5E-5		2.7E-5		1.2E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	89	61	88	62	87	63

[0727] 仅sCr

[0728]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组
中值	44300	62000	44300	62000	44300	62000
平均值	46700	64800	46700	64800	46700	64800
标准偏差	20400	28800	20400	28800	20400	28800
p（t-检验）		1.6E-5		1.6E-5		1.6E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	79	71	79	71	79	71

[0729] 仅UO

[0730]

恢复期持续时间（小时）	24		48		72	
	恢复组	未恢复组	恢复组	未恢复组	恢复组	未恢复组

[0731]

中值	47400	64300	47400	64300	47200	64600
平均值	48800	67300	48800	67300	48300	67500
标准偏差	20800	31300	20800	31300	20700	30800
p（t-检验）		3.2E-5		3.2E-5		1.1E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	98	51	98	51	96	53

[0732]

恢复期持续时间（小时）	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.68	0.69	0.68	0.68	0.69	0.68	0.69	0.69	0.69
SE	0.045	0.043	0.048	0.045	0.043	0.048	0.044	0.043	0.047
p 值	6.9E-5	1.0E-5	2.2E-4	3.8E-5	1.0E-5	2.2E-4	1.2E-5	1.0E-5	4.4E-5
n 恢复组	89	79	98	88	79	98	87	79	96
n 未恢复组	61	71	51	62	71	51	63	71	53
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	80%	82%	80%	81%	82%	80%	81%	82%	81%
特异性	29%	32%	28%	30%	32%	28%	30%	32%	28%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	64%	63%	67%	65%	63%	67%	65%	63%	68%
特异性	60%	62%	58%	60%	62%	58%	61%	62%	59%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	41%	41%	41%	40%	41%	41%	41%	41%	42%
特异性	85%	89%	83%	85%	89%	83%	86%	89%	83%
OR 四分位 2	1.69	2.07	1.56	1.75	2.07	1.56	1.81	2.07	1.68
p 值	0.19	0.063	0.29	0.16	0.063	0.29	0.13	0.063	0.21
95% CI 的下限	0.773	0.960	0.686	0.802	0.960	0.686	0.832	0.960	0.742

[0733]

95% CI 的上限	3.67	4.44	3.54	3.81	4.44	3.54	3.95	4.44	3.82
OR 四分位 3	2.61	2.83	2.78	2.75	2.83	2.78	2.91	2.83	3.10
p 值	0.0052	0.0021	0.0046	0.0032	0.0021	0.0046	0.0019	0.0021	0.0017
95% CI 的下限	1.33	1.46	1.37	1.40	1.46	1.37	1.48	1.46	1.53
95% CI 的上限	5.11	5.49	5.64	5.40	5.49	5.64	5.70	5.49	6.27
OR 四分位 4	4.06	5.37	3.34	3.90	5.37	3.34	4.39	5.37	3.55
p 值	4.2E-4	8.8E-5	0.0020	6.0E-4	8.8E-5	0.0020	2.4E-4	8.8E-5	0.0012
95% CI 的下限	1.86	2.32	1.55	1.79	2.32	1.55	1.99	2.32	1.65
95% CI 的上限	8.85	12.4	7.16	8.48	12.4	7.16	9.67	12.4	7.63

[0734] 实施例14.使用卵泡抑素相关蛋白3评价进入ICU的患者的肾状态:在RIFLE F持续

[0735] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的卵泡抑素相关蛋白3。

[0736] 通过基于血清肌酸酐、排尿量或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“持续”和“非持续”群体。“持续”表示在24、48或72小时的时间段内最小RIFLE阶段是衰竭(F)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。“非持续”表示衰竭(F)不持续并且在24、48或72小时的时间段内最小RIFLE阶段内无损伤(RIFLE 0)、具有损伤危险(R)或损伤(I)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。如果患者在衰竭(F)后死亡或在从样品收集至样品收集后24、48、72、96或168小时的任何时间被置于肾替代疗法(RRT),则患者视为“持续”。

[0737] 使用接收器操作特征(ROC)分析确定区分“持续”和“非持续”组的能力。

[0738] 表14.1:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后24小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0739] sCr或UO

[0740]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	49500	81000	50300	81000	52000	77400
平均值	81100	87400	82200	86200	81800	88000
标准偏差	141000	43300	136000	42000	132000	43500
p（t-检验）		0.75		0.84		0.77
最小值	10500	20700	10500	20700	10500	20700
最大值	1230000	204000	1230000	204000	1230000	204000
n（患者）	95	55	103	47	110	40

[0741] 仅sCr

[0742]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	49300	81400	50300	81000	50500	80900
平均值	80700	88100	82800	84800	82300	86300
标准偏差	142000	43200	137000	38700	134000	38800
p（t-检验）		0.70		0.92		0.85
最小值	10500	20700	10500	20700	10500	20700
最大值	1230000	204000	1230000	162000	1230000	162000
n（患者）	94	56	103	47	108	42

[0743] 仅UO

[0744]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	60000	80700	60000	80700	60400	74700
平均值	82700	90800	82700	90800	82900	89400
标准偏差	123000	44800	123000	44800	122000	45600
p（t-检验）		0.77		0.77		0.82
最小值	10500	34800	10500	34800	10500	34800
最大值	1230000	204000	1230000	204000	1230000	204000
n（患者）	130	19	130	19	131	18

[0745]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.67	0.68	0.65	0.66	0.65	0.65	0.65	0.66	0.63
SE	0.047	0.046	0.072	0.050	0.050	0.072	0.053	0.052	0.074
p 值	2.1E-4	7.8E-5	0.044	0.0017	0.0021	0.044	0.0033	0.0018	0.074
n 非持续组	95	94	130	103	103	130	110	108	131
n 持续组	55	56	19	47	47	19	40	42	18
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	85%	86%	89%	85%	85%	89%	88%	88%	89%
特异性	32%	32%	27%	30%	30%	27%	30%	31%	27%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	69%	70%	68%	70%	70%	68%	70%	71%	67%
特异性	61%	62%	52%	59%	59%	52%	57%	58%	52%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	40%	41%	37%	38%	38%	37%	38%	38%	33%
特异性	83%	84%	76%	81%	81%	76%	79%	80%	76%
OR 四分位 2	2.71	2.81	3.13	2.46	2.46	3.13	3.00	3.26	2.92

[0746]

p 值	0.024	0.019	0.14	0.052	0.052	0.14	0.035	0.023	0.17
95% CI 的下限	1.14	1.18	0.688	0.994	0.994	0.688	1.08	1.17	0.638
95% CI 的上限	6.44	6.68	14.3	6.09	6.09	14.3	8.34	9.03	13.3
OR 四分位 3	3.50	3.70	2.38	3.42	3.42	2.38	3.13	3.50	2.16
p 值	4.9E-4	2.8E-4	0.098	0.0011	0.0011	0.098	0.0039	0.0015	0.15
95% CI 的下限	1.73	1.83	0.851	1.64	1.64	0.851	1.44	1.62	0.764
95% CI 的上限	7.09	7.48	6.63	7.16	7.16	6.63	6.79	7.57	6.10
OR 四分位 4	3.29	3.67	1.86	2.58	2.58	1.86	2.27	2.41	1.55
p 值	0.0022	8.9E-4	0.23	0.015	0.015	0.23	0.041	0.027	0.42
95% CI 的下限	1.54	1.70	0.675	1.20	1.20	0.675	1.03	1.10	0.537
95% CI 的上限	7.05	7.90	5.14	5.53	5.53	5.14	4.99	5.24	4.46

[0747] 表14.2:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0748] sCr或UO

[0749]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	48000	80900	48800	80900	49500	80700
平均值	68600	104000	70400	105000	70400	110000
标准偏差	77500	152000	76700	159000	74400	169000
p(t-检验)		0.060		0.072		0.046
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n(患者)	88	62	94	56	101	49

[0750] 仅sCr

[0751]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	48000	80900	48400	80700	49100	80700
平均值	81200	86600	82500	84900	81700	86900
标准偏差	146000	42900	143000	40800	139000	41200
p（t-检验）		0.78		0.90		0.80
最小值	10500	20700	10500	20700	10500	20700
最大值	1230000	204000	1230000	204000	1230000	204000
n（患者）	88	62	93	57	99	51

[0752] 仅UO

[0753]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	55100	81600	55100	81600	55200	80700
平均值	72800	136000	72800	136000	73100	136000
标准偏差	69600	228000	69600	228000	69400	233000
p（t-检验）		0.011		0.011		0.012
最小值	10500	34800	10500	34800	10500	34800
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	123	26	123	26	124	25

[0754]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.68	0.68	0.68	0.67	0.67	0.68	0.68	0.67	0.67
SE	0.045	0.045	0.062	0.047	0.047	0.062	0.048	0.048	0.063
p 值	3.9E-5	5.8E-5	0.0029	1.9E-4	3.8E-4	0.0029	2.0E-4	2.9E-4	0.0058
n 非持续	88	88	123	94	93	123	101	99	124

[0755]

组									
n 持续组	62	62	26	56	57	26	49	51	25
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	85%	85%	92%	86%	86%	92%	88%	88%	92%
特异性	33%	33%	28%	32%	32%	28%	32%	32%	28%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	66%	66%	69%	68%	67%	69%	69%	69%	68%
特异性	61%	61%	54%	61%	60%	54%	59%	60%	53%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	39%	39%	42%	38%	37%	42%	39%	37%	40%
特异性	84%	84%	78%	82%	82%	78%	81%	81%	77%
OR 四分位 2	2.89	2.89	4.77	2.81	2.92	4.77	3.32	3.58	4.52
p 值	0.013	0.013	0.040	0.019	0.015	0.040	0.013	0.0085	0.048
95% CI 的下限	1.26	1.26	1.07	1.18	1.23	1.07	1.28	1.38	1.01
95% CI 的上限	6.67	6.67	21.3	6.68	6.92	21.3	8.61	9.26	20.2
OR 四分位 3	3.10	3.10	2.61	3.25	3.03	2.61	3.32	3.23	2.42
p 值	0.0011	0.0011	0.038	9.1E-4	0.0016	0.038	0.0012	0.0013	0.058
95% CI 的下限	1.57	1.57	1.05	1.62	1.52	1.05	1.61	1.58	0.972
95% CI 的上限	6.11	6.11	6.44	6.53	6.03	6.44	6.85	6.59	6.02
OR 四分位 4	3.34	3.34	2.61	2.72	2.61	2.61	2.73	2.50	2.29
p 值	0.0021	0.0021	0.034	0.0094	0.013	0.034	0.0096	0.018	0.073
95% CI 的下限	1.55	1.55	1.07	1.28	1.23	1.07	1.28	1.17	0.925
95% CI 的上限	7.18	7.18	6.33	5.78	5.53	6.33	5.85	5.33	5.65

[0756] 表14.3:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47100	74000	47300	77400	48200	73900
平均值	68100	102000	68200	104000	69800	106000
标准偏差	79600	146000	78800	149000	76600	159000
p（t-检验）		0.069		0.060		0.060
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	83	67	86	64	94	56

[0757]

[0758] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	46500	77400	47300	80900	47900	80700
平均值	67400	103000	67600	105000	69100	107000
标准偏差	79800	145000	78500	149000	76800	157000
p（t-检验）		0.061		0.051		0.051
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	82	68	86	64	93	57

[0759]

[0760] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	53300	77200	53300	77200	53900	73800
平均值	72300	122000	72300	122000	72700	123000
标准偏差	71600	200000	71600	200000	71400	204000
p（t-检验）		0.026		0.026		0.028
最小值	10500	34800	10500	34800	10500	34800
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	115	34	115	34	116	33

[0761]

[0762]

[0763]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.70	0.70	0.68	0.70	0.71	0.68	0.69	0.70	0.68
SE	0.044	0.043	0.055	0.044	0.044	0.055	0.046	0.045	0.056
p 值	7.5E-6	2.0E-6	8.3E-4	4.0E-6	1.6E-6	8.3E-4	3.6E-5	1.0E-5	0.0017
n 非持续组	83	82	115	86	86	115	94	93	116
n 持续组	67	68	34	64	64	34	56	57	33
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	87%	87%	94%	88%	88%	94%	89%	89%	94%
特异性	35%	35%	30%	35%	35%	30%	34%	34%	30%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	67%	68%	71%	69%	69%	71%	70%	70%	70%
特异性	64%	65%	56%	64%	64%	56%	62%	62%	55%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	37%	38%	35%	38%	39%	35%	36%	37%	33%
特异性	84%	85%	77%	84%	85%	77%	81%	82%	77%
OR 四分位 2	3.46	3.59	7.00	3.75	3.75	7.00	4.30	4.46	6.70
p 值	0.0036	0.0027	0.010	0.0027	0.0027	0.010	0.0026	0.0020	0.012
95% CI 的下限	1.50	1.56	1.59	1.58	1.58	1.59	1.67	1.73	1.52
95% CI 的上限	7.97	8.27	30.8	8.89	8.89	30.8	11.1	11.5	29.5
OR 四分位 3	3.61	3.82	3.01	3.90	3.90	3.01	3.70	3.90	2.83
p 值	2.1E-4	1.1E-4	0.0088	1.0E-4	1.0E-4	0.0088	2.8E-4	1.6E-4	0.014
95% CI 的下限	1.83	1.93	1.32	1.96	1.96	1.32	1.83	1.93	1.24

[0764]

95% CI 的上限	7.12	7.55	6.87	7.77	7.77	6.87	7.48	7.90	6.48
OR 四分位 4	3.21	3.61	1.87	3.09	3.60	1.87	2.35	2.61	1.65
p 值	0.0031	0.0013	0.14	0.0038	0.0012	0.14	0.026	0.013	0.24
95% CI 的下限	1.48	1.65	0.816	1.44	1.66	0.816	1.11	1.23	0.710
95% CI 的上限	6.93	7.91	4.27	6.63	7.81	4.27	4.97	5.53	3.83

[0765] 表14.4:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0766] sCr或UO

[0767]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47100	74000	47500	74000	48400	73800
平均值	67800	102000	68500	103000	70300	104000
标准偏差	80400	144000	79200	148000	77700	155000
p(t-检验)		0.072		0.069		0.083
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n(患者)	81	69	85	65	91	59

[0768] 仅sCr

[0769]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47100	74000	47300	77400	48200	73900
平均值	67700	102000	67800	103000	69700	104000
标准偏差	80300	144000	79400	147000	78000	154000

[0770]

p(t-检验)		0.069		0.061		0.073
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n(患者)	81	69	84	66	90	60

[0771] 仅UO

[0772]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	52900	77200	53100	73800	53300	72700
平均值	71300	118000	71700	118000	72100	118000
标准偏差	72600	186000	72400	188000	72200	190000
p（t-检验）		0.029		0.032		0.035
最小值	10500	34800	10500	34800	10500	34800
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	109	40	110	39	111	38

[0773]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.70	0.70	0.69	0.70	0.70	0.68	0.68	0.69	0.67
SE	0.043	0.043	0.052	0.044	0.043	0.053	0.046	0.045	0.053
p 值	5.2E-6	4.3E-6	2.9E-4	8.5E-6	2.3E-6	6.2E-4	1.1E-4	3.9E-5	0.0013
n 非持续组	81	81	109	85	84	110	91	90	111
n 持续组	69	69	40	65	66	39	59	60	38
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	87%	87%	92%	88%	88%	92%	88%	88%	92%
特异性	36%	36%	31%	35%	36%	31%	34%	34%	31%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	67%	67%	70%	68%	68%	69%	68%	68%	68%

[0774]

特异性	64%	64%	57%	64%	64%	56%	62%	62%	56%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	38%	38%	38%	37%	38%	36%	34%	35%	34%
特异性	85%	85%	79%	84%	85%	78%	80%	81%	77%
OR 四分位 2	3.72	3.72	5.59	3.89	4.03	5.37	3.84	3.98	5.15
p 值	0.0021	0.0021	0.0067	0.0021	0.0016	0.0082	0.0034	0.0026	0.0099
95% CI 的下限	1.61	1.61	1.61	1.64	1.70	1.55	1.56	1.62	1.48
95% CI 的上限	8.57	8.57	19.4	9.22	9.55	18.6	9.44	9.79	17.9
OR 四分位 3	3.59	3.59	3.08	3.65	3.86	2.91	3.37	3.55	2.74
p 值	2.1E-4	2.1E-4	0.0045	2.0E-4	1.1E-4	0.0072	5.6E-4	3.2E-4	0.011
95% CI 的下限	1.82	1.82	1.42	1.85	1.95	1.34	1.69	1.78	1.26
95% CI 的上限	7.05	7.05	6.68	7.22	7.64	6.32	6.72	7.09	5.98
OR 四分位 4	3.48	3.48	2.24	2.97	3.33	2.01	2.08	2.31	1.79
p 值	0.0018	0.0018	0.045	0.0052	0.0023	0.086	0.054	0.028	0.16
95% CI 的下限	1.59	1.59	1.02	1.38	1.54	0.906	0.986	1.09	0.800
95% CI 的上限	7.61	7.61	4.94	6.37	7.21	4.45	4.39	4.89	4.00

[0775] 表14.5:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0776] sCr或UO

[0777]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	45600	73900	45900	74000	47700	73900

[0778]

平均值	67300	101000	67400	102000	69300	103000
标准偏差	81600	141000	80700	144000	78700	151000
p（t-检验）		0.073		0.065		0.074
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	78	72	81	69	88	62

[0779] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	45900	73800	46500	73900	47700	72700
平均值	67900	101000	68000	102000	69900	103000
标准偏差	81300	142000	80400	145000	78800	151000
p（t-检验）		0.081		0.072		0.086
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	79	71	82	68	88	62

[0780]

[0781] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	51800	80700	51800	80700	52900	77200
平均值	70400	119000	70400	119000	70900	119000
标准偏差	72400	183000	72400	183000	72200	186000
p（t-检验）		0.022		0.022		0.024
最小值	10500	34800	10500	34800	10500	34800
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	108	41	108	41	109	40

[0782]

[0783]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.70	0.70	0.70	0.71	0.70	0.70	0.69	0.68	0.69
SE	0.043	0.043	0.051	0.043	0.043	0.051	0.045	0.045	0.052
p 值	1.5E-6	5.0E-6	8.2E-5	8.5E-7	2.8E-6	8.2E-5	1.9E-5	4.8E-5	1.9E-4
n 非持续组	78	79	108	81	82	108	88	88	109
n 持续组	72	71	41	69	68	41	62	62	40
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	88%	87%	93%	88%	88%	93%	89%	89%	92%
特异性	37%	37%	31%	37%	37%	31%	35%	35%	31%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	67%	66%	71%	68%	68%	71%	68%	68%	70%
特异性	65%	65%	57%	65%	65%	57%	62%	62%	57%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	38%	37%	39%	38%	37%	39%	35%	34%	38%
特异性	86%	85%	80%	85%	84%	80%	82%	81%	79%
OR 四分位 2	4.14	4.00	5.82	4.49	4.33	5.82	4.27	4.27	5.59
p 值	8.6E-4	0.0012	0.0055	6.6E-4	8.9E-4	0.0055	0.0016	0.0016	0.0067
95% CI 的下限	1.80	1.73	1.68	1.89	1.82	1.68	1.74	1.74	1.61
95% CI 的上限	9.56	9.21	20.2	10.6	10.3	20.2	10.5	10.5	19.4
OR 四分位 3	3.78	3.57	3.26	4.04	3.82	3.26	3.50	3.50	3.08
p 值	1.2E-4	2.2E-4	0.0028	6.0E-5	1.1E-4	0.0028	3.4E-4	3.4E-4	0.0045
95% CI 的下限	1.92	1.82	1.50	2.04	1.93	1.50	1.76	1.76	1.42
95% CI 的上限	7.43	7.00	7.06	8.00	7.55	7.06	6.95	6.95	6.68
OR 四分位 4	3.65	3.23	2.50	3.48	3.09	2.50	2.48	2.14	2.24
p 值	0.0014	0.0033	0.022	0.0018	0.0042	0.022	0.018	0.046	0.045
95% CI	1.65	1.48	1.14	1.59	1.43	1.14	1.17	1.01	1.02

[0784]

的下限									
95% CI 的上限	8.10	7.05	5.47	7.61	6.67	5.47	5.25	4.51	4.94

[0785] 实施例15.使用卵泡抑素相关蛋白3评价进入ICU的患者的肾状态:在RIFLE I或F持续

[0786] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的卵泡抑素相关蛋白3。

[0787] 通过基于血清肌酸酐、排尿量或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“持续”和“非持续”群体。“持续”表示在24、48或72小时的时间段内最小RIFLE阶段损伤(I)或衰竭(F)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。“非持续”表示损伤(I)或衰竭(F)不持续并且在24、48或72小时的时间段内最小RIFLE阶段是无损伤(RIFLE 0)或具有损伤危险(R)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。如果患者在损伤(I)或衰竭(F)后死亡或在从样品收集至样品收集后24、48、72、96或168小时的任何时间被置于肾替代疗法(RRT),则患者视为“持续”。

[0788] 使用接收器操作特征(ROC)分析确定区分“持续”和“非持续”组的能力。

[0789] 表15.1:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后24小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0790] sCr或UO

[0791]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	41100	71900	45900	71700	47900	74000
平均值	52000	99200	84100	82800	82300	84900
标准偏差	40900	136000	158000	41000	149000	41400
p(t-检验)		0.018		0.95		0.89
最小值	10500	20700	10500	20700	10500	20700
最大值	265000	1230000	1230000	204000	1230000	204000
n(患者)	50	100	75	75	85	65

[0792] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	41800	71900	45400	74000	48500	80900
平均值	64000	93800	66800	99300	69700	102000
标准偏差	96900	123000	83700	137000	79800	149000
p（t-检验）		0.13		0.084		0.089
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	52	98	73	77	86	64

[0793]

[0794] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	54800	82000	55600	80700	55800	77200
平均值	77300	103000	83200	85900	82700	89000
标准偏差	118000	107000	127000	41900	125000	43000
p（t-检验）		0.24		0.91		0.81
最小值	10500	24400	10500	24400	10500	34000
最大值	1230000	689000	1230000	204000	1230000	204000

[0795]

n（患者）	112	37	120	29	125	24

[0796]

[0797]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.77	0.76	0.66	0.67	0.71	0.63	0.68	0.68	0.64
SE	0.038	0.039	0.054	0.044	0.042	0.061	0.045	0.045	0.065
p 值	9.5E-13	3.3E-11	0.0029	7.4E-5	7.4E-7	0.036	8.9E-5	3.8E-5	0.027
n 非持续组	50	52	112	75	73	120	85	86	125
n 持续组	100	98	37	75	77	29	65	64	24
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	87%	87%	89%	85%	86%	86%	86%	86%	88%
特异性	50%	48%	29%	36%	37%	28%	34%	34%	27%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	65%	65%	70%	65%	68%	69%	68%	69%	71%
特异性	80%	79%	56%	65%	68%	54%	64%	64%	54%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	33%	33%	38%	35%	38%	31%	35%	38%	33%
特异性	90%	88%	79%	84%	88%	76%	82%	84%	76%

[0798]

OR 四分位 2	6.69	6.05	3.45	3.27	3.52	2.37	3.22	3.11	2.62
p 值	3.6E-6	9.7E-6	0.030	0.0035	0.0019	0.13	0.0060	0.0077	0.14
95% CI 的下限	2.99	2.73	1.13	1.48	1.59	0.767	1.40	1.35	0.733
95% CI 的上限	15.0	13.4	10.5	7.25	7.80	7.33	7.42	7.16	9.33
OR 四分位 3	7.43	7.02	3.04	3.55	4.52	2.63	3.65	3.90	2.81
p 值	1.1E-6	1.1E-6	0.0063	2.2E-4	1.7E-5	0.029	2.0E-4	1.0E-4	0.033
95% CI 的下限	3.32	3.20	1.37	1.81	2.28	1.11	1.85	1.96	1.09
95% CI 的上限	16.6	15.4	6.75	6.96	8.98	6.24	7.22	7.77	7.24
OR 四分位 4	4.43	3.72	2.23	2.79	4.30	1.41	2.56	3.09	1.58
p 值	0.0040	0.0067	0.050	0.0100	6.3E-4	0.45	0.015	0.0038	0.34
95% CI 的下限	1.61	1.44	1.000	1.28	1.86	0.579	1.20	1.44	0.617
95% CI 的上限	12.2	9.61	4.98	6.07	9.91	3.44	5.44	6.63	4.06

[0799] 表15.2:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0800] sCr或UO

[0801]

持续期持续时间(h)	24		48		72	
	非持续	持续组	非持续	持续组	非持续	持续组

[0802]

	组		组		组	
中值	40400	72000	45000	73900	45900	81000
平均值	50500	99400	66400	98400	66400	102000
标准偏差	39900	135000	85200	135000	81100	142000
p（t-检验）		0.014		0.090		0.056
最小值	10500	20700	10500	20700	10500	20700
最大值	265000	1230000	689000	1230000	689000	1230000
n（患者）	49	101	70	80	79	71

[0803] 仅sCr

[0804]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	41800	72000	45000	73900	45900	80700
平均值	62700	94100	66200	98500	67500	101000
标准偏差	97500	122000	85100	135000	81500	142000
p（t-检验）		0.11		0.087		0.074
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	51	99	70	80	79	71

[0805] 仅UO

[0806]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	50300	85100	52900	82200	53100	82400
平均值	64600	127000	71900	118000	71800	125000
标准偏差	41700	193000	72400	190000	71100	203000
p（t-检验）		0.0022		0.032		0.018
最小值	10500	24400	10500	24400	10500	34000
最大值	265000	1230000	689000	1230000	689000	1230000
n（患者）	103	46	111	38	116	33

[0807]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.79	0.77	0.71	0.71	0.72	0.68	0.72	0.71	0.69
SE	0.037	0.038	0.048	0.042	0.041	0.053	0.042	0.043	0.056
p 值	1.0E-14	7.6E-13	1.9E-5	2.5E-7	1.9E-7	7.7E-4	1.7E-7	1.2E-6	4.7E-4
n 非持续组	49	51	103	70	70	111	79	79	116
n 持续组	101	99	46	80	80	38	71	71	33
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	87%	87%	91%	86%	86%	89%	87%	87%	91%
特异性	51%	49%	32%	39%	39%	30%	37%	37%	29%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	65%	66%	72%	66%	66%	71%	69%	68%	73%
特异性	82%	80%	59%	69%	69%	57%	67%	66%	56%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	34%	33%	41%	38%	38%	37%	39%	38%	39%
特异性	92%	90%	82%	89%	89%	78%	87%	86%	78%
OR 四分位 2	7.05	6.36	4.95	3.94	3.94	3.60	4.00	4.00	4.15
p 值	2.2E-6	6.0E-6	0.0046	7.6E-4	7.6E-4	0.024	0.0012	0.0012	0.026
95% CI 的下限	3.14	2.86	1.64	1.77	1.77	1.18	1.73	1.73	1.19
95% CI 的上限	15.8	14.2	15.0	8.75	8.75	10.9	9.21	9.21	14.5
OR 四分位 3	8.38	7.84	3.69	4.28	4.28	3.22	4.54	4.02	3.40
p 值	5.4E-7	5.6E-7	6.8E-4	3.2E-5	3.2E-5	0.0039	1.6E-5	6.2E-5	0.0048
95% CI 的下限	3.65	3.50	1.74	2.16	2.16	1.45	2.28	2.04	1.45
95% CI 的上限	19.2	17.6	7.83	8.50	8.50	7.14	9.03	7.94	7.95
OR 四分位 4	5.71	4.60	3.11	4.65	4.65	2.11	4.49	3.79	2.37

[0808]

p 值	0.0020	0.0032	0.0038	4.9E-4	4.9E-4	0.066	3.1E-4	0.0010	0.041
95% CI 的下限	1.90	1.67	1.44	1.96	1.96	0.951	1.99	1.71	1.04
95% CI 的上限	17.2	12.7	6.72	11.0	11.0	4.70	10.2	8.42	5.41

[0809] 表15.3:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0810] sCr或UO

[0811]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	40400	72000	44700	73800	45200	74000
平均值	50500	99400	66500	97800	66600	100000
标准偏差	39900	135000	85900	134000	83200	139000
p（t-检验）		0.014		0.097		0.074
最小值	10500	20700	10500	20700	10500	20700
最大值	265000	1230000	689000	1230000	689000	1230000
n（患者）	49	101	69	81	75	75

[0812] 仅sCr

[0813]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	41800	72000	44700	73800	45200	74000
平均值	62700	94100	66400	98000	66500	100000
标准偏差	97500	122000	85800	134000	83100	139000
p（t-检验）		0.11		0.094		0.072
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000

[0814]

n（患者）	51	99	69	81	75	75

[0815] 仅UO

[0816]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	50100	82000	52900	77200	53100	73800
平均值	63900	122000	71900	112000	71800	117000
标准偏差	41800	184000	73900	178000	72600	188000
p（t-检验）		0.0034		0.053		0.034
最小值	10500	24400	10500	24400	10500	34000
最大值	265000	1230000	689000	1230000	689000	1230000
n（患者）	98	51	105	44	110	39

[0817]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.79	0.77	0.71	0.71	0.71	0.67	0.72	0.72	0.68
SE	0.037	0.038	0.047	0.042	0.041	0.051	0.042	0.041	0.052
p 值	1.0E-14	7.6E-13	9.0E-6	2.9E-7	2.3E-7	7.8E-4	1.2E-7	9.1E-8	5.7E-4
n 非持续组	49	51	98	69	69	105	75	75	110
n 持续组	101	99	51	81	81	44	75	75	39
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	87%	87%	92%	86%	86%	91%	88%	88%	92%
特异性	51%	49%	34%	39%	39%	31%	39%	39%	31%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	65%	66%	71%	65%	65%	68%	68%	68%	69%
特异性	82%	80%	60%	68%	68%	57%	68%	68%	56%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300

[0818]

灵敏度	34%	33%	39%	37%	37%	34%	37%	37%	36%
特异性	92%	90%	82%	88%	88%	78%	87%	87%	78%
OR 四分位 2	7.05	6.36	5.97	4.09	4.09	4.58	4.62	4.62	5.37
p 值	2.2E-6	6.0E-6	0.0015	5.5E-4	5.5E-4	0.0070	3.4E-4	3.4E-4	0.0082
95% CI 的下限	3.14	2.86	1.98	1.84	1.84	1.51	2.00	2.00	1.55
95% CI 的上限	15.8	14.2	18.0	9.09	9.09	13.9	10.7	10.7	18.6
OR 四分位 3	8.38	7.84	3.63	4.04	4.04	2.86	4.52	4.52	2.91
p 值	5.4E-7	5.6E-7	5.0E-4	6.0E-5	6.0E-5	0.0056	1.7E-5	1.7E-5	0.0072
95% CI 的下限	3.65	3.50	1.76	2.04	2.04	1.36	2.27	2.27	1.34
95% CI 的上限	19.2	17.6	7.50	8.00	8.00	6.01	8.97	8.97	6.32
OR 四分位 4	5.71	4.60	2.87	4.49	4.49	1.84	3.87	3.87	2.01
p 值	0.0020	0.0032	0.0066	6.6E-4	6.6E-4	0.12	0.0011	0.0011	0.086
95% CI 的下限	1.90	1.67	1.34	1.89	1.89	0.849	1.72	1.72	0.906
95% CI 的上限	17.2	12.7	6.13	10.6	10.6	4.01	8.74	8.74	4.45

[0819] 表15.4:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0820] sCr或UO

[0821]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	40400	72000	45000	72700	45300	73900
平均值	50500	99400	66900	97200	66900	99500
标准偏差	39900	135000	86400	133000	83700	138000
p(t-检验)		0.014		0.11		0.083

[0822]

最小值	10500	20700	10500	20700	10500	20700
最大值	265000	1230000	689000	1230000	689000	1230000
n(患者)	49	101	68	82	74	76

[0823] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	41800	72000	45000	72700	45300	73900
平均值	62700	94100	66700	97300	66800	99600
标准偏差	97500	122000	86400	133000	83700	138000
p（t-检验）		0.11		0.11		0.081
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	51	99	68	82	74	76

[0824]

[0825] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	50300	81200	51800	73800	52900	72700
平均值	64200	118000	71900	108000	71900	112000
标准偏差	42300	179000	75500	169000	74000	178000
p（t-检验）		0.0059		0.075		0.053
最小值	10500	24400	10500	24400	10500	34000
最大值	265000	1230000	689000	1230000	689000	1230000
n（患者）	95	54	100	49	105	44

[0826]

[0827]

持续期持续时间(h)	24	48	72

[0828]

	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.79	0.77	0.69	0.71	0.71	0.66	0.71	0.72	0.67
SE	0.037	0.038	0.046	0.042	0.042	0.049	0.042	0.042	0.051
p 值	1.0E-14	7.6E-13	3.3E-5	6.3E-7	5.0E-7	0.0010	2.7E-7	2.1E-7	8.3E-4
n 非持续组	49	51	95	68	68	100	74	74	105
n 持续组	101	99	54	82	82	49	76	76	44
截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	87%	87%	91%	87%	87%	90%	88%	88%	91%
特异性	51%	49%	34%	40%	40%	32%	39%	39%	31%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	65%	66%	69%	65%	65%	67%	67%	67%	68%
特异性	82%	80%	60%	68%	68%	58%	68%	68%	57%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	34%	33%	37%	37%	37%	33%	37%	37%	34%
特异性	92%	90%	81%	88%	88%	78%	86%	86%	78%
OR 四分位 2	7.05	6.36	4.98	4.25	4.25	4.14	4.80	4.80	4.58
p 值	2.2E-6	6.0E-6	0.0019	3.9E-4	3.9E-4	0.0061	2.4E-4	2.4E-4	0.0070
95% CI 的下限	3.14	2.86	1.81	1.91	1.91	1.50	2.08	2.08	1.51
95% CI 的上限	15.8	14.2	13.7	9.46	9.46	11.4	11.1	11.1	13.9
OR 四分位 3	8.38	7.84	3.26	3.82	3.82	2.85	4.25	4.25	2.86

[0829]

p值	5.4E-7	5.6E-7	0.0010	1.1E-4	1.1E-4	0.0042	3.3E-5	3.3E-5	0.0056
95% CI的下限	3.65	3.50	1.61	1.93	1.93	1.39	2.15	2.15	1.36
95% CI的上限	19.2	17.6	6.61	7.55	7.55	5.83	8.41	8.41	6.01
OR四分位4	5.71	4.60	2.52	4.33	4.33	1.72	3.73	3.73	1.84
p值	0.0020	0.0032	0.016	8.9E-4	8.9E-4	0.16	0.0015	0.0015	0.12
95% CI的下限	1.90	1.67	1.18	1.82	1.82	0.802	1.66	1.66	0.849
95% CI的上限	17.2	12.7	5.35	10.3	10.3	3.68	8.42	8.42	4.01

[0830] 表15.5:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0831] sCr或UO

[0832]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	40400	72000	43900	73800	44300	77400
平均值	49300	99000	56600	104000	56800	107000
标准偏差	39000	134000	40100	146000	40300	150000
p(t-检验)		0.014		0.012		0.0076
最小值	10500	20700	10500	20700	10500	20700
最大值	265000	1230000	265000	1230000	265000	1230000
n(患者)	47	103	65	85	70	80

[0833] 仅sCr

[0834]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	41800	71900	45000	71300	45300	72700
平均值	63400	93500	67500	96000	67500	98200
标准偏差	98400	122000	87500	132000	84700	136000
p（t-检验）		0.13		0.13		0.10
最小值	10500	20700	10500	20700	10500	20700
最大值	689000	1230000	689000	1230000	689000	1230000
n（患者）	50	100	66	84	72	78

[0835] 仅UO

[0836]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	49500	81800	49800	81200	50300	77200
平均值	62900	117000	64000	118000	64600	122000
标准偏差	41600	175000	42100	179000	41900	186000
p（t-检验）		0.0049		0.0054		0.0041
最小值	10500	24400	10500	24400	10500	34000
最大值	265000	1230000	265000	1230000	265000	1230000
n（患者）	92	57	95	54	99	50

[0837]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.79	0.76	0.71	0.73	0.70	0.70	0.74	0.70	0.70
SE	0.036	0.039	0.045	0.040	0.042	0.046	0.040	0.042	0.047
p 值	1.6E-15	1.0E-11	4.3E-6	9.7E-9	2.5E-6	2.3E-5	7.3E-10	1.2E-6	3.7E-5
n 非持续组	47	50	92	65	66	95	70	72	99
n 持续组	103	100	57	85	84	54	80	78	50

[0838]

截止四分位 2	40800	40800	40400	40800	40800	40400	40800	40800	40400
灵敏度	86%	86%	91%	87%	86%	91%	89%	87%	92%
特异性	51%	48%	35%	42%	39%	34%	41%	39%	33%
截止四分位 3	63600	63600	63900	63600	63600	63900	63600	63600	63900
灵敏度	65%	65%	68%	65%	63%	69%	68%	65%	68%
特异性	83%	80%	61%	69%	67%	60%	70%	67%	59%
截止四分位 4	91200	91200	91300	91200	91200	91300	91200	91200	91300
灵敏度	34%	33%	39%	38%	36%	37%	39%	36%	38%
特异性	94%	90%	83%	91%	88%	81%	90%	86%	81%
OR 四分位 2	6.63	5.67	5.55	4.78	3.90	4.98	5.58	4.33	5.75
p 值	3.9E-6	1.7E-5	9.2E-4	1.3E-4	6.9E-4	0.0019	6.1E-5	4.3E-4	0.0019
95% CI 的下限	2.97	2.57	2.01	2.14	1.78	1.81	2.41	1.91	1.91
95% CI 的上限	14.8	12.5	15.3	10.7	8.56	13.7	12.9	9.78	17.3
OR 四分位 3	9.07	7.43	3.37	4.12	3.42	3.26	4.85	3.78	3.01
p 值	5.3E-7	1.1E-6	6.5E-4	5.6E-5	3.7E-4	0.0010	8.1E-6	1.2E-4	0.0026
95% CI 的下限	3.83	3.32	1.68	2.07	1.74	1.61	2.42	1.92	1.47
95% CI 的上限	21.5	16.6	6.77	8.22	6.73	6.61	9.69	7.43	6.15
OR 四分位 4	7.55	4.43	2.99	5.94	4.03	2.52	5.69	3.47	2.58
p 值	0.0014	0.0040	0.0047	2.3E-4	0.0016	0.016	1.5E-4	0.0027	0.014
95% CI 的下限	2.19	1.61	1.40	2.30	1.70	1.18	2.31	1.54	1.21
95% CI 的上限	26.0	12.2	6.37	15.3	9.55	5.35	14.0	7.82	5.51

[0839] 实施例16.使用Basigin评价进入ICU的患者的肾状态:在RIFLE F持续

[0840] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的Basigin。

[0841] 通过基于血清肌酸酐、排尿量或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“持续”和“非持续”群体。“持续”表示在24、48或72小时的时间段内最

小RIFLE阶段是衰竭(F)的那些患者，其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。“非持续”表示衰竭(F)不持续并且在24、48或72小时的时间段内最小RIFLE阶段是无损伤(RIFLE 0)、具有损伤危险(R)或损伤(I)的那些患者，其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。如果患者在衰竭(F)后死亡或在从样品收集至样品收集后24、48、72、96或168小时的任何时间被置于肾替代疗法(RRT)，则患者视为“持续”。

[0842] 使用接收器操作特征(ROC)分析确定区分“持续”和“非持续”组的能力。

[0843] 表16.1：“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较，其中持续在样品收集后24小时内开始，并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0844] sCr或UO

[0845]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8720	16900	8860	16900	9030	15600
平均值	13300	20300	14200	19400	14500	19500
标准偏差	12900	14700	13800	13800	13500	14800
p（t-检验）		0.0027		0.034		0.053
最小值	1970	3580	1970	3580	1970	3580

[0846]

最大值	72100	69500	72100	69500	72100	69500
n（患者）	95	55	103	47	110	40

[0847] 仅sCr

[0848]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8730	16800	8930	16700	9030	14300
平均值	13300	20100	14200	19500	14500	19300
标准偏差	12900	14600	13600	14200	13400	14900
p（t-检验）		0.0038		0.030		0.060
最小值	1970	3580	1970	3580	1970	3580
最大值	72100	69500	72100	69500	72100	69500
n（患者）	94	56	103	47	108	42

[0849] 仅UO

[0850]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	9370	18800	9370	18800	9380	18300
平均值	14900	22800	14900	22800	14900	23000
标准偏差	13600	15100	13600	15100	13500	15500
p(t-检验)		0.020		0.020		0.021
最小值	1970	5570	1970	5570	1970	5570
最大值	72100	69500	72100	69500	72100	69500
n(患者)	130	19	130	19	131	18

[0851]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.70	0.71	0.68	0.67	0.71	0.65	0.65	0.71

[0852]

SE	0.046	0.046	0.070	0.049	0.049	0.070	0.053	0.052	0.072
p 值	6.5E-6	1.2E-5	0.0026	2.0E-4	3.9E-4	0.0026	0.0035	0.0050	0.0043
n 非持续组	95	94	130	103	103	130	110	108	131
n 持续组	55	56	19	47	47	19	40	42	18
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	91%	91%	95%	91%	91%	95%	90%	90%	94%
特异性	35%	35%	28%	33%	33%	28%	31%	31%	27%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	75%	73%	84%	74%	72%	84%	72%	69%	83%
特异性	64%	64%	55%	61%	60%	55%	58%	57%	54%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	36%	36%	42%	34%	34%	42%	30%	29%	44%
特异性	81%	81%	77%	79%	79%	77%	76%	76%	77%
OR 四分位 2	5.32	5.52	6.89	5.30	5.30	6.89	4.03	4.36	6.44
p 值	0.0012	9.3E-4	0.065	0.0031	0.0031	0.065	0.014	0.0091	0.075
95% CI 的下限	1.94	2.01	0.887	1.76	1.76	0.887	1.33	1.44	0.827
95% CI 的上限	14.6	15.2	53.6	16.0	16.0	53.6	12.2	13.2	50.2
OR 四分位 3	5.25	4.82	6.42	4.59	3.95	6.42	3.67	3.01	5.92
p 值	1.0E-5	2.1E-5	0.0044	9.6E-5	3.3E-4	0.0044	0.0013	0.0044	0.0068
95% CI 的下限	2.51	2.33	1.78	2.14	1.87	1.78	1.66	1.41	1.63
95% CI 的上限	11.0	9.97	23.1	9.88	8.38	23.1	8.09	6.41	21.4
OR 四分位 4	2.44	2.35	2.42	1.90	1.90	2.42	1.38	1.26	2.69
p 值	0.020	0.026	0.082	0.10	0.10	0.082	0.43	0.57	0.056
95% CI 的下限	1.15	1.11	0.894	0.884	0.884	0.894	0.618	0.566	0.976
95% CI 的上限	5.18	4.97	6.58	4.09	4.09	6.58	3.10	2.81	7.43

[0853] 表16.2:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0854] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8330	16200	8730	16800	8930	16700
平均值	12600	20500	13100	20500	13500	20700
标准偏差	11600	15700	12400	15300	12100	16200
p（t-检验）		4.6E-4		0.0016		0.0027
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	88	62	94	56	101	49

[0855]

[0856] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8580	15100	8740	15700	8930	14100
平均值	12800	20200	13400	19900	13800	19900
标准偏差	11700	15700	12600	15200	12300	16000
p(t-检验)		0.0013		0.0047		0.011
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	88	62	93	57	99	51

[0857]

[0858] 仅UO

[0859]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	9260	17500	9260	17500	9310	17200
平均值	14700	21500	14700	21500	14800	21600
标准偏差	13700	14300	13700	14300	13600	14600
p（t-检验）		0.024		0.024		0.026
最小值	1970	4850	1970	4850	1970	4850
最大值	72100	69500	72100	69500	72100	69500
n（患者）	123	26	123	26	124	25

[0860]

[0861]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.70	0.70	0.71	0.69	0.70	0.68	0.66	0.69
SE	0.044	0.044	0.061	0.045	0.046	0.061	0.048	0.048	0.063
p 值	1.1E-6	7.7E-6	0.0015	4.7E-6	2.1E-5	0.0015	2.0E-4	7.7E-4	0.0025
n 非持续组	88	88	123	94	93	123	101	99	124
n 持续组	62	62	26	56	57	26	49	51	25
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	89%	89%	92%	89%	89%	92%	88%	88%	92%
特异性	35%	35%	28%	34%	34%	28%	32%	32%	28%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	74%	73%	81%	75%	74%	81%	73%	71%	80%
特异性	67%	66%	56%	65%	65%	56%	61%	61%	56%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	35%	34%	38%	36%	33%	38%	33%	29%	40%
特异性	82%	81%	77%	81%	80%	77%	78%	77%	77%
OR 四分位 2	4.27	4.27	4.77	4.30	4.46	4.77	3.32	3.58	4.52
p 值	0.0016	0.0016	0.040	0.0026	0.0020	0.040	0.013	0.0085	0.048
95% CI 的下限	1.74	1.74	1.07	1.67	1.73	1.07	1.28	1.38	1.01
95% CI	10.5	10.5	21.3	11.1	11.5	21.3	8.61	9.26	20.2

[0862]

的上限									
OR 四分位 3	5.85	5.12	5.37	5.55	5.09	5.37	4.40	3.69	5.02
p 值	1.6E-6	6.8E-6	0.0015	5.4E-6	1.1E-5	0.0015	1.1E-4	4.1E-4	0.0024
95% CI 的下限	2.84	2.51	1.90	2.65	2.46	1.90	2.08	1.79	1.77
95% CI 的上限	12.0	10.4	15.2	11.6	10.5	15.2	9.32	7.62	14.2
OR 四分位 4	2.48	2.14	2.12	2.35	1.95	2.12	1.74	1.38	2.29
p 值	0.018	0.046	0.100	0.026	0.080	0.100	0.15	0.41	0.073
95% CI 的下限	1.17	1.01	0.866	1.11	0.923	0.866	0.813	0.643	0.925
95% CI 的上限	5.25	4.51	5.19	4.97	4.11	5.19	3.73	2.95	5.65

[0863] 表16.3:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0864] sCr或UO

[0865]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8000	15700	8050	16200	8730	16800
平均值	11900	20800	11900	21100	12300	21900
标准偏差	11000	15600	11000	15700	10700	16600
p(t-检验)		6.4E-5		4.5E-5		3.1E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n(患者)	83	67	86	64	94	56

[0866] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8010	15100	8160	15100	8740	14500
平均值	11900	20600	12300	20700	12600	21100
标准偏差	11100	15600	11300	15700	11000	16500
p（t-检验）		9.9E-5		2.0E-4		2.2E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	82	68	86	64	93	57

[0867]

[0868] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	9000	18300	9000	18300	9030	17700
平均值	13400	24500	13400	24500	13400	24700
标准偏差	11700	17400	11700	17400	11700	17600
p（t-检验）		2.7E-5		2.7E-5		2.8E-5
最小值	1970	4850	1970	4850	1970	4850
最大值	67300	72100	67300	72100	67300	72100
n（患者）	115	34	115	34	116	33

[0869]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.74	0.73	0.74	0.74	0.73	0.74	0.73	0.71	0.74
SE	0.041	0.042	0.053	0.042	0.042	0.053	0.044	0.045	0.053
p 值	7.7E-9	1.6E-8	4.5E-6	3.9E-9	6.4E-8	4.5E-6	3.4E-7	4.2E-6	9.4E-6
n 非持续组	83	82	115	86	86	115	94	93	116
n 持续组	67	68	34	64	64	34	56	57	33
截止四分	6820	6820	6810	6820	6820	6810	6820	6820	6810

[0870]

[0871]

位 2									
灵敏度	90%	90%	94%	91%	91%	94%	89%	89%	94%
特异性	37%	38%	30%	37%	37%	30%	34%	34%	30%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	76%	75%	82%	78%	77%	82%	77%	74%	82%
特异性	71%	71%	59%	71%	70%	59%	66%	65%	59%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	36%	35%	44%	36%	34%	44%	36%	33%	45%
特异性	83%	83%	80%	83%	81%	80%	81%	80%	80%
OR 四分位 2	5.11	5.30	7.00	5.73	5.73	7.00	4.30	4.46	6.70
p 值	3.8E-4	2.9E-4	0.010	3.1E-4	3.1E-4	0.010	0.0026	0.0020	0.012
95% CI 的下限	2.08	2.15	1.59	2.22	2.22	1.59	1.67	1.73	1.52
95% CI 的上限	12.6	13.0	30.8	14.8	14.8	30.8	11.1	11.5	29.5
OR 四分位 3	7.84	7.25	6.75	8.71	7.54	6.75	6.41	5.09	6.38
p 值	4.1E-8	9.0E-8	9.2E-5	1.8E-8	8.5E-8	9.2E-5	1.3E-6	1.1E-5	1.5E-4
95% CI 的下限	3.76	3.51	2.59	4.10	3.60	2.59	3.02	2.46	2.44
95% CI 的上限	16.3	15.0	17.6	18.5	15.8	17.6	13.6	10.5	16.6
OR 四分位 4	2.75	2.65	3.16	2.66	2.29	3.16	2.35	1.95	3.37
p 值	0.0092	0.012	0.0058	0.011	0.030	0.0058	0.026	0.080	0.0038
95% CI 的下限	1.28	1.24	1.40	1.25	1.08	1.40	1.11	0.923	1.48
95% CI 的上限	5.89	5.67	7.15	5.65	4.85	7.15	4.97	4.11	7.68

[0872] 表16.4:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0873] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	7920	16700	8000	16700	8440	16900
平均值	11400	21000	11900	21100	12100	21600
标准偏差	10700	15500	11100	15600	10800	16200
p(t-检验)		1.6E-5		4.0E-5		3.3E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n(患者)	81	69	85	65	91	59

[0874]

[0875] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	7920	15700	8010	16200	8580	16800
平均值	11800	20600	11900	20900	12200	21400
标准偏差	11100	15400	11100	15600	10900	16200
p(t-检验)		8.7E-5		6.3E-5		5.5E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n(患者)	81	69	84	66	90	60

[0876]

[0877] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8930	18400	8940	18000	8950	17900
平均值	12600	24800	12900	24500	12900	24600
标准偏差	10500	18000	10700	18100	10700	18300
p(t-检验)		1.0E-6		4.3E-6		4.5E-6
最小值	1970	4850	1970	4850	1970	4850
最大值	60400	72100	60400	72100	60400	72100

[0878]

n(患者)	109	40	110	39	111	38

[0879]

[0880]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.76	0.74	0.75	0.75	0.75	0.74	0.73	0.73	0.74
SE	0.040	0.041	0.049	0.041	0.041	0.050	0.043	0.043	0.050
p 值	1.9E-10	4.8E-9	2.2E-7	1.1E-9	2.6E-9	1.2E-6	5.9E-8	1.3E-7	2.8E-6
n 非持续组	81	81	109	85	84	110	91	90	111
n 持续组	69	69	40	65	66	39	59	60	38
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	90%	90%	92%	91%	91%	92%	90%	90%	92%
特异性	38%	38%	31%	38%	38%	31%	35%	36%	31%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	77%	75%	82%	78%	77%	82%	76%	75%	82%
特异性	73%	72%	61%	72%	71%	61%	67%	67%	60%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	36%	35%	42%	35%	35%	41%	36%	35%	42%
特异性	84%	83%	81%	82%	82%	80%	81%	81%	80%
OR 四分位 2	5.49	5.49	5.59	5.94	6.15	5.37	4.79	4.97	5.15
p 值	2.1E-4	2.1E-4	0.0067	2.3E-4	1.7E-4	0.0082	0.0012	9.2E-4	0.0099
95% CI 的下限	2.23	2.23	1.61	2.30	2.39	1.55	1.86	1.93	1.48
95% CI 的上限	13.5	13.5	19.4	15.3	15.9	18.6	12.4	12.8	17.9
OR 四分位 3	8.88	7.71	7.52	9.26	8.50	7.12	6.54	6.00	6.74
p 值	8.4E-9	4.2E-8	1.2E-5	8.2E-9	1.8E-8	2.0E-5	7.1E-7	1.5E-6	3.5E-5
95% CI 的下限	4.23	3.72	3.05	4.34	4.03	2.89	3.11	2.89	2.73
95% CI 的上限	18.7	16.0	18.5	19.7	17.9	17.6	13.7	12.5	16.7

[0881]

OR 四分位 4	2.97	2.55	3.10	2.56	2.46	2.78	2.41	2.31	2.94
p 值	0.0056	0.016	0.0049	0.015	0.019	0.011	0.022	0.028	0.0078
95% CI 的下限	1.38	1.19	1.41	1.20	1.16	1.26	1.14	1.09	1.33
95% CI 的上限	6.42	5.46	6.81	5.44	5.23	6.14	5.09	4.89	6.52

[0882] 表16.5:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0883] sCr或UO

[0884]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	7630	15100	7700	15700	8330	16800
平均值	11500	20500	11700	20800	11900	21400
标准偏差	10900	15400	10900	15500	10600	16100
p(t-检验)		5.7E-5		4.2E-5		2.5E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n(患者)	78	72	81	69	88	62

[0885] 仅sCr

[0886]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	7700	14500	7810	15100	8330	15600
平均值	11900	20300	12000	20500	12300	21000
标准偏差	11200	15300	11200	15500	11000	16100
p(t-检验)		1.8E-4		1.4E-4		1.3E-4
最小值	1970	3580	1970	3580	1970	3580

[0887]

最大值	60400	72100	60400	72100	60400	72100
n(患者)	79	71	82	68	88	62

[0888] 仅UO

[0889]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8900	18000	8900	18000	8930	17900
平均值	12600	24600	12600	24600	12700	24700
标准偏差	10600	17900	10600	17900	10500	18100
p（t-检验）		1.5E-6		1.5E-6		1.6E-6
最小值	1970	4850	1970	4850	1970	4850
最大值	60400	72100	60400	72100	60400	72100
n（患者）	108	41	108	41	109	40

[0890]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.75	0.73	0.75	0.75	0.74	0.75	0.74	0.72	0.75
SE	0.040	0.041	0.048	0.040	0.041	0.048	0.043	0.043	0.049
p 值	1.2E-9	1.2E-8	1.9E-7	6.8E-10	6.9E-9	1.9E-7	3.1E-8	3.1E-7	4.5E-7
n 非持续组	78	79	108	81	82	108	88	88	109
n 持续组	72	71	41	69	68	41	62	62	40
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	90%	90%	93%	91%	91%	93%	90%	90%	92%
特异性	40%	39%	31%	40%	39%	31%	36%	36%	31%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	74%	73%	83%	75%	75%	83%	74%	73%	82%
特异性	72%	71%	62%	72%	71%	62%	67%	66%	61%
截止四分	19900	19900	20100	19900	19900	20100	19900	19900	20100

[0891]

位 4									
灵敏度	35%	34%	41%	35%	34%	41%	35%	34%	42%
特异性	83%	82%	81%	83%	82%	81%	82%	81%	81%
OR 四分位 2	6.12	5.90	5.82	6.86	6.61	5.82	5.33	5.33	5.59
p 值	8.2E-5	1.1E-4	0.0055	6.9E-5	9.4E-5	0.0055	5.3E-4	5.3E-4	0.0067
95% CI 的下限	2.49	2.40	1.68	2.66	2.56	1.68	2.07	2.07	1.61
95% CI 的上限	15.1	14.5	20.2	17.7	17.1	20.2	13.8	13.8	19.4
OR 四分位 3	7.10	6.66	7.94	7.71	7.25	7.94	5.85	5.12	7.52
p 值	9.4E-8	2.0E-7	6.7E-6	4.2E-8	9.0E-8	6.7E-6	1.6E-6	6.8E-6	1.2E-5
95% CI 的下限	3.46	3.26	3.22	3.72	3.51	3.22	2.84	2.51	3.05
95% CI 的上限	14.6	13.6	19.6	16.0	15.0	19.6	12.0	10.4	18.5
OR 四分位 4	2.66	2.37	2.93	2.55	2.28	2.93	2.48	2.14	3.10
p 值	0.013	0.026	0.0070	0.016	0.031	0.0070	0.018	0.046	0.0049
95% CI 的下限	1.23	1.11	1.34	1.19	1.08	1.34	1.17	1.01	1.41
95% CI 的上限	5.73	5.06	6.42	5.46	4.84	6.42	5.25	4.51	6.81

[0892] 实施例17.使用Basigin评价进入ICU的患者的肾状态:在RIFLE I或F持续

[0893] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的Basigin。

[0894] 通过基于血清肌酸酐、排尿量或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“持续”和“非持续”群体。“持续”表示在24、48或72小时的时间段内最小RIFLE阶段损伤(I)或衰竭(F)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。“非持续”表示损伤(I)或衰竭(F)不持续并且在24、48或72小时的时间段内最小RIFLE阶段是无损伤(RIFLE 0)或具有损伤危险(R)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。如果患者在损伤(I)或衰竭(F)后死亡或在从样品收集至样品收集后24、48、72、96或168小时的任何时间被置于肾替代疗法(RRT),则患者视为“持续”。

[0895] 使用接收器操作特征(ROC)分析确定区分“持续”和“非持续”组的能力。

[0896] 表17.1:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后24小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿

量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0897] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	5980	14300	7700	14500	8440	16700
平均值	6980	20300	11700	20000	12100	20700
标准偏差	4140	15000	11300	15100	10900	16000
p（t-检验）		6.6E-9		2.1E-4		1.3E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	25700	72100	60400	72100	60400	72100
n（患者）	50	100	75	75	85	65

[0898]

[0899] 仅sCr

[0900]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	6250	14100	7530	14500	8580	15000
平均值	8250	19900	11300	20100	12800	19900
标准偏差	7670	14800	11200	15000	12200	15200
p（t-检验）		4.3E-7		8.3E-5		0.0019
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	60400	72100	60400	72100
n（患者）	52	98	73	77	86	64

[0901]

[0902] 仅UO

[0903]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	9030	18000	9190	19600	9370	21700
平均值	14200	21200	14400	22300	14500	23100
标准偏差	13700	13600	13600	14100	13400	15000
p(t-检验)		0.0077		0.0054		0.0052
最小值	1970	3580	1970	3580	1970	3580
最大值	72100	69500	72100	69500	72100	69500
n(患者)	112	37	120	29	125	24

[0904]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.87	0.84	0.70	0.73	0.75	0.71	0.71	0.70	0.71
SE	0.028	0.032	0.053	0.041	0.039	0.058	0.043	0.044	0.063
p 值	0	0	1.7E-4	1.2E-8	1.7E-10	3.4E-4	1.9E-6	9.5E-6	0.0011
n 非持续组	50	52	112	75	73	120	85	86	125
n 持续组	100	98	37	75	77	29	65	64	24
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	91%	91%	92%	88%	90%	90%	86%	88%	92%
特异性	58%	56%	30%	39%	41%	28%	34%	35%	28%

[0905]

截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	69%	68%	78%	71%	71%	79%	71%	70%	79%
特异性	88%	85%	59%	71%	73%	57%	66%	65%	55%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	37%	36%	43%	36%	36%	48%	38%	36%	50%
特异性	98%	94%	80%	85%	86%	80%	85%	83%	79%
OR 四分位 2	14.0	12.5	4.94	4.62	6.02	3.43	3.22	3.75	4.28
p 值	5.4E-9	1.7E-8	0.012	3.4E-4	5.1E-5	0.055	0.0060	0.0027	0.057
95% CI 的下限	5.76	5.19	1.42	2.00	2.53	0.973	1.40	1.58	0.955
95% CI 的上限	33.9	30.0	17.2	10.7	14.3	12.1	7.42	8.89	19.2
OR 四分位 3	16.3	11.9	5.20	5.80	6.62	5.01	4.68	4.42	4.68
p 值	9.1E-9	2.1E-8	2.0E-4	9.4E-7	2.1E-7	0.0011	1.5E-5	2.8E-5	0.0038
95% CI 的下限	6.30	5.00	2.18	2.87	3.25	1.90	2.33	2.20	1.64
95% CI 的上限	42.3	28.2	12.4	11.7	13.5	13.2	9.39	8.87	13.3
OR 四分位 4	28.8	9.07	3.12	3.27	3.60	3.73	3.46	2.66	3.81
p 值	0.0011	4.7E-4	0.0054	0.0035	0.0020	0.0025	0.0017	0.011	0.0040
95% CI 的下限	3.81	2.63	1.40	1.48	1.60	1.59	1.60	1.25	1.53
95% CI 的上限	217	31.3	6.94	7.25	8.12	8.78	7.50	5.65	9.45

[0906] 表17.2:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0907] sCr或UO

[0908]

持续期持续时间(h)	24	48	72

[0909]

	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	5750	14100	7520	15000	8000	16700
平均值	6860	20200	10900	20200	11400	20800
标准偏差	4090	14900	10900	14900	10600	15500
p（t-检验）		7.0E-9		3.3E-5		2.1E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	25700	72100	60400	72100	60400	72100
n（患者）	49	101	70	80	79	71

[0910] 仅sCr

[0911]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	6200	14100	7520	14300	8090	15600
平均值	8160	19800	11400	19800	12400	19800
标准偏差	7720	14800	11400	14800	12300	14700
p（t-检验）		4.7E-7		1.7E-4		0.0010
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	60400	72100	60400	72100
n（患者）	51	99	70	80	79	71

[0912] 仅UO

[0913]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8860	18400	8950	21700	9030	24500
平均值	12500	23500	12900	24800	13100	25800
标准偏差	11200	16500	11300	17200	11200	18000
p（t-检验）		5.4E-6		2.4E-6		1.9E-6
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	103	46	111	38	116	33

[0914]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.88	0.84	0.74	0.77	0.75	0.75	0.74	0.72	0.75
SE	0.028	0.031	0.046	0.038	0.039	0.050	0.041	0.042	0.053
p 值	0	0	1.6E-7	4.5E-12	2.1E-10	4.8E-7	3.5E-9	3.0E-7	2.6E-6
n 非持续组	49	51	103	70	70	111	79	79	116
n 持续组	101	99	46	80	80	38	71	71	33
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	91%	91%	91%	89%	89%	89%	87%	87%	91%
特异性	59%	57%	32%	41%	41%	30%	37%	37%	29%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	69%	69%	80%	72%	71%	82%	73%	72%	82%
特异性	90%	86%	63%	76%	74%	60%	71%	70%	59%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	37%	35%	46%	36%	35%	50%	38%	35%	52%
特异性	98%	94%	83%	87%	86%	83%	86%	84%	82%
OR 四分位 2	14.8	13.2	4.95	5.58	5.58	3.60	4.00	4.00	4.15
p 值	3.0E-9	9.7E-9	0.0046	6.1E-5	6.1E-5	0.024	0.0012	0.0012	0.026
95% CI 的下限	6.08	5.46	1.64	2.41	2.41	1.18	1.73	1.73	1.19
95% CI 的上限	36.1	31.8	15.0	12.9	12.9	10.9	9.21	9.21	14.5
OR 四分位 3	19.9	13.8	7.03	8.22	7.16	6.74	6.66	5.84	6.38
p 值	8.4E-9	1.3E-8	4.2E-6	1.9E-8	9.2E-8	3.5E-5	2.0E-7	9.3E-7	1.5E-4
95% CI 的下限	7.19	5.59	3.06	3.94	3.48	2.73	3.26	2.89	2.44
95% CI 的上限	54.9	34.0	16.1	17.1	14.7	16.7	13.6	11.8	16.6
OR 四分位 4	27.8	8.75	4.25	3.85	3.23	4.84	3.79	2.76	4.81

[0915]

p值	0.0013	5.9E-4	2.7E-4	0.0015	0.0046	1.2E-4	0.0010	0.0097	2.1E-4
95% CI的下限	3.68	2.54	1.95	1.67	1.43	2.16	1.71	1.28	2.10
95% CI的上限	209	30.1	9.26	8.88	7.28	10.8	8.42	5.95	11.0

[0916] 表17.3:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0917] sCr或UO

[0918]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	5750	14100	7500	14500	7700	15600
平均值	6860	20200	10900	20000	11300	20400
标准偏差	4090	14900	11000	14900	10800	15200
p(t-检验)		7.0E-9		4.5E-5		4.4E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	25700	72100	60400	72100	60400	72100
n(患者)	49	101	69	81	75	75

[0919] 仅sCr

[0920]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	6200	14100	7500	14100	7700	14500
平均值	8160	19800	11400	19700	11700	20000
标准偏差	7720	14800	11500	14800	11300	15200
p(t-检验)		4.7E-7		2.2E-4		2.1E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	60400	72100	60400	72100

[0921]

n(患者)	51	99	69	81	75	75

[0922] 仅UO

[0923]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8730	18000	8860	19200	8940	18800
平均值	11700	24100	12100	25000	12400	25800
标准偏差	9830	17000	10000	17600	10100	18300
p（t-检验）		8.3E-8		9.4E-8		8.0E-8
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	98	51	105	44	110	39

[0924]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.88	0.84	0.77	0.77	0.75	0.76	0.75	0.73	0.76
SE	0.028	0.031	0.043	0.038	0.039	0.046	0.040	0.041	0.049
p 值	0	0	5.1E-10	4.2E-12	2.1E-10	1.5E-8	4.6E-10	1.1E-8	1.3E-7
n 非持续组	49	51	98	69	69	105	75	75	110
n 持续组	101	99	51	81	81	44	75	75	39
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	91%	91%	92%	89%	89%	91%	88%	88%	92%
特异性	59%	57%	34%	42%	42%	31%	39%	39%	31%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	69%	69%	82%	72%	70%	82%	73%	72%	82%
特异性	90%	86%	66%	75%	74%	63%	73%	72%	61%
截止四	19900	19900	20100	19900	19900	20100	19900	19900	20100

[0925]

分位 4									
灵敏度	37%	35%	45%	36%	35%	48%	36%	35%	49%
特异性	98%	94%	85%	87%	86%	84%	85%	84%	83%
OR 四分位 2	14.8	13.2	5.97	5.80	5.80	4.58	4.62	4.62	5.37
p 值	3.0E-9	9.7E-9	0.0015	4.3E-5	4.3E-5	0.0070	3.4E-4	3.4E-4	0.0082
95% CI 的下限	6.08	5.46	1.98	2.50	2.50	1.51	2.00	2.00	1.55
95% CI 的上限	36.1	31.8	18.0	13.5	13.5	13.9	10.7	10.7	18.6
OR 四分位 3	19.9	13.8	9.19	7.71	6.73	7.62	7.56	6.61	7.12
p 值	8.4E-9	1.3E-8	1.8E-7	4.2E-8	2.0E-7	3.9E-6	4.3E-8	2.1E-7	2.0E-5
95% CI 的下限	7.19	5.59	4.00	3.72	3.28	3.22	3.67	3.24	2.89
95% CI 的上限	54.9	34.0	21.1	16.0	13.8	18.0	15.6	13.5	17.6
OR 四分位 4	27.8	8.75	4.55	3.72	3.12	4.73	3.27	2.79	4.55
p 值	0.0013	5.9E-4	1.4E-4	0.0021	0.0061	1.1E-4	0.0035	0.0100	2.0E-4
95% CI 的下限	3.68	2.54	2.09	1.61	1.38	2.15	1.48	1.28	2.05
95% CI 的上限	209	30.1	9.90	8.57	7.02	10.4	7.25	6.07	10.1

[0926] 表17.4:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0927] sCr或UO

[0928]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	5750	14100	7330	15000	7630	15700
平均值	6860	20200	10800	20000	11200	20400
标准偏差	4090	14900	11000	14800	10900	15100

[0929]

p（t-检验）		7.0E-9		3.7E-5		3.7E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	25700	72100	60400	72100	60400	72100
n（患者）	49	101	68	82	74	76

[0930] 仅sCr

[0931]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	6200	14100	7330	14300	7630	15000
平均值	8160	19800	11300	19700	11600	20000
标准偏差	7720	14800	11500	14700	11300	15100
p(t-检验)		4.7E-7		1.9E-4		1.8E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	60400	72100	60400	72100
n（患者）	51	99	68	82	74	76

[0932] 仅UO

[0933]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8720	17900	8800	18000	8860	17900
平均值	11700	23300	12100	23700	12400	24300
标准偏差	9930	16800	10200	17200	10200	17800
p（t-检验）		3.7E-7		8.1E-7		9.1E-7
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n（患者）	95	54	100	49	105	44

[0934]

持续期持续时间(h)	24	48	72

[0935]

	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.88	0.84	0.76	0.77	0.76	0.75	0.75	0.74	0.74
SE	0.028	0.031	0.043	0.038	0.039	0.045	0.039	0.040	0.047
p 值	0	0	2.5E-9	5.4E-13	3.6E-11	3.6E-8	9.8E-11	2.9E-9	3.8E-7
n 非持续组	49	51	95	68	68	100	74	74	105
n 持续组	101	99	54	82	82	49	76	76	44
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	91%	91%	91%	89%	89%	90%	88%	88%	91%
特异性	59%	57%	34%	43%	43%	32%	39%	39%	31%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	69%	69%	80%	72%	71%	80%	74%	72%	80%
特异性	90%	86%	66%	76%	75%	64%	74%	73%	62%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	37%	35%	43%	35%	34%	43%	36%	34%	43%
特异性	98%	94%	84%	87%	85%	83%	85%	84%	82%
OR 四分位 2	14.8	13.2	4.98	6.03	6.03	4.14	4.80	4.80	4.58
p 值	3.0E-9	9.7E-9	0.0019	2.9E-5	2.9E-5	0.0061	2.4E-4	2.4E-4	0.0070
95% CI 的下限	6.08	5.46	1.81	2.60	2.60	1.50	2.08	2.08	1.51
95% CI 的上限	36.1	31.8	13.7	14.0	14.0	11.4	11.1	11.1	13.9
OR 四分位 3	19.9	13.8	7.70	8.34	7.25	6.93	8.11	7.07	6.32
p 值	8.4E-9	1.3E-8	3.7E-7	1.9E-8	9.0E-8	2.5E-6	1.9E-8	9.4E-8	1.4E-5
95% CI 的下限	7.19	5.59	3.50	3.98	3.51	3.10	3.91	3.45	2.75
95% CI 的上限	54.9	34.0	16.9	17.5	15.0	15.5	16.8	14.5	14.5
OR 四分位 4	27.8	8.75	3.96	3.59	3.01	3.66	3.16	2.69	3.44
p 值	0.0013	5.9E-4	4.7E-4	0.0027	0.0078	9.5E-4	0.0046	0.013	0.0018
95% CI 的下限	3.68	2.54	1.83	1.56	1.34	1.70	1.43	1.23	1.58
95% CI 的上限	209	30.1	8.56	8.27	6.77	7.91	6.98	5.85	7.48

[0936] 表17.5:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿

量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0937] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	5750	14100	7010	14500	7520	15700
平均值	6870	20000	10400	20000	10700	20400
标准偏差	4170	14900	10500	14800	10400	15100
p（t-检验）		2.3E-8		1.8E-5		1.2E-5
最小值	1970	3580	1970	3580	1970	3580
最大值	25700	72100	60400	72100	60400	72100
n（患者）	47	103	65	85	70	80

[0938]

[0939] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	6250	14000	7330	14000	7630	14300
平均值	8220	19700	11400	19400	11700	19600
标准偏差	7790	14800	11700	14600	11500	15000
p（t-检验）		8.9E-7		4.2E-4		4.3E-4
最小值	1970	3580	1970	3580	1970	3580
最大值	42400	72100	60400	72100	60400	72100
n（患者）	50	100	66	84	72	78

[0940]

[0941] 仅UO

[0942]

持续期持续时间(h)	24	48	72

[0943]

	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	8350	17700	8440	18400	8720	18400
平均值	11400	23100	11400	23800	11700	24300
标准偏差	9790	16600	9650	16800	9670	17200
p(t-检验)		2.6E-7		6.4E-8		5.1E-8
最小值	1970	3580	1970	3580	1970	3580
最大值	60400	72100	60400	72100	60400	72100
n(患者)	92	57	95	54	99	50

[0944]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.87	0.84	0.76	0.78	0.75	0.77	0.77	0.73	0.77
SE	0.028	0.032	0.042	0.037	0.039	0.042	0.038	0.041	0.044
p 值	0	0	3.9E-10	3.3E-14	4.0E-10	1.7E-10	1.7E-12	2.3E-8	8.7E-10
n 非持续组	47	50	92	65	66	95	70	72	99
n 持续组	103	100	57	85	84	54	80	78	50
截止四分位 2	6820	6820	6810	6820	6820	6810	6820	6820	6810
灵敏度	90%	90%	91%	89%	88%	91%	89%	87%	92%
特异性	60%	56%	35%	45%	42%	34%	41%	39%	33%
截止四分位 3	11000	11000	11000	11000	11000	11000	11000	11000	11000
灵敏度	68%	68%	79%	71%	69%	80%	72%	71%	80%
特异性	89%	86%	67%	77%	74%	66%	76%	72%	65%
截止四分位 4	19900	19900	20100	19900	19900	20100	19900	19900	20100
灵敏度	36%	35%	42%	35%	33%	44%	36%	33%	46%
特异性	98%	94%	85%	88%	85%	85%	87%	83%	85%
OR 四分位 2	13.7	11.5	5.55	6.80	5.45	4.98	5.58	4.33	5.75
p 值	4.4E-9	2.7E-8	9.2E-4	9.0E-6	5.2E-5	0.0019	6.1E-5	4.3E-4	0.0019
95%	5.72	4.85	2.01	2.92	2.40	1.81	2.41	1.91	1.91

[0945]

CI 的下限								
95% CI 的上限	32.9	27.1	15.3	15.9	12.4	13.7	12.9	9.78	17.3
OR 四分位 3	17.8	13.1	7.75	8.00	6.43	7.70	8.22	6.22	7.31
p 值	2.7E-8	2.4E-8	2.0E-7	4.0E-8	4.1E-7	3.7E-7	1.9E-8	4.4E-7	1.3E-6
95% CI 的下限	6.45	5.29	3.58	3.81	3.13	3.50	3.94	3.06	3.27
95% CI 的上限	49.2	32.2	16.8	16.8	13.2	16.9	17.1	12.6	16.4
OR 四分位 4	25.8	8.44	4.05	3.89	2.80	4.63	3.85	2.50	4.77
p 值	0.0016	7.3E-4	4.0E-4	0.0021	0.013	1.2E-4	0.0015	0.021	9.0E-5
95% CI 的下限	3.42	2.45	1.87	1.64	1.24	2.12	1.67	1.15	2.18
95% CI 的上限	195	29.1	8.79	9.22	6.30	10.1	8.88	5.44	10.4

[0946] 实施例18.使用组织蛋白酶B评价进入ICU的患者的肾状态:在RIFLE F持续

[0947] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的组织蛋白酶B。

[0948] 通过基于血清肌酸酐、排尿量或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“持续”和“非持续”群体。“持续”表示在24、48或72小时的时间段内最小RIFLE阶段是衰竭(F)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。“非持续”表示衰竭(F)不持续并且在24、48或72小时的时间段内最小RIFLE阶段是无损伤(RIFLE 0)、具有损伤危险(R)或损伤(I)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。如果患者在衰竭(F)后死亡或在从样品收集至样品收集后24、48、72、96或168小时的任何时间被置于肾替代疗法(RRT),则患者视为“持续”。

[0949] 使用接收器操作特征(ROC)分析确定区分“持续”和“非持续”组的能力。

[0950] 表18.1:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后24小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0951] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.42	8.44	2.42	8.44	2.83	7.78
平均值	6.51	22.2	7.06	23.8	8.21	23.5
标准偏差	10.3	29.0	10.9	30.7	14.2	30.1
p(t-检验)		3.8E-6		2.6E-6		5.9E-5
最小值	0.0435	0.240	0.0435	0.366	0.0435	0.366
最大值	57.5	111	57.5	111	103	111
n(患者)	97	51	105	43	112	36

[0952]

[0953] 仅sCr

[0954]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.46	8.29	2.51	8.44	3.04	6.80
平均值	6.57	21.8	6.84	24.3	8.05	23.1
标准偏差	10.4	28.8	10.4	30.8	13.9	29.8
p(t-检验)		7.2E-6		7.9E-7		5.4E-5
最小值	0.0435	0.172	0.0435	0.172	0.0435	0.172
最大值	57.5	111	57.5	111	103	111
n(患者)	96	52	105	43	110	38

[0955]

[0956] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.62	6.68	3.61	8.62	3.61	8.62
平均值	10.2	25.1	10.1	26.4	10.1	26.4
标准偏差	17.9	30.5	17.9	30.8	17.9	30.8
p(t-检验)		0.0032		0.0016		0.0016
最小值	0.0435	0.592	0.0435	0.592	0.0435	0.592
最大值	111	91.6	111	91.6	111	91.6
n(患者)	129	18	130	17	130	17

[0957]

[0958]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.70	0.68	0.64	0.71	0.70	0.66	0.68	0.66	0.66
SE	0.047	0.047	0.074	0.049	0.050	0.076	0.054	0.054	0.076
p 值	2.9E-5	1.4E-4	0.052	2.4E-5	9.8E-5	0.038	8.1E-4	0.0029	0.038
n 非持续组	97	96	129	105	105	130	112	110	130
n 持续组	51	52	18	43	43	17	36	38	17
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	86%	85%	83%	88%	86%	82%	86%	84%	82%
特异性	31%	30%	26%	30%	30%	26%	29%	28%	26%

[0959]

截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	67%	65%	56%	70%	67%	59%	67%	63%	59%
特异性	59%	58%	50%	58%	57%	51%	55%	55%	51%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	43%	42%	44%	42%	44%	47%	44%	45%	47%
特异性	85%	84%	78%	82%	83%	78%	81%	82%	78%
OR 四分位 2	2.81	2.38	1.79	3.33	2.58	1.65	2.48	2.09	1.65
p 值	0.025	0.051	0.38	0.021	0.052	0.45	0.084	0.13	0.45
95% CI 的下限	1.14	0.997	0.488	1.20	0.990	0.447	0.886	0.797	0.447
95% CI 的上限	6.97	5.68	6.57	9.25	6.74	6.11	6.94	5.50	6.11
OR 四分位 3	2.85	2.64	1.27	3.20	2.76	1.47	2.48	2.06	1.47
p 值	0.0038	0.0065	0.64	0.0026	0.0076	0.46	0.024	0.062	0.46
95% CI 的下限	1.40	1.31	0.471	1.50	1.31	0.528	1.13	0.963	0.528
95% CI 的上限	5.79	5.33	3.42	6.82	5.82	4.11	5.45	4.39	4.11
OR 四分位 4	4.15	3.96	2.76	3.26	3.83	3.10	3.47	3.64	3.10
p 值	3.6E-4	5.3E-4	0.051	0.0031	8.4E-4	0.033	0.0027	0.0016	0.033
95% CI 的下限	1.90	1.82	0.997	1.49	1.74	1.10	1.54	1.63	1.10
95% CI 的上限	9.06	8.63	7.63	7.13	8.41	8.74	7.80	8.13	8.74

[0960] 表18.2:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0961] sCr或UO

[0962]

持续期持续时间(h)	24	48	72

[0963]

	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.30	8.29	2.37	8.44	2.57	7.54
平均值	5.93	21.2	6.29	22.6	7.68	21.9
标准偏差	9.88	27.6	10.1	28.9	13.9	28.2
p（t-检验）		4.0E-6		1.4E-6		6.5E-5
最小值	0.0435	0.240	0.0435	0.366	0.0435	0.366
最大值	57.5	111	57.5	111	103	111
n（患者）	90	58	97	51	104	44

[0964] 仅sCr

[0965]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.40	7.97	2.40	7.97	2.83	6.80
平均值	6.34	20.6	6.66	21.6	8.10	20.4
标准偏差	10.4	27.7	10.6	28.8	14.3	27.8
p（t-检验）		1.9E-5		1.0E-5		5.3E-4
最小值	0.0435	0.172	0.0435	0.172	0.0435	0.172
最大值	57.5	111	57.5	111	103	111
n（患者）	90	58	96	52	102	46

[0966] 仅UO

[0967]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.63	4.73	3.62	6.43	3.62	6.43
平均值	10.1	21.0	10.1	21.8	10.1	21.8
标准偏差	18.1	27.5	18.1	27.8	18.1	27.8
p(t-检验)		0.014		0.0091		0.0091
最小值	0.0435	0.592	0.0435	0.592	0.0435	0.592
最大值	111	91.6	111	91.6	111	91.6
n（患者）	122	25	123	24	123	24

[0968]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.68	0.60	0.72	0.69	0.61	0.68	0.65	0.61
SE	0.045	0.046	0.065	0.046	0.047	0.066	0.050	0.050	0.066
p 值	4.9E-6	8.5E-5	0.13	3.3E-6	4.3E-5	0.10	3.1E-4	0.0031	0.10
n 非持续组	90	90	122	97	96	123	104	102	123
n 持续组	58	58	25	51	52	24	44	46	24
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	84%	83%	76%	86%	85%	75%	84%	83%	75%
特异性	31%	30%	25%	31%	30%	25%	29%	28%	25%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	67%	66%	52%	69%	67%	54%	66%	63%	54%
特异性	61%	60%	50%	60%	59%	50%	57%	56%	50%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	43%	41%	40%	43%	40%	42%	43%	39%	42%
特异性	87%	86%	78%	85%	83%	78%	83%	81%	78%
OR 四分位 2	2.46	2.06	1.08	2.81	2.38	1.01	2.14	1.89	1.01
p 值	0.036	0.084	0.88	0.025	0.051	0.98	0.10	0.16	0.98
95% CI 的下限	1.06	0.909	0.395	1.14	0.997	0.368	0.860	0.786	0.368
95% CI 的上限	5.69	4.66	2.94	6.97	5.68	2.77	5.34	4.53	2.77
OR 四分位 3	3.23	2.85	1.08	3.25	3.01	1.20	2.53	2.16	1.20
p 值	9.3E-4	0.0028	0.86	0.0013	0.0023	0.68	0.013	0.035	0.68
95% CI 的下限	1.61	1.43	0.458	1.59	1.48	0.500	1.22	1.06	0.500
95% CI 的上限	6.45	5.66	2.56	6.67	6.11	2.89	5.28	4.42	2.89
OR 四分位 4	4.92	4.18	2.35	4.15	3.39	2.54	3.63	2.81	2.54
p 值	9.3E-5	3.6E-4	0.065	3.6E-4	0.0019	0.046	0.0013	0.0089	0.046

[0969]

95% CI 的下限	2.21	1.90	0.947	1.90	1.57	1.02	1.66	1.30	1.02
95% CI 的上限	11.0	9.18	5.81	9.06	7.33	6.35	7.95	6.09	6.35

[0970] 表18.3:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0971] sCr或UO

[0972]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.23	8.44	2.20	8.46	2.42	8.14
平均值	5.84	20.1	5.84	21.1	7.59	20.2
标准偏差	10.0	26.8	9.98	27.4	14.3	26.6
p(t-检验)		1.3E-5		3.7E-6		2.6E-4
最小值	0.0435	0.240	0.0435	0.267	0.0435	0.267
最大值	57.5	111	57.5	111	103	111
n(患者)	85	63	89	59	97	51

[0973] 仅sCr

[0974]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.30	8.29	2.23	8.44	2.57	7.37
平均值	5.91	19.8	6.04	20.8	7.84	19.4
标准偏差	10.1	26.7	10.1	27.5	14.4	26.6
p(t-检验)		2.2E-5		8.4E-6		7.4E-4
最小值	0.0435	0.172	0.0435	0.172	0.0435	0.172
最大值	57.5	111	57.5	111	103	111
n(患者)	84	64	89	59	96	52

[0975] 仅UO

[0976]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.60	8.30	3.46	8.46	3.46	8.46
平均值	10.2	18.5	10.1	19.0	10.1	19.0
标准偏差	18.6	24.8	18.5	25.1	18.5	25.1
p（t-检验）		0.041		0.030		0.030
最小值	0.0435	0.267	0.0435	0.267	0.0435	0.267
最大值	111	91.6	111	91.6	111	91.6
n（患者）	115	32	116	31	116	31

[0977]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.70	0.69	0.61	0.73	0.71	0.61	0.68	0.66	0.61
SE	0.044	0.045	0.058	0.044	0.045	0.059	0.048	0.048	0.059
p 值	4.0E-6	2.1E-5	0.066	1.6E-7	3.9E-6	0.054	1.1E-4	0.0013	0.054
n 非持续组	85	84	115	89	89	116	97	96	116
n 持续组	63	64	32	59	59	31	51	52	31
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	84%	83%	78%	86%	85%	77%	84%	83%	77%
特异性	32%	31%	26%	33%	31%	26%	30%	29%	26%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	67%	66%	56%	69%	68%	58%	67%	63%	58%
特异性	62%	62%	51%	63%	62%	52%	59%	57%	52%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	41%	41%	38%	42%	41%	39%	41%	38%	39%
特异性	87%	87%	78%	87%	85%	78%	84%	82%	78%

[0978]

OR 四分位 2	2.47	2.16	1.26	3.08	2.55	1.20	2.29	1.97	1.20
p 值	0.030	0.058	0.63	0.011	0.029	0.71	0.062	0.12	0.71
95% CI 的下限	1.09	0.973	0.494	1.29	1.10	0.468	0.959	0.847	0.468
95% CI 的上限	5.58	4.79	3.21	7.33	5.90	3.06	5.48	4.57	3.06
OR 四分位 3	3.31	3.10	1.35	3.87	3.41	1.48	2.85	2.33	1.48
p 值	5.9E-4	0.0011	0.45	1.6E-4	5.3E-4	0.33	0.0038	0.017	0.33
95% CI 的下限	1.67	1.57	0.616	1.92	1.70	0.666	1.40	1.16	0.666
95% CI 的上限	6.56	6.11	2.98	7.80	6.81	3.30	5.79	4.67	3.30
OR 四分位 4	4.73	4.54	2.16	4.72	4.01	2.30	3.54	2.90	2.30
p 值	1.6E-4	2.4E-4	0.073	1.4E-4	5.2E-4	0.054	0.0013	0.0064	0.054
95% CI 的下限	2.11	2.03	0.931	2.12	1.83	0.985	1.63	1.35	0.985
95% CI 的上限	10.6	10.2	5.01	10.5	8.79	5.37	7.68	6.25	5.37

[0979] 表18.4:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0980] sCr或UO

[0981]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.22	8.29	2.20	8.46	2.42	8.14
平均值	5.83	19.9	5.84	21.1	6.65	21.4
标准偏差	10.1	26.7	9.98	27.4	10.6	28.6
p(t-检验)		1.7E-5		3.7E-6		1.4E-5
最小值	0.0435	0.240	0.0435	0.267	0.0435	0.267
最大值	57.5	111	57.5	111	57.5	111

[0982]

n(患者)	84	64	89	59	95	53

[0983] 仅sCr

[0984]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.30	8.29	2.22	8.45	2.46	7.97
平均值	5.91	19.8	5.90	20.7	6.72	21.0
标准偏差	10.1	26.7	10.0	27.3	10.6	28.5
p(t-检验)		2.2E-5		6.7E-6		2.4E-5
最小值	0.0435	0.172	0.0435	0.172	0.0435	0.172
最大值	57.5	111	57.5	111	57.5	111
n(患者)	84	64	88	60	94	54

[0985] 仅UO

[0986]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.29	7.34	3.29	8.30	3.29	8.30
平均值	9.60	19.3	9.51	20.2	9.51	20.2
标准偏差	17.4	26.4	17.3	26.9	17.3	26.9
p(t-检验)		0.012		0.0067		0.0067
最小值	0.0435	0.267	0.0435	0.267	0.0435	0.267
最大值	111	91.6	111	91.6	111	91.6
n(患者)	111	36	113	34	113	34

[0987]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.69	0.63	0.73	0.71	0.63	0.69	0.68	0.63
SE	0.044	0.045	0.056	0.044	0.044	0.057	0.047	0.047	0.057

[0988]

p 值	2.6E-6	2.1E-5	0.024	1.6E-7	1.2E-6	0.022	4.3E-5	1.9E-4	0.022
n 非持续组	84	84	111	89	88	113	95	94	113
n 持续组	64	64	36	59	60	34	53	54	34
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	84%	83%	81%	86%	85%	79%	85%	83%	79%
特异性	32%	31%	27%	33%	32%	27%	31%	30%	27%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	67%	66%	61%	69%	68%	62%	66%	65%	62%
特异性	63%	62%	53%	63%	62%	53%	59%	59%	53%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	41%	41%	36%	42%	42%	38%	42%	41%	38%
特异性	87%	87%	78%	87%	86%	79%	84%	84%	79%
OR 四分位 2	2.56	2.16	1.53	3.08	2.64	1.39	2.47	2.12	1.39
p 值	0.024	0.058	0.36	0.011	0.023	0.48	0.041	0.080	0.48
95% CI 的下限	1.13	0.973	0.608	1.29	1.14	0.550	1.04	0.915	0.550
95% CI 的上限	5.78	4.79	3.87	7.33	6.12	3.53	5.90	4.92	3.53
OR 四分位 3	3.50	3.10	1.78	3.87	3.60	1.83	2.79	2.60	1.83
p 值	3.3E-4	0.0011	0.14	1.6E-4	3.0E-4	0.13	0.0041	0.0069	0.13
95% CI 的下限	1.77	1.57	0.828	1.92	1.80	0.835	1.39	1.30	0.835
95% CI 的上限	6.94	6.11	3.84	7.80	7.20	4.01	5.62	5.20	4.01
OR 四分位 4	4.54	4.54	2.05	4.72	4.52	2.30	3.78	3.62	2.30
p 值	2.4E-4	2.4E-4	0.085	1.4E-4	2.0E-4	0.049	7.8E-4	0.0011	0.049
95% CI 的下限	2.03	2.03	0.906	2.12	2.04	1.01	1.74	1.67	1.01
95% CI 的上限	10.2	10.2	4.64	10.5	10.0	5.24	8.23	7.85	5.24

[0989] 表18.5:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[0990] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.20	8.44	2.13	8.46	2.40	7.97
平均值	5.32	19.9	5.34	20.8	6.69	20.5
标准偏差	9.01	26.4	9.01	26.9	10.8	28.0
p(t-检验)		7.4E-6		2.2E-6		3.8E-5
最小值	0.0435	0.172	0.0435	0.172	0.0435	0.172
最大值	57.5	111	57.5	111	57.5	111
n(患者)	81	67	85	63	92	56

[0991]

[0992] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	2.22	8.45	2.17	8.53	2.40	8.30
平均值	5.34	20.1	5.36	21.0	6.23	21.3
标准偏差	8.96	26.6	8.95	27.1	9.78	28.2
p(t-检验)		5.7E-6		1.6E-6		6.5E-6
最小值	0.0435	0.172	0.0435	0.172	0.0435	0.172
最大值	57.5	111	57.5	111	57.5	111
n(患者)	82	66	86	62	92	56

[0993]

[0994] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.17	8.14	3.05	8.30	3.05	8.30
平均值	8.68	21.8	8.62	22.4	8.62	22.4
标准偏差	14.5	30.1	14.5	30.3	14.5	30.3
p(t-检验)		5.5E-4		3.4E-4		3.4E-4
最小值	0.0435	0.267	0.0435	0.267	0.0435	0.267
最大值	103	111	103	111	103	111
n(患者)	110	37	111	36	111	36

[0995]

[0996]

[0997]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.71	0.64	0.73	0.73	0.65	0.68	0.69	0.65
SE	0.043	0.043	0.055	0.043	0.043	0.055	0.046	0.046	0.055
p 值	1.3E-6	2.1E-6	0.0097	4.6E-8	8.0E-8	0.0075	7.7E-5	2.9E-5	0.0075
n 非持续组	81	82	110	85	86	111	92	92	111
n 持续组	67	66	37	63	62	36	56	56	36
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	84%	83%	81%	86%	85%	81%	84%	84%	81%
特异性	32%	32%	27%	33%	33%	27%	30%	30%	27%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	67%	67%	62%	70%	69%	64%	66%	66%	64%
特异性	64%	63%	54%	65%	64%	54%	60%	60%	54%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	40%	41%	38%	41%	42%	39%	39%	41%	39%
特异性	88%	88%	79%	87%	87%	79%	84%	85%	79%
OR 四分位 2	2.41	2.32	1.61	2.95	2.84	1.53	2.28	2.28	1.53
p 值	0.031	0.038	0.31	0.011	0.015	0.36	0.054	0.054	0.36
95% CI 的下限	1.08	1.05	0.638	1.27	1.23	0.608	0.986	0.986	0.608
95% CI 的上限	5.34	5.15	4.05	6.81	6.57	3.87	5.29	5.29	3.87

[0998]

OR 四分位 3	3.67	3.47	1.90	4.25	4.02	2.08	2.89	2.89	2.08
p 值	1.9E-4	3.5E-4	0.099	4.9E-5	9.2E-5	0.064	0.0026	0.0026	0.064
95% CI 的下限	1.85	1.75	0.886	2.11	2.00	0.958	1.45	1.45	0.958
95% CI 的上限	7.26	6.85	4.08	8.53	8.06	4.52	5.79	5.79	4.52
OR 四分位 4	4.79	4.98	2.30	4.73	4.92	2.43	3.32	3.88	2.43
p 值	1.9E-4	1.3E-4	0.043	1.6E-4	1.1E-4	0.032	0.0023	6.4E-4	0.032
95% CI 的下限	2.11	2.19	1.03	2.11	2.19	1.08	1.54	1.78	1.08
95% CI 的上限	10.9	11.4	5.16	10.6	11.1	5.49	7.18	8.46	5.49

[0999] 表18.6:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后24小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1000] sCr或UO

[1001]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	90.7	129	94.2	135	94.2	136
平均值	102	133	103	136	105	137
标准偏差	53.6	79.7	55.0	81.2	55.4	85.0
p(t-检验)		0.0056		0.0045		0.0085
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	253	401	253	401	253	401
n(患者)	95	55	103	47	110	40

[1002] 仅sCr

[1003]

持续期持续时间(h)	24	48	72

[1004]

	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	92.4	128	94.2	129	95.2	124
平均值	103	131	104	133	107	131
标准偏差	53.5	80.0	55.4	81.5	56.1	84.5
p（t-检验）		0.010		0.012		0.044
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	253	401	253	401	253	401
n（患者）	94	56	103	47	108	42

[1005] 仅UO

[1006]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	97.5	157	97.5	157	98.9	148
平均值	108	155	108	155	108	154
标准偏差	59.5	91.2	59.5	91.2	59.5	93.8
p（t-检验）		0.0034		0.0034		0.0056
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	284	401	284	401	284	401
n（患者）	130	19	130	19	131	18

[1007]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.61	0.60	0.66	0.62	0.60	0.66	0.60	0.57	0.65
SE	0.049	0.049	0.072	0.051	0.051	0.072	0.054	0.053	0.074
p 值	0.021	0.041	0.022	0.021	0.054	0.022	0.057	0.20	0.041
n 非持续组	95	94	130	103	103	130	110	108	131
n 持续组	55	56	19	47	47	19	40	42	18
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	80%	79%	84%	81%	79%	84%	80%	76%	83%

[1008]

特异性	28%	28%	26%	28%	27%	26%	27%	26%	26%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	62%	61%	68%	62%	62%	68%	62%	60%	67%
特异性	57%	56%	52%	55%	55%	52%	55%	54%	52%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	36%	36%	53%	36%	34%	53%	38%	33%	50%
特异性	81%	81%	78%	80%	79%	78%	79%	78%	78%
OR 四分位 2	1.59	1.40	1.89	1.65	1.38	1.89	1.50	1.12	1.75
p 值	0.26	0.40	0.34	0.24	0.44	0.34	0.37	0.79	0.40
95% CI 的下限	0.716	0.641	0.518	0.711	0.607	0.518	0.621	0.488	0.478
95% CI 的上限	3.52	3.06	6.89	3.85	3.14	6.89	3.62	2.57	6.43
OR 四分位 3	2.13	2.00	2.38	2.00	2.00	2.38	2.00	1.71	2.16
p 值	0.029	0.044	0.098	0.055	0.055	0.098	0.067	0.15	0.15
95% CI 的下限	1.08	1.02	0.851	0.987	0.987	0.851	0.952	0.828	0.764
95% CI 的上限	4.20	3.92	6.63	4.04	4.04	6.63	4.20	3.52	6.10
OR 四分位 4	2.44	2.35	4.05	2.21	1.90	4.05	2.27	1.75	3.52
p 值	0.020	0.026	0.0058	0.042	0.10	0.0058	0.041	0.16	0.015
95% CI 的下限	1.15	1.11	1.50	1.03	0.884	1.50	1.03	0.798	1.28
95% CI 的上限	5.18	4.97	10.9	4.75	4.09	10.9	4.99	3.84	9.67

[1009] 表18.7:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1010] sCr或UO

[1011]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	89.6	121	92.5	120	94.3	118
平均值	101	131	103	131	105	131
标准偏差	53.2	77.7	54.7	78.7	55.1	81.7
p（t-检验）		0.0063		0.012		0.025
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	253	401	253	401	253	401
n（患者）	88	62	94	56	101	49

[1012] 仅sCr

[1013]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	92.5	119	96.1	113	98.9	111
平均值	103	127	105	126	108	124
标准偏差	55.2	76.9	56.7	77.4	56.9	79.9
p（t-检验）		0.029		0.059		0.15
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	253	401	253	401	253	401
n（患者）	88	62	93	57	99	51

[1014] 仅UO

[1015]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	101	124	101	124	101	111
平均值	109	137	109	137	109	136
标准偏差	58.7	90.7	58.7	90.7	58.7	92.3
p（t-检验）		0.046		0.046		0.067
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	284	401	284	401	284	401

[1016]

n（患者）	123	26	123	26	124	25

[1017]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.61	0.59	0.58	0.60	0.57	0.58	0.58	0.54	0.56
SE	0.047	0.048	0.064	0.049	0.049	0.064	0.051	0.050	0.065
p 值	0.021	0.072	0.22	0.046	0.15	0.22	0.12	0.41	0.32
n 非持续组	88	88	123	94	93	123	101	99	124
n 持续组	62	62	26	56	57	26	49	51	25
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	82%	81%	81%	82%	81%	81%	82%	78%	80%
特异性	31%	30%	26%	30%	29%	26%	29%	27%	26%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	60%	58%	54%	59%	56%	54%	59%	55%	52%
特异性	57%	56%	50%	55%	54%	50%	54%	53%	50%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	34%	32%	42%	32%	30%	42%	33%	29%	40%
特异性	81%	80%	78%	79%	77%	78%	78%	77%	77%
OR 四分位 2	2.05	1.75	1.48	1.95	1.71	1.48	1.79	1.36	1.39
p 值	0.076	0.16	0.47	0.11	0.19	0.47	0.18	0.45	0.54
95% CI 的下限	0.928	0.802	0.514	0.864	0.772	0.514	0.771	0.612	0.482
95% CI 的上限	4.54	3.81	4.24	4.41	3.79	4.24	4.15	3.04	4.01
OR 四分位 3	1.95	1.74	1.19	1.78	1.49	1.19	1.73	1.35	1.08
p 值	0.048	0.098	0.69	0.093	0.24	0.69	0.12	0.39	0.86
95% CI 的下限	1.01	0.902	0.508	0.909	0.767	0.508	0.868	0.684	0.458
95% CI 的上限	3.77	3.36	2.77	3.47	2.89	2.77	3.46	2.65	2.56
OR 四分位	2.14	1.85	2.61	1.75	1.46	2.61	1.74	1.38	2.29

[1018]

4									
p 值	0.046	0.10	0.034	0.14	0.32	0.034	0.15	0.41	0.073
95% CI 的下限	1.01	0.881	1.07	0.830	0.690	1.07	0.813	0.643	0.925
95% CI 的上限	4.51	3.89	6.33	3.70	3.08	6.33	3.73	2.95	5.65

[1019] 表18.8:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1020] sCr或UO

[1021]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	88.6	122	89.6	124	94.2	120
平均值	98.0	132	98.0	134	102	132
标准偏差	50.6	77.1	50.5	77.9	53.8	79.5
p(t-检验)		0.0013		8.3E-4		0.0083
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	253	401
n(患者)	83	67	86	64	94	56

[1022] 仅sCr

[1023]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	89.6	121	92.5	120	96.1	113
平均值	98.7	131	99.8	131	105	127
标准偏差	50.5	77.3	51.3	78.3	54.4	79.6
p(t-检验)		0.0026		0.0035		0.038
最小值	16.4	13.2	16.4	13.2	16.4	13.2

[1024]

最大值	246	401	246	401	253	401
n(患者)	82	68	86	64	93	57

[1025] 仅UO

[1026]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	99.1	121	99.1	121	99.8	113
平均值	107	135	107	135	108	134
标准偏差	58.0	85.1	58.0	85.1	58.0	86.2
p（t-检验）		0.028		0.028		0.041
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	284	401	284	401	284	401
n（患者）	115	34	115	34	116	33

[1027]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.63	0.62	0.59	0.63	0.61	0.59	0.60	0.57	0.58
SE	0.046	0.046	0.057	0.046	0.047	0.057	0.048	0.049	0.058
p 值	0.0046	0.0099	0.13	0.0039	0.017	0.13	0.039	0.16	0.19
n 非持续组	83	82	115	86	86	115	94	93	116
n 持续组	67	68	34	64	64	34	56	57	33
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	84%	82%	82%	84%	83%	82%	84%	81%	82%
特异性	33%	32%	27%	33%	31%	27%	31%	29%	27%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	60%	59%	56%	59%	58%	56%	59%	56%	55%
特异性	58%	57%	51%	57%	56%	51%	55%	54%	51%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	34%	34%	38%	34%	33%	38%	32%	30%	36%

[1028]

特异性	82%	82%	78%	81%	80%	78%	79%	77%	78%
OR 四分位2	2.45	2.17	1.72	2.61	2.20	1.72	2.33	1.71	1.64
p 值	0.026	0.051	0.27	0.021	0.051	0.27	0.048	0.19	0.32
95% CI 的下限	1.11	0.995	0.651	1.16	0.998	0.651	1.01	0.772	0.619
95% CI 的上限	5.42	4.72	4.56	5.87	4.87	4.56	5.38	3.79	4.35
OR 四分位3	2.03	1.92	1.33	1.94	1.73	1.33	1.78	1.49	1.24
p 值	0.034	0.050	0.46	0.049	0.100	0.46	0.093	0.24	0.58
95% CI 的下限	1.06	1.000	0.618	1.00	0.900	0.618	0.909	0.767	0.572
95% CI 的上限	3.91	3.68	2.88	3.73	3.33	2.88	3.47	2.89	2.70
OR 四分位4	2.37	2.28	2.23	2.29	1.98	2.23	1.75	1.46	1.98
p 值	0.025	0.031	0.056	0.030	0.072	0.056	0.14	0.32	0.11
95% CI 的下限	1.12	1.08	0.980	1.08	0.942	0.980	0.830	0.690	0.860
95% CI 的上限	5.03	4.84	5.07	4.85	4.17	5.07	3.70	3.08	4.55

[1029] 表18.9:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1030] sCr或UO

[1031]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	87.0	122	88.6	127	94.2	122
平均值	96.4	133	96.5	135	100	133
标准偏差	49.1	77.0	48.8	78.2	51.3	79.8
p(t-检验)		5.4E-4		2.7E-4		0.0023
最小值	16.4	13.2	16.4	13.2	16.4	13.2

[1032]

最大值	246	401	246	401	253	401
n(患者)	81	69	85	65	91	59

[1033] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	88.6	122	89.6	124	94.2	120
平均值	97.1	132	97.1	134	101	132
标准偏差	48.7	77.7	48.7	78.4	51.2	80.1
p（t-检验）		9.4E-4		5.8E-4		0.0043
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	253	401
n（患者）	81	69	84	66	90	60

[1034]

[1035] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	94.3	123	95.2	129	96.1	123
平均值	104	139	104	140	105	139
标准偏差	55.7	83.5	55.5	84.3	55.6	85.3
p（t-检验）		0.0038		0.0030		0.0048
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	274	401	274	401	274	401
n（患者）	109	40	110	39	111	38

[1036]

[1037]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.64	0.63	0.62	0.64	0.63	0.62	0.61	0.60	0.61

[1038]

SE	0.045	0.046	0.054	0.046	0.046	0.054	0.048	0.048	0.055
p 值	0.0019	0.0044	0.027	0.0016	0.0037	0.026	0.016	0.031	0.043
n 非持续组	81	81	109	85	84	110	91	90	111
n 持续组	69	69	40	65	66	39	59	60	38
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	84%	83%	85%	85%	83%	85%	83%	82%	84%
特异性	33%	32%	28%	33%	32%	28%	31%	30%	28%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	59%	59%	60%	60%	59%	62%	59%	58%	61%
特异性	58%	58%	53%	58%	57%	54%	56%	56%	53%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	35%	35%	38%	35%	35%	38%	34%	33%	37%
特异性	83%	83%	79%	82%	82%	79%	80%	80%	78%
OR 四分位 2	2.64	2.25	2.25	2.70	2.37	2.16	2.18	1.91	2.07
p 值	0.017	0.042	0.098	0.016	0.033	0.12	0.061	0.11	0.14
95% CI 的下限	1.19	1.03	0.860	1.20	1.07	0.823	0.966	0.863	0.787
95% CI 的上限	5.83	4.89	5.90	6.08	5.23	5.66	4.91	4.22	5.43
OR 四分位 3	2.02	2.02	1.71	2.04	1.93	1.85	1.86	1.75	1.74
p 值	0.034	0.034	0.15	0.033	0.049	0.11	0.067	0.097	0.15
95% CI 的下限	1.05	1.05	0.817	1.06	1.00	0.878	0.957	0.904	0.822
95% CI 的上限	3.89	3.89	3.56	3.94	3.70	3.90	3.61	3.39	3.68
OR 四分位 4	2.55	2.55	2.24	2.56	2.46	2.36	2.08	2.00	2.11
p 值	0.016	0.016	0.045	0.015	0.019	0.033	0.054	0.068	0.066
95% CI 的下限	1.19	1.19	1.02	1.20	1.16	1.07	0.986	0.950	0.951
95% CI 的上限	5.46	5.46	4.94	5.44	5.23	5.22	4.39	4.21	4.70

[1039] 表18.10:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1040] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	86.1	121	87.0	122	92.8	120
平均值	96.0	132	96.0	133	100.0	132
标准偏差	48.8	76.4	48.7	77.1	51.1	79.1
p（t-检验）		6.8E-4		4.2E-4		0.0029
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	253	401
n（患者）	78	72	81	69	88	62

[1041]

[1042] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	87.0	122	87.8	124	92.8	120
平均值	96.0	132	96.1	134	100.0	132
标准偏差	48.4	76.9	48.4	77.6	51.1	79.1
p（t-检验）		5.9E-4		3.6E-4		0.0029
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	246	401	246	401	253	401
n（患者）	79	71	82	68	88	62

[1043]

[1044] 仅UO

[1045]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	94.2	129	94.2	129	94.3	123
平均值	103	143	103	143	103	142
标准偏差	53.5	85.1	53.5	85.1	53.7	86.0
p（t-检验）		8.4E-4		8.4E-4		0.0014
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	260	401	260	401	260	401
n（患者）	108	41	108	41	109	40

[1046]

[1047]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.64	0.64	0.63	0.64	0.64	0.63	0.61	0.61	0.62
SE	0.045	0.045	0.053	0.045	0.046	0.053	0.047	0.047	0.053
p 值	0.0022	0.0022	0.012	0.0019	0.0018	0.012	0.019	0.019	0.021
n 非持续组	78	79	108	81	82	108	88	88	109
n 持续组	72	71	41	69	68	41	62	62	40
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	83%	83%	85%	84%	84%	85%	82%	82%	85%
特异性	33%	33%	29%	33%	33%	29%	31%	31%	28%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	58%	59%	61%	58%	59%	61%	58%	58%	60%
特异性	58%	58%	54%	57%	57%	54%	56%	56%	53%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	35%	35%	39%	35%	35%	39%	34%	34%	38%
特异性	83%	84%	80%	83%	83%	80%	81%	81%	79%
OR 四分位 2	2.50	2.41	2.35	2.64	2.54	2.35	2.05	2.05	2.25
p 值	0.021	0.027	0.082	0.017	0.021	0.082	0.076	0.076	0.098
95% CI 的下限	1.15	1.11	0.898	1.19	1.15	0.898	0.928	0.928	0.860
95% CI 的上限	5.44	5.25	6.14	5.83	5.62	6.14	4.54	4.54	5.90
OR 四分位 3	1.91	2.02	1.81	1.81	1.92	1.81	1.74	1.74	1.71

[1048]

	p 值	0.051	0.034	0.11	0.073	0.050	0.11	0.098	0.098	0.15
	95% CI 的下限	0.998	1.05	0.871	0.947	1.000	0.871	0.902	0.902	0.817
	95% CI 的上限	3.65	3.87	3.77	3.47	3.68	3.77	3.36	3.36	3.56
	OR 四分位 4	2.66	2.76	2.50	2.55	2.65	2.50	2.14	2.14	2.24
	p 值	0.013	0.0097	0.022	0.016	0.012	0.022	0.046	0.046	0.045
	95% CI 的下限	1.23	1.28	1.14	1.19	1.24	1.14	1.01	1.01	1.02
	95% CI 的上限	5.73	5.95	5.47	5.46	5.67	5.47	4.51	4.51	4.94

[1049] 实施例19.使用组织蛋白酶B评价进入ICU的患者的肾状态:在RIFLE I或F持续

[1050] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的组织蛋白酶B。

[1051] 通过基于血清肌酸酐、排尿量或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“持续”和“非持续”群体。“持续”表示在24、48或72小时的时间段内最小RIFLE阶段是损伤(I)或衰竭(F)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。“非持续”表示损伤(I)或衰竭(F)不持续并且在24、48或72小时的时间段内最小RIFLE阶段是无损伤(RIFLE 0)或具有损伤危险(R)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。如果患者在损伤(I)或衰竭(F)后死亡或在从样品收集至样品收集后24、48、72、96或168小时的任何时间被置于肾替代疗法(RRT),则患者视为“持续”。

[1052] 使用接收器操作特征(ROC)分析确定区分“持续”和“非持续”组的能力。

[1053] 表19.1:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后24小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1054] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.57	7.50	2.42	6.67	2.42	8.44
平均值	2.92	17.1	6.68	17.6	6.52	19.6
标准偏差	3.60	23.8	10.8	25.9	10.4	27.4
p（t-检验）		2.7E-5		9.0E-4		7.7E-5
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n（患者）	54	94	77	71	87	61

[1055]

[1056] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.74	7.97	2.37	7.81	2.29	8.53
平均值	3.01	17.3	5.59	18.4	5.56	21.2
标准偏差	3.56	24.0	9.35	25.8	8.93	27.5
p（t-检验）		1.9E-5		8.4E-5		1.8E-6
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n（患者）	56	92	75	73	88	60

[1057]

[1058] 仅UO

[1059]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.29	5.69	3.46	8.62	3.46	8.62
平均值	10.6	16.7	10.2	19.8	10.1	22.0
标准偏差	19.0	24.0	18.5	26.1	18.2	27.6
p（t-检验）		0.12		0.026		0.0095
最小值	0.0435	0.592	0.0435	0.592	0.0435	0.592
最大值	111	91.6	111	91.6	111	91.6
n（患者）	113	34	120	27	124	23

[1060]

[1061]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.75	0.74	0.61	0.66	0.68	0.64	0.68	0.71	0.65
SE	0.039	0.040	0.057	0.045	0.044	0.062	0.045	0.044	0.066
p 值	1.2E-10	1.5E-9	0.049	5.1E-4	4.8E-5	0.029	7.8E-5	2.2E-6	0.028
n 非持续组	54	56	113	77	75	120	87	88	124
n 持续组	94	92	34	71	73	27	61	60	23
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	83%	83%	85%	83%	84%	85%	85%	87%	83%
特异性	39%	38%	28%	32%	33%	28%	32%	33%	27%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	64%	63%	62%	62%	63%	59%	64%	67%	61%
特异性	74%	71%	53%	61%	63%	52%	60%	61%	52%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	36%	37%	32%	34%	37%	41%	38%	42%	43%
特异性	94%	95%	77%	83%	87%	78%	84%	86%	78%
OR 四分位 2	3.10	2.85	2.29	2.36	2.54	2.18	2.74	3.19	1.72
p 值	0.0038	0.0072	0.12	0.031	0.020	0.18	0.018	0.0086	0.35
95% CI 的下限	1.44	1.33	0.815	1.08	1.16	0.701	1.19	1.34	0.546
95% CI 的	6.68	6.12	6.44	5.17	5.56	6.78	6.34	7.60	5.44

[1062]

上限									
OR 四分位 3	5.04	4.26	1.83	2.55	2.86	1.55	2.63	3.18	1.66
p 值	1.8E-5	7.5E-5	0.13	0.0056	0.0020	0.31	0.0050	9.8E-4	0.27
95% CI 的下限	2.41	2.08	0.835	1.32	1.47	0.667	1.34	1.60	0.669
95% CI 的上限	10.6	8.74	4.01	4.95	5.57	3.63	5.18	6.32	4.12
OR 四分位 4	9.63	10.4	1.60	2.51	3.82	2.49	3.16	4.52	2.76
p 值	3.4E-4	2.1E-4	0.27	0.019	0.0013	0.043	0.0035	2.0E-4	0.032
95% CI 的下限	2.79	3.00	0.690	1.16	1.68	1.03	1.46	2.04	1.09
95% CI 的上限	33.2	35.7	3.71	5.45	8.64	6.00	6.83	10.0	6.99

[1063] 表19.2:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1064] sCr或UO

[1065]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.55	7.19	2.17	7.37	2.13	8.46
平均值	2.90	16.9	5.39	18.1	5.35	19.9
标准偏差	3.63	23.8	9.40	25.3	9.10	26.4
p(t-检验)		3.5E-5		1.0E-4		8.2E-6
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n(患者)	53	95	72	76	81	67

[1066] 仅sCr

[1067]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.60	7.81	2.29	7.37	2.20	8.44
平均值	2.99	17.2	5.48	18.0	5.50	19.7
标准偏差	3.59	23.9	9.38	25.4	9.13	26.5
p（t-检验）		2.4E-5		1.3E-4		1.4E-5
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n（患者）	55	93	72	76	81	67

[1068] 仅UO

[1069]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.05	6.73	3.30	8.62	3.30	8.62
平均值	9.45	18.3	9.15	21.1	9.08	22.8
标准偏差	17.6	25.1	17.1	26.6	16.8	27.7
p（t-检验）		0.016		0.0022		6.8E-4
最小值	0.0435	0.592	0.0435	0.592	0.0435	0.592
最大值	111	91.6	111	91.6	111	91.6
n（患者）	105	42	112	35	116	31

[1070]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.76	0.74	0.63	0.70	0.68	0.65	0.72	0.70	0.66
SE	0.039	0.040	0.053	0.043	0.044	0.056	0.043	0.044	0.058
p 值	7.0E-11	9.2E-10	0.011	4.1E-6	3.3E-5	0.0065	1.9E-7	3.2E-6	0.0064
n 非持续组	53	55	105	72	72	112	81	81	116
n 持续组	95	93	42	76	76	35	67	67	31

[1071]

截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	83%	83%	83%	84%	83%	83%	87%	85%	81%
特异性	40%	38%	29%	35%	33%	28%	35%	33%	27%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	64%	63%	62%	64%	63%	60%	67%	66%	61%
特异性	75%	73%	54%	65%	64%	53%	64%	63%	53%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	36%	37%	36%	37%	37%	43%	40%	39%	45%
特异性	94%	95%	79%	88%	88%	80%	88%	86%	80%
OR 四分位 2	3.24	2.97	2.00	2.84	2.42	1.85	3.40	2.85	1.52
p 值	0.0027	0.0053	0.14	0.0092	0.025	0.21	0.0042	0.012	0.40
95% CI 的下限	1.50	1.38	0.801	1.29	1.12	0.700	1.47	1.26	0.570
95% CI 的上限	6.99	6.39	5.00	6.22	5.25	4.89	7.87	6.44	4.05
OR 四分位 3	5.52	4.63	1.93	3.41	3.03	1.67	3.67	3.25	1.76
p 值	8.8E-6	3.7E-5	0.078	3.7E-4	0.0012	0.19	1.9E-4	6.3E-4	0.17
95% CI 的下限	2.60	2.23	0.928	1.74	1.55	0.772	1.85	1.65	0.782
95% CI 的上限	11.7	9.58	4.01	6.70	5.93	3.61	7.26	6.40	3.95
OR 四分位 4	9.29	9.99	2.10	4.08	4.08	3.07	4.79	4.04	3.33
p 值	4.2E-4	2.7E-4	0.065	0.0010	0.0010	0.0071	1.9E-4	6.7E-4	0.0051
95% CI 的下限	2.69	2.90	0.954	1.76	1.76	1.36	2.11	1.81	1.43
95% CI 的上限	32.0	34.4	4.60	9.46	9.46	6.94	10.9	9.01	7.73

[1072] 表19.3:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1073] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.55	7.19	2.13	6.94	2.13	8.14
平均值	2.90	16.9	5.41	17.9	5.45	18.9
标准偏差	3.63	23.8	9.46	25.2	9.30	25.9
p（t-检验）		3.5E-5		1.3E-4		3.5E-5
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n（患者）	53	95	71	77	77	71

[1074]

[1075] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.60	7.81	2.20	6.94	2.20	8.14
平均值	2.99	17.2	5.50	17.8	5.53	18.8
标准偏差	3.59	23.9	9.44	25.3	9.28	26.0
p（t-检验）		2.4E-5		1.7E-4		4.4E-5
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n（患者）	55	93	71	77	77	71

[1076]

[1077] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.05	6.73	3.29	8.30	3.29	8.30
平均值	9.69	16.7	9.36	18.6	9.27	19.8
标准偏差	18.1	23.9	17.6	25.0	17.3	25.9
p（t-检验）		0.049		0.013		0.0058
最小值	0.0435	0.267	0.0435	0.267	0.0435	0.267
最大值	111	91.6	111	91.6	111	91.6
n（患者）	99	48	105	42	109	38

[1078]

[1079]

[1080]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.76	0.74	0.61	0.70	0.68	0.63	0.71	0.69	0.63
SE	0.039	0.040	0.051	0.043	0.044	0.053	0.043	0.043	0.054
p 值	7.0E-11	9.2E-10	0.026	3.5E-6	2.9E-5	0.013	9.9E-7	9.3E-6	0.014
n 非持续组	53	55	99	71	71	105	77	77	109
n 持续组	95	93	48	77	77	42	71	71	38
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	83%	83%	81%	84%	83%	81%	86%	85%	79%
特异性	40%	38%	28%	35%	34%	28%	35%	34%	27%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	64%	63%	60%	65%	64%	60%	66%	65%	61%
特异性	75%	73%	55%	66%	65%	53%	65%	64%	53%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	36%	37%	33%	36%	36%	38%	38%	38%	39%
特异性	94%	95%	79%	87%	87%	80%	87%	87%	80%
OR 四分位 2	3.24	2.97	1.71	2.94	2.51	1.62	3.29	2.78	1.36
p 值	0.0027	0.0053	0.21	0.0070	0.019	0.28	0.0042	0.012	0.50
95% CI 的下限	1.50	1.38	0.733	1.34	1.16	0.672	1.46	1.25	0.559
95% CI 的上限	6.99	6.39	3.98	6.45	5.45	3.91	7.45	6.17	3.30
OR 四分位 3	5.52	4.63	1.83	3.63	3.22	1.68	3.63	3.22	1.74
p 值	8.8E-6	3.7E-5	0.091	2.0E-4	6.6E-4	0.16	2.0E-4	6.6E-4	0.15
95% CI 的下限	2.60	2.23	0.909	1.84	1.64	0.813	1.84	1.64	0.823

[1081]

95% CI 的上限	11.7	9.58	3.69	7.15	6.31	3.47	7.15	6.31	3.70
OR 四分位 4	9.29	9.99	1.86	3.94	3.94	2.46	4.11	4.11	2.58
p 值	4.2E-4	2.7E-4	0.11	0.0014	0.0014	0.025	7.2E-4	7.2E-4	0.020
95% CI 的下限	2.69	2.90	0.860	1.70	1.70	1.12	1.81	1.81	1.16
95% CI 的上限	32.0	34.4	4.01	9.11	9.11	5.40	9.33	9.33	5.75

[1082] 表19.4:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1083] sCr或UO

[1084]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.55	7.19	2.13	6.94	2.13	8.14
平均值	2.90	16.9	5.41	17.9	5.45	18.9
标准偏差	3.63	23.8	9.46	25.2	9.30	25.9
p(t-检验)		3.5E-5		1.3E-4		3.5E-5
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n(患者)	53	95	71	77	77	71

[1085] 仅sCr

[1086]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.60	7.81	2.20	6.94	2.20	8.14
平均值	2.99	17.2	5.50	17.8	5.53	18.8
标准偏差	3.59	23.9	9.44	25.3	9.28	26.0

[1087]

p(t-检验)		2.4E-5		1.7E-4		4.4E-5
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n(患者)	55	93	71	77	77	71

[1088] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.05	6.20	3.17	7.81	3.17	7.81
平均值	9.81	16.2	9.51	17.6	9.42	18.6
标准偏差	18.2	23.5	17.8	24.4	17.5	25.3
p（t-检验）		0.071		0.026		0.013
最小值	0.0435	0.267	0.0435	0.267	0.0435	0.267
最大值	111	91.6	111	91.6	111	91.6
n（患者）	97	50	102	45	106	41

[1089]

[1090]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.76	0.74	0.61	0.70	0.68	0.62	0.71	0.69	0.63
SE	0.039	0.040	0.050	0.043	0.044	0.051	0.043	0.043	0.053
p 值	7.0E-11	9.2E-10	0.031	3.5E-6	2.9E-5	0.015	9.9E-7	9.3E-6	0.017
n 非持续组	53	55	97	71	71	102	77	77	106
n 持续组	95	93	50	77	77	45	71	71	41
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	83%	83%	82%	84%	83%	82%	86%	85%	80%
特异性	40%	38%	29%	35%	34%	28%	35%	34%	27%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	64%	63%	60%	65%	64%	60%	66%	65%	61%

[1091]

特异性	75%	73%	55%	66%	65%	54%	65%	64%	54%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	36%	37%	32%	36%	36%	36%	38%	38%	37%
特异性	94%	95%	78%	87%	87%	79%	87%	87%	79%
OR 四分位 2	3.24	2.97	1.85	2.94	2.51	1.84	3.29	2.78	1.55
p 值	0.0027	0.0053	0.15	0.0070	0.019	0.17	0.0042	0.012	0.33
95% CI 的下限	1.50	1.38	0.794	1.34	1.16	0.764	1.46	1.25	0.643
95% CI 的上限	6.99	6.39	4.30	6.45	5.45	4.42	7.45	6.17	3.76
OR 四分位 3	5.52	4.63	1.81	3.63	3.22	1.76	3.63	3.22	1.82
p 值	8.8E-6	3.7E-5	0.094	2.0E-4	6.6E-4	0.12	2.0E-4	6.6E-4	0.11
95% CI 的下限	2.60	2.23	0.904	1.84	1.64	0.861	1.84	1.64	0.872
95% CI 的上限	11.7	9.58	3.61	7.15	6.31	3.58	7.15	6.31	3.79
OR 四分位 4	9.29	9.99	1.70	3.94	3.94	2.13	4.11	4.11	2.20
p 值	4.2E-4	2.7E-4	0.17	0.0014	0.0014	0.057	7.2E-4	7.2E-4	0.050
95% CI 的下限	2.69	2.90	0.792	1.70	1.70	0.979	1.81	1.81	1.000
95% CI 的上限	32.0	34.4	3.66	9.11	9.11	4.63	9.33	9.33	4.85

[1092] 表19.5:“持续”和“非持续”组的尿样中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1093] sCr或UO

[1094]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.55	7.19	2.17	6.80	2.13	7.81

[1095]

平均值	2.73	16.8	5.50	17.4	5.54	18.1
标准偏差	3.28	23.6	9.62	24.9	9.51	25.5
p（t-检验）		4.2E-5		3.1E-4		1.2E-4
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n（患者）	51	97	68	80	73	75

[1096] 仅sCr

[1097]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	1.57	7.97	2.13	7.81	2.13	8.44
平均值	2.78	17.2	5.32	17.7	5.36	18.7
标准偏差	3.25	23.8	9.50	25.0	9.34	25.7
p（t-检验）		2.0E-5		1.6E-4		4.5E-5
最小值	0.0435	0.156	0.0435	0.156	0.0435	0.156
最大值	17.5	111	57.5	111	57.5	111
n（患者）	54	94	69	79	75	73

[1098] 仅UO

[1099]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	3.03	6.73	3.04	7.81	3.03	7.97
平均值	8.75	17.9	8.61	18.7	8.55	19.5
标准偏差	15.1	26.6	14.9	27.2	14.7	27.8
p(t-检验)		0.0087		0.0041		0.0021
最小值	0.0435	0.267	0.0435	0.267	0.0435	0.267
最大值	103	111	103	111	103	111
n（患者）	95	52	98	49	101	46

[1100]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.75	0.75	0.63	0.68	0.70	0.63	0.69	0.71	0.64
SE	0.039	0.039	0.049	0.043	0.043	0.050	0.043	0.043	0.051
p 值	1.2E-10	9.8E-11	0.0095	2.6E-5	4.8E-6	0.0082	6.9E-6	1.5E-6	0.0065
n 非持续组	51	54	95	68	69	98	73	75	101
n 持续组	97	94	52	80	79	49	75	73	46
截止四分位 2	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
灵敏度	82%	83%	83%	82%	84%	82%	84%	85%	80%
特异性	39%	39%	29%	34%	35%	29%	34%	35%	28%
截止四分位 3	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63	3.63
灵敏度	64%	64%	62%	64%	65%	61%	65%	66%	63%
特异性	76%	74%	56%	66%	67%	55%	66%	65%	55%
截止四分位 4	12.8	12.8	13.1	12.8	12.8	13.1	12.8	12.8	13.1
灵敏度	36%	37%	33%	35%	37%	35%	36%	38%	35%
特异性	96%	96%	79%	87%	88%	80%	86%	88%	79%
OR 四分位 2	3.04	3.10	2.00	2.41	2.71	1.78	2.73	2.99	1.58
p 值	0.0046	0.0038	0.11	0.024	0.012	0.18	0.012	0.0072	0.29
95% CI 的下限	1.41	1.44	0.859	1.12	1.25	0.763	1.25	1.35	0.675
95% CI 的上限	6.54	6.68	4.64	5.18	5.87	4.14	5.99	6.64	3.68
OR 四分位 3	5.76	5.04	2.02	3.44	3.64	1.94	3.62	3.62	2.12
p 值	8.0E-6	1.8E-5	0.046	3.6E-4	2.0E-4	0.064	2.0E-4	2.0E-4	0.039
95% CI 的下限	2.67	2.41	1.01	1.75	1.84	0.963	1.84	1.84	1.04
95% CI 的上限	12.4	10.6	4.03	6.78	7.19	3.90	7.13	7.13	4.34
OR 四分位 4	13.8	15.4	1.82	3.53	4.42	2.07	3.54	4.56	2.03
p 值	4.8E-4	2.7E-4	0.12	0.0032	7.8E-4	0.062	0.0024	4.0E-4	0.073
95% CI	3.17	3.54	0.851	1.53	1.86	0.963	1.57	1.97	0.937

[1101]

的下限									
95% CI 的上限	60.4	67.3	3.90	8.16	10.5	4.46	8.02	10.6	4.41

[1102] 表19.6:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后24小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1103] sCr或UO

[1104]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	67.7	118	88.6	113	91.4	118
平均值	83.0	128	100	126	101	130
标准偏差	42.9	70.2	54.3	73.9	51.8	78.0
p(t-检验)		4.6E-5		0.017		0.0068
最小值	23.6	13.2	16.4	13.2	16.4	13.2
最大值	174	401	251	401	251	401
n(患者)	50	100	75	75	85	65

[1105] 仅sCr

[1106]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	77.0	117	88.6	118	92.8	120
平均值	87.3	127	99.0	127	101	129
标准偏差	44.7	71.1	51.5	74.9	52.8	77.7
p(t-检验)		3.4E-4		0.0095		0.0095
最小值	23.6	13.2	16.4	13.2	16.4	13.2
最大值	182	401	246	401	253	401
n(患者)	52	98	73	77	86	64

[1107] 仅UO

[1108]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	90.0	136	95.2	136	96.1	132
平均值	106	137	107	139	108	142
标准偏差	61.7	73.4	60.7	80.5	59.9	87.1
p（t-检验）		0.014		0.019		0.020
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	284	401	284	401	284	401
n（患者）	112	37	120	29	125	24

[1109]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.67	0.64	0.60	0.60	0.63	0.60	0.60	0.62
SE	0.043	0.044	0.055	0.046	0.046	0.060	0.047	0.047	0.066
p 值	1.5E-6	1.2E-4	0.0098	0.029	0.024	0.035	0.030	0.039	0.075
n 非持续组	50	52	112	75	73	120	85	86	125
n 持续组	100	98	37	75	77	29	65	64	24
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	85%	84%	86%	81%	81%	86%	80%	80%	83%
特异性	46%	42%	29%	32%	32%	28%	29%	29%	26%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	59%	58%	68%	55%	56%	62%	57%	58%	62%
特异性	68%	65%	55%	55%	56%	52%	55%	56%	52%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	32%	31%	38%	31%	31%	41%	34%	33%	42%
特异性	88%	85%	79%	80%	81%	78%	81%	80%	78%
OR 四分	4.83	3.76	2.56	2.05	1.90	2.37	1.67	1.61	1.79

[1110]

位 2									
p 值	7.9E-5	7.3E-4	0.073	0.063	0.093	0.13	0.19	0.22	0.32
95% CI 的下限	2.21	1.74	0.916	0.962	0.898	0.767	0.775	0.747	0.571
95% CI 的上限	10.5	8.10	7.16	4.37	4.02	7.33	3.59	3.46	5.63
OR 四分位 3	3.06	2.63	2.58	1.45	1.62	1.81	1.63	1.73	1.81
p 值	0.0022	0.0067	0.017	0.25	0.14	0.16	0.14	0.100	0.20
95% CI 的下限	1.50	1.31	1.18	0.765	0.850	0.788	0.852	0.900	0.736
95% CI 的上限	6.25	5.28	5.65	2.77	3.09	4.15	3.13	3.33	4.43
OR 四分位 4	3.45	2.43	2.23	1.77	1.91	2.55	2.21	1.98	2.47
p 值	0.011	0.045	0.050	0.14	0.094	0.032	0.038	0.072	0.052
95% CI 的下限	1.33	1.02	1.000	0.837	0.896	1.08	1.04	0.942	0.992
95% CI 的上限	8.93	5.78	4.98	3.74	4.07	6.01	4.66	4.17	6.17

[1111] 表19.7:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1112] sCr或UO

[1113]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	67.1	119	86.1	115	88.6	118
平均值	81.4	129	97.7	127	98.3	130
标准偏差	41.9	69.9	52.5	73.3	50.3	76.7
p(t-检验)		2.3E-5		0.0062		0.0031
最小值	23.6	13.2	16.4	13.2	16.4	13.2
最大值	174	401	246	401	246	401

[1114]

n(患者)	49	101	70	80	79	71

[1115] 仅sCr

[1116]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	73.7	118	87.8	115	94.3	113
平均值	85.8	127	98.5	126	101	127
标准偏差	43.9	70.8	52.1	73.8	52.8	76.0
p（t-检验）		1.9E-4		0.0097		0.017
最小值	23.6	13.2	16.4	13.2	16.4	13.2
最大值	182	401	246	401	253	401
n（患者）	51	99	70	80	79	71

[1117] 仅UO

[1118]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	91.4	125	96.1	117	97.5	113
平均值	105	134	106	136	107	137
标准偏差	59.4	75.2	58.4	81.0	57.7	85.9
p（t-检验）		0.011		0.016		0.020
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	274	401	274	401	274	401
n（患者）	103	46	111	38	116	33

[1119]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.72	0.68	0.63	0.62	0.61	0.61	0.62	0.59	0.59
SE	0.042	0.044	0.051	0.046	0.046	0.055	0.046	0.047	0.058
p 值	2.7E-7	3.6E-5	0.014	0.0095	0.019	0.050	0.012	0.052	0.10

[1120]

n 非持续组	49	51	103	70	70	111	79	79	116
n 持续组	101	99	46	80	80	38	71	71	33
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	85%	84%	87%	82%	81%	87%	82%	80%	85%
特异性	47%	43%	30%	34%	33%	29%	32%	30%	28%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	59%	59%	63%	55%	55%	58%	56%	55%	58%
特异性	69%	67%	55%	56%	56%	52%	56%	54%	52%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	33%	31%	35%	31%	31%	37%	34%	32%	36%
特异性	90%	86%	79%	81%	81%	78%	82%	81%	78%
OR 四分位 2	5.07	3.94	2.87	2.46	2.12	2.67	2.07	1.78	2.13
p 值	5.0E-5	4.9E-4	0.031	0.020	0.050	0.060	0.063	0.14	0.15
95% CI 的下限	2.31	1.82	1.10	1.15	1.00	0.958	0.960	0.834	0.758
95% CI 的上限	11.1	8.50	7.47	5.25	4.49	7.46	4.44	3.78	6.01
OR 四分位 3	3.32	2.83	2.11	1.54	1.54	1.50	1.62	1.46	1.45
p 值	0.0012	0.0039	0.040	0.19	0.19	0.28	0.14	0.25	0.35
95% CI 的下限	1.61	1.40	1.04	0.806	0.806	0.715	0.850	0.765	0.666
95% CI 的上限	6.85	5.73	4.32	2.93	2.93	3.17	3.09	2.77	3.17
OR 四分位 4	4.27	2.87	1.96	1.99	1.99	2.11	2.37	2.04	1.98
p 值	0.0050	0.022	0.085	0.078	0.078	0.066	0.026	0.062	0.11
95% CI 的下限	1.55	1.16	0.911	0.927	0.927	0.951	1.11	0.965	0.860
95% CI 的上限	11.8	7.07	4.23	4.29	4.29	4.70	5.06	4.33	4.55

[1121] 表19.8:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1122] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	67.1	119	85.2	113	88.6	113
平均值	81.4	129	97.7	127	98.2	128
标准偏差	41.9	69.9	52.9	72.9	51.4	75.0
p（t-检验）		2.3E-5		0.0071		0.0046
最小值	23.6	13.2	16.4	13.2	16.4	13.2
最大值	174	401	246	401	246	401
n（患者）	49	101	69	81	75	75

[1123]

[1124] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	73.7	118	87.0	113	91.4	113
平均值	85.8	127	98.5	126	98.9	128
标准偏差	43.9	70.8	52.4	73.4	51.0	75.6
p（t-检验）		1.9E-4		0.011		0.0073
最小值	23.6	13.2	16.4	13.2	16.4	13.2
最大值	182	401	246	401	246	401
n（患者）	51	99	69	81	75	75

[1125]

[1126] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	92.8	122	98.9	112	99.7	111
平均值	103	134	106	133	107	134
标准偏差	58.8	74.4	57.8	79.7	57.1	83.9
p（t-检验）		0.0073		0.022		0.028
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	274	401	274	401	274	401
n（患者）	98	51	105	44	110	39

[1127]

[1128]

[1129]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.72	0.68	0.63	0.62	0.61	0.60	0.62	0.60	0.58
SE	0.042	0.044	0.049	0.046	0.046	0.052	0.046	0.046	0.054
p 值	2.7E-7	3.6E-5	0.0086	0.0099	0.020	0.065	0.012	0.023	0.13
n 非持续组	49	51	98	69	69	105	75	75	110
n 持续组	101	99	51	81	81	44	75	75	39
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	85%	84%	88%	83%	81%	86%	83%	81%	85%
特异性	47%	43%	32%	35%	33%	30%	33%	32%	28%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	59%	59%	61%	54%	54%	55%	55%	55%	54%
特异性	69%	67%	55%	55%	55%	51%	55%	55%	51%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	33%	31%	33%	31%	31%	34%	32%	32%	33%
特异性	90%	86%	79%	81%	81%	78%	81%	81%	77%
OR 四分位 2	5.07	3.94	3.47	2.55	2.20	2.65	2.38	2.05	2.16
p 值	5.0E-5	4.9E-4	0.010	0.016	0.040	0.046	0.026	0.063	0.12
95% CI 的下限	2.31	1.82	1.34	1.19	1.04	1.02	1.11	0.962	0.823
95% CI 的上限	11.1	8.50	8.99	5.46	4.66	6.91	5.13	4.37	5.66
OR 四分位 3	3.32	2.83	1.90	1.46	1.46	1.27	1.45	1.45	1.21
p 值	0.0012	0.0039	0.067	0.25	0.25	0.51	0.25	0.25	0.61

[1130]

	95% CI 的下限	1.61	1.40	0.955	0.765	0.765	0.627	0.765	0.765	0.582
	95% CI 的上限	6.85	5.73	3.79	2.78	2.78	2.57	2.77	2.77	2.52
	OR 四分位 4	4.27	2.87	1.83	1.92	1.92	1.84	2.05	2.05	1.70
	p 值	0.0050	0.022	0.12	0.094	0.094	0.12	0.063	0.063	0.19
	95% CI 的下限	1.55	1.16	0.861	0.894	0.894	0.849	0.962	0.962	0.763
	95% CI 的上限	11.8	7.07	3.91	4.14	4.14	4.01	4.37	4.37	3.79

[1131] 表19.9:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1132] sCr或UO

[1133]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	67.1	119	84.6	115	87.8	115
平均值	81.4	129	95.8	128	96.4	130
标准偏差	41.9	69.9	50.8	73.3	49.4	75.4
p(t-检验)		2.3E-5		0.0028		0.0018
最小值	23.6	13.2	16.4	13.2	16.4	13.2
最大值	174	401	246	401	246	401
n(患者)	49	101	68	82	74	76

[1134] 仅sCr

[1135]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	73.7	118	86.1	115	90.0	115

[1136]

平均值	85.8	127	96.6	127	97.2	129
标准偏差	43.9	70.8	50.4	73.9	49.0	76.0
p（t-检验）		1.9E-4		0.0045		0.0029
最小值	23.6	13.2	16.4	13.2	16.4	13.2
最大值	182	401	246	401	246	401
n（患者）	51	99	68	82	74	76

[1137] 仅UO

[1138]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	91.4	120	95.2	113	96.1	112
平均值	102	133	105	132	106	133
标准偏差	58.2	74.3	57.6	77.6	56.9	81.2
p（t-检验）		0.0056		0.015		0.020
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	274	401	274	401	274	401
n（患者）	95	54	100	49	105	44

[1139]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.72	0.68	0.63	0.63	0.62	0.60	0.63	0.62	0.59
SE	0.042	0.044	0.048	0.045	0.046	0.050	0.045	0.046	0.052
p 值	2.7E-7	3.6E-5	0.0069	0.0042	0.0091	0.039	0.0052	0.011	0.085
n 非持续组	49	51	95	68	68	100	74	74	105
n 持续组	101	99	54	82	82	49	76	76	44
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	85%	84%	87%	83%	82%	86%	83%	82%	84%
特异性	47%	43%	32%	35%	34%	30%	34%	32%	29%
截止四分位 3	101	101	101	101	101	101	101	101	101

[1140]

灵敏度	59%	59%	61%	55%	55%	57%	55%	55%	57%
特异性	69%	67%	56%	56%	56%	53%	55%	55%	52%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	33%	31%	33%	32%	32%	33%	33%	33%	32%
特异性	90%	86%	79%	82%	82%	78%	82%	82%	77%
OR 四分位 2	5.07	3.94	3.10	2.65	2.28	2.57	2.47	2.13	2.11
p 值	5.0E-5	4.9E-4	0.014	0.012	0.031	0.041	0.021	0.051	0.11
95% CI 的下限	2.31	1.82	1.25	1.24	1.08	1.04	1.15	0.997	0.849
95% CI 的上限	11.1	8.50	7.65	5.67	4.84	6.37	5.32	4.53	5.26
OR 四分位 3	3.32	2.83	1.98	1.54	1.54	1.50	1.53	1.53	1.45
p 值	0.0012	0.0039	0.049	0.19	0.19	0.25	0.19	0.19	0.31
95% CI 的下限	1.61	1.40	1.00	0.807	0.807	0.755	0.806	0.806	0.712
95% CI 的上限	6.85	5.73	3.92	2.94	2.94	2.99	2.92	2.92	2.94
OR 四分位 4	4.27	2.87	1.88	2.17	2.17	1.72	2.30	2.30	1.58
p 值	0.0050	0.022	0.10	0.051	0.051	0.16	0.033	0.033	0.25
95% CI 的下限	1.55	1.16	0.885	0.995	0.995	0.802	1.07	1.07	0.721
95% CI 的上限	11.8	7.07	3.97	4.72	4.72	3.68	4.95	4.95	3.44

[1141] 表19.10:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1142] sCr或UO

[1143]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组

	中值	67.1	118	84.0	118	86.1	118
	平均值	82.3	127	94.5	128	95.0	129
	标准偏差	42.4	69.9	50.0	72.9	48.9	74.4
[1144]	p（t-检验）		7.1E-5		0.0020		0.0013
	最小值	23.6	13.2	16.4	13.2	16.4	13.2
	最大值	174	401	246	401	246	401
	n（患者）	47	103	65	85	70	80

[1145] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	71.0	117	86.1	115	90.0	115
[1146] 平均值	86.0	127	95.6	127	96.3	129
标准偏差	44.4	70.6	50.0	73.4	48.7	75.4
p（t-检验）		2.6E-4		0.0033		0.0022
最小值	23.6	13.2	16.4	13.2	16.4	13.2
最大值	182	401	246	401	246	401
n（患者）	50	100	66	84	72	78

[1147] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	90.0	122	94.2	118	94.3	115
[1148] 平均值	101	135	102	134	104	134
标准偏差	55.1	76.3	55.1	78.2	54.7	80.7
p（t-检验）		0.0019		0.0046		0.0079
最小值	16.4	13.2	16.4	13.2	16.4	13.2
最大值	260	401	260	401	260	401
n（患者）	92	57	95	54	99	50

[1149]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.70	0.68	0.64	0.64	0.62	0.62	0.64	0.62	0.60
SE	0.043	0.044	0.048	0.045	0.045	0.049	0.045	0.045	0.050
p 值	2.2E-6	5.3E-5	0.0036	0.0024	0.0058	0.014	0.0025	0.0073	0.038
n 非持续组	47	50	92	65	66	95	70	72	99
n 持续组	103	100	57	85	84	54	80	78	50
截止四分位 2	63.3	63.3	66.7	63.3	63.3	66.7	63.3	63.3	66.7
灵敏度	84%	84%	86%	82%	82%	85%	82%	82%	84%
特异性	47%	44%	32%	35%	35%	31%	34%	33%	29%
截止四分位 3	101	101	101	101	101	101	101	101	101
灵敏度	58%	58%	61%	55%	55%	59%	56%	55%	58%
特异性	68%	66%	57%	57%	56%	55%	57%	56%	54%
截止四分位 4	142	142	142	142	142	142	142	142	142
灵敏度	32%	31%	35%	33%	32%	35%	34%	33%	34%
特异性	89%	86%	80%	85%	83%	80%	84%	83%	79%
OR 四分位 2	4.78	4.12	2.82	2.56	2.46	2.53	2.46	2.29	2.17
p 值	8.8E-5	3.3E-4	0.019	0.015	0.019	0.036	0.020	0.033	0.080
95% CI 的下限	2.19	1.90	1.18	1.20	1.16	1.06	1.15	1.07	0.910
95% CI 的上限	10.5	8.94	6.71	5.44	5.23	6.02	5.25	4.88	5.20
OR 四分位 3	2.98	2.68	2.07	1.63	1.54	1.76	1.71	1.54	1.59
p 值	0.0033	0.0063	0.035	0.14	0.19	0.10	0.10	0.19	0.18
95% CI 的下限	1.44	1.32	1.05	0.852	0.807	0.894	0.897	0.806	0.801
95% CI 的上限	6.16	5.44	4.06	3.13	2.95	3.46	3.28	2.93	3.16
OR 四分位 4	3.96	2.76	2.22	2.70	2.37	2.17	2.73	2.50	1.91
p 值	0.0079	0.028	0.037	0.016	0.033	0.043	0.013	0.021	0.093
95% CI 的	1.43	1.12	1.05	1.20	1.07	1.02	1.24	1.15	0.897

[1150]

下限								
95% CI 的上限	10.9	6.82	4.70	6.08	5.23	4.60	6.04	5.44	4.08

[1151] 实施例20.使用腱生蛋白评价进入ICU的患者的肾状态:在RIFLE F持续

[1152] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的腱生蛋白。

[1153] 通过基于血清肌酸酐、排尿量或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“持续”和“非持续”群体。“持续”表示在24、48或72小时的时间段内最小RIFLE阶段是衰竭(F)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。“非持续”表示衰竭(F)不持续并且在24、48或72小时的时间段内最小RIFLE阶段是无损伤(RIFLE 0)、具有损伤危险(R)或损伤(I)的那些患者,其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。如果患者在衰竭(F)后死亡或在从样品收集至样品收集后24、48、72、96或168小时的任何时间被置于肾替代疗法(RRT),则患者视为“持续”。

[1154] 使用接收器操作特征(ROC)分析确定区分“持续”和“非持续”组的能力。

[1155] 表20.1:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后24小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1156] sCr或UO

[1157]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47000	59300	47500	58200	48100	58800
平均值	51400	61900	52200	62100	52800	62200
标准偏差	24600	27900	24700	28500	25000	28700
p(t-检验)		0.018		0.031		0.051
最小值	17100	15600	17100	15600	17100	15600
最大值	140000	141000	140000	141000	140000	141000
n(患者)	95	55	103	47	110	40

[1158] 仅sCr

[1159]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	45800	59600	47500	59300	48100	58800
平均值	51200	62200	52200	61900	53100	60900
标准偏差	24700	27700	25000	28000	25400	28000
p（t-检验）		0.013		0.035		0.10
最小值	17100	15600	17100	15600	17100	15600
最大值	140000	141000	140000	141000	140000	141000
n（患者）	94	56	103	47	108	42

[1160] 仅UO

[1161]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	51300	62000	51300	62000	51700	61000
平均值	53600	65600	53600	65600	53800	65100
标准偏差	24700	34600	24700	34600	24600	35500
p（t-检验）		0.062		0.062		0.085
最小值	17100	15600	17100	15600	17100	15600
最大值	140000	141000	140000	141000	140000	141000

[1162]

n（患者）	130	19	130	19	131	18

[1163]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.62	0.62	0.60	0.61	0.61	0.60	0.60	0.59	0.59
SE	0.048	0.048	0.073	0.051	0.051	0.073	0.054	0.053	0.075
p 值	0.015	0.0093	0.17	0.038	0.033	0.17	0.063	0.10	0.24
n 非持续组	95	94	130	103	103	130	110	108	131
n 持续组	55	56	19	47	47	19	40	42	18
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	80%	80%	79%	81%	81%	79%	82%	81%	78%
特异性	28%	29%	25%	28%	28%	25%	28%	28%	25%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	60%	61%	63%	60%	62%	63%	60%	60%	61%
特异性	56%	56%	52%	54%	55%	52%	54%	54%	51%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	33%	34%	37%	34%	34%	37%	32%	31%	33%
特异性	79%	80%	76%	79%	79%	76%	77%	77%	76%
OR 四分位 2	1.59	1.65	1.28	1.65	1.65	1.28	1.85	1.63	1.18
p 值	0.26	0.22	0.68	0.24	0.24	0.68	0.19	0.27	0.78
95% CI 的下限	0.716	0.743	0.395	0.711	0.711	0.395	0.741	0.680	0.362
95% CI 的上限	3.52	3.66	4.12	3.85	3.85	4.12	4.62	3.93	3.83
OR 四分位 3	1.89	2.00	1.82	1.76	2.00	1.82	1.74	1.71	1.65
p 值	0.064	0.044	0.24	0.11	0.055	0.24	0.14	0.15	0.33
95% CI 的下限	0.964	1.02	0.675	0.872	0.987	0.675	0.832	0.828	0.601
95% CI 的上限	3.72	3.92	4.92	3.54	4.04	4.92	3.62	3.52	4.51
OR 四分位 4	1.82	2.03	1.86	1.90	1.90	1.86	1.64	1.49	1.55

[1164]

p值	0.12	0.064	0.23	0.10	0.10	0.23	0.23	0.33	0.42
95% CI的下限	0.863	0.959	0.675	0.884	0.884	0.675	0.737	0.674	0.537
95% CI的上限	3.86	4.28	5.14	4.09	4.09	5.14	3.64	3.29	4.46

[1165] 表20.2:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1166] sCr或UO

[1167]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	45800	58800	47200	58800	47500	59300
平均值	49800	63100	50400	63500	51200	63700
标准偏差	22700	29100	22900	29500	23400	29900
p(t-检验)		0.0021		0.0027		0.0058
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n(患者)	88	62	94	56	101	49

[1168] 仅sCr

[1169]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	45800	58800	47500	58200	47900	58200
平均值	50500	62000	51100	62000	52200	61300
标准偏差	24500	27400	24700	27600	25000	27800
p(t-检验)		0.0080		0.013		0.043
最小值	17100	15600	17100	15600	17100	15600
最大值	140000	141000	140000	141000	140000	141000

[1170]

n(患者)	88	62	93	57	99	51

[1171] 仅UO

[1172]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	50800	61000	50800	61000	51300	59900
平均值	52600	67100	52600	67100	52800	66800
标准偏差	23600	34500	23600	34500	23600	35200
p（t-检验）		0.010		0.010		0.014
最小值	17100	15600	17100	15600	17100	15600
最大值	129000	141000	129000	141000	129000	141000
n（患者）	123	26	123	26	124	25

[1173]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.63	0.63	0.62	0.63	0.62	0.62	0.62	0.60	0.61
SE	0.047	0.047	0.063	0.048	0.048	0.063	0.050	0.050	0.065
p 值	0.0040	0.0059	0.054	0.0056	0.011	0.054	0.013	0.042	0.082
n 非持续组	88	88	123	94	93	123	101	99	124
n 持续组	62	62	26	56	57	26	49	51	25
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	81%	81%	81%	80%	81%	81%	82%	80%	80%
特异性	30%	30%	26%	29%	29%	26%	29%	28%	26%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	60%	60%	62%	61%	60%	62%	59%	57%	60%
特异性	57%	57%	52%	56%	56%	52%	54%	54%	52%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	34%	34%	38%	36%	35%	38%	35%	33%	36%

[1174]

特异性	81%	81%	77%	81%	81%	77%	79%	79%	77%
OR四分位2	1.75	1.75	1.48	1.65	1.71	1.48	1.79	1.62	1.39
p值	0.16	0.16	0.47	0.22	0.19	0.47	0.18	0.25	0.54
95% CI的下限	0.802	0.802	0.514	0.743	0.772	0.514	0.771	0.714	0.482
95% CI的上限	3.81	3.81	4.24	3.66	3.79	4.24	4.15	3.66	4.01
OR四分位3	1.95	1.95	1.74	2.00	1.87	1.74	1.73	1.52	1.60
p值	0.048	0.048	0.21	0.044	0.066	0.21	0.12	0.23	0.29
95% CI的下限	1.01	1.01	0.730	1.02	0.960	0.730	0.868	0.769	0.667
95% CI的上限	3.77	3.77	4.12	3.92	3.66	4.12	3.46	3.00	3.84
OR四分位4	2.14	2.14	2.12	2.35	2.25	2.12	2.02	1.86	1.84
p值	0.046	0.046	0.100	0.026	0.034	0.100	0.069	0.11	0.19
95% CI的下限	1.01	1.01	0.866	1.11	1.07	0.866	0.947	0.872	0.737
95% CI的上限	4.51	4.51	5.19	4.97	4.76	5.19	4.33	3.95	4.61

[1175] 表20.3:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1176] sCr或UO

[1177]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	43800	59900	44100	60600	45800	61000
平均值	48000	64300	48000	65100	48900	66000
标准偏差	21700	28700	21500	28900	21800	29700
p(t-检验)		1.1E-4		5.3E-5		8.3E-5
最小值	17100	15600	17100	15600	17100	15600

[1178]

最大值	123000	141000	123000	141000	123000	141000
n(患者)	83	67	86	64	94	56

[1179] 仅sCr

[1180]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	43700	60600	44100	60600	47000	59900
平均值	47600	64500	48200	64800	49300	64900
标准偏差	21600	28500	22000	28700	22200	29600
p（t-检验）		6.7E-5		9.8E-5		3.3E-4
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	82	68	86	64	93	57

[1181] 仅UO

[1182]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47500	64800	47500	64800	47600	64300
平均值	50300	71300	50300	71300	50600	71200
标准偏差	22200	32500	22200	32500	22200	33000
p（t-检验）		2.9E-5		2.9E-5		4.7E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	129000	141000	129000	141000	129000	141000
n（患者）	115	34	115	34	116	33

[1183]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.67	0.68	0.70	0.68	0.68	0.70	0.67	0.66	0.69

[1184]

SE	0.045	0.044	0.055	0.045	0.045	0.055	0.047	0.047	0.056
p 值	1.3E-4	5.3E-5	3.5E-4	6.4E-5	8.9E-5	3.5E-4	2.2E-4	7.5E-4	7.0E-4
n 非持续组	83	82	115	86	86	115	94	93	116
n 持续组	67	68	34	64	64	34	56	57	33
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	82%	82%	85%	83%	83%	85%	84%	82%	85%
特异性	31%	32%	28%	31%	31%	28%	31%	30%	28%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	63%	63%	71%	64%	64%	71%	62%	61%	70%
特异性	60%	61%	56%	60%	60%	56%	57%	57%	55%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	37%	38%	47%	39%	39%	47%	39%	39%	45%
特异性	84%	85%	81%	85%	85%	81%	83%	83%	80%
OR 四分位 2	2.09	2.17	2.24	2.20	2.20	2.24	2.33	2.02	2.13
p 值	0.063	0.051	0.13	0.051	0.051	0.13	0.048	0.089	0.15
95% CI 的下限	0.960	0.995	0.796	0.998	0.998	0.796	1.01	0.897	0.758
95% CI 的上限	4.55	4.72	6.28	4.87	4.87	6.28	5.38	4.57	6.01
OR 四分位 3	2.55	2.69	3.01	2.73	2.73	3.01	2.25	2.11	2.83
p 值	0.0057	0.0035	0.0088	0.0033	0.0033	0.0088	0.019	0.030	0.014
95% CI 的下限	1.31	1.38	1.32	1.40	1.40	1.32	1.14	1.08	1.24
95% CI 的上限	4.94	5.22	6.87	5.32	5.32	6.87	4.43	4.13	6.48
OR 四分位 4	3.21	3.61	3.76	3.60	3.60	3.76	3.15	3.02	3.37
p 值	0.0031	0.0013	0.0015	0.0012	0.0012	0.0015	0.0030	0.0042	0.0038
95% CI 的下限	1.48	1.65	1.66	1.66	1.66	1.66	1.48	1.42	1.48
95% CI 的上限	6.93	7.91	8.52	7.81	7.81	8.52	6.74	6.45	7.68

[1185] 表20.4:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1186] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	43800	59900	44300	59900	47000	59900
平均值	48000	63800	48200	64500	48800	65200
标准偏差	21800	28600	21500	29100	21300	30000
p（t-检验）		1.9E-4		1.2E-4		1.4E-4
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	81	69	85	65	91	59

[1187]

[1188] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	43800	59900	44100	60600	45800	61000
平均值	47900	63900	47900	64700	48500	65400
标准偏差	21600	28600	21500	28900	21200	29800
p（t-检验）		1.5E-4		7.2E-5		8.4E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	81	69	84	66	90	60

[1189]

[1190] 仅UO

持续期持续时间(h)	24		48		72	
	非持续	持续组	非持续	持续组	非持续	持续组

[1191]

[1192]

	组		组		组	
中值	47500	64800	47500	64300	47500	63200
平均值	49600	70200	49700	70400	50000	70200
标准偏差	21100	32800	21000	33200	21100	33600
p（t-检验）		1.3E-5		1.6E-5		2.6E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	109	40	110	39	111	38

[1193]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.67	0.67	0.69	0.67	0.68	0.68	0.66	0.67	0.68
SE	0.045	0.045	0.052	0.045	0.045	0.052	0.046	0.046	0.053
p 值	2.0E-4	1.6E-4	2.6E-4	1.9E-4	8.3E-5	4.4E-4	5.3E-4	2.5E-4	8.6E-4
n 非持续组	81	81	109	85	84	110	91	90	111
n 持续组	69	69	40	65	66	39	59	60	38
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	81%	81%	82%	82%	82%	82%	81%	82%	82%
特异性	31%	31%	28%	31%	31%	27%	30%	30%	27%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	62%	62%	70%	63%	64%	69%	61%	62%	68%
特异性	60%	60%	57%	60%	61%	56%	57%	58%	56%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	36%	38%	45%	38%	39%	46%	39%	40%	45%
特异性	84%	85%	82%	85%	86%	82%	84%	84%	81%
OR 四分位 2	1.92	1.92	1.79	1.95	2.02	1.71	1.84	1.91	1.64
p 值	0.094	0.094	0.21	0.093	0.077	0.25	0.13	0.11	0.29
95% CI 的下限	0.894	0.894	0.715	0.894	0.927	0.684	0.832	0.863	0.653
95% CI	4.14	4.14	4.48	4.24	4.39	4.30	4.08	4.22	4.12

[1194]

的上限									
OR 四分位 3	2.53	2.53	3.08	2.56	2.70	2.91	2.09	2.20	2.74
p 值	0.0058	0.0058	0.0045	0.0055	0.0034	0.0072	0.031	0.021	0.011
95% CI 的下限	1.31	1.31	1.42	1.32	1.39	1.34	1.07	1.13	1.26
95% CI 的上限	4.90	4.90	6.68	4.98	5.26	6.32	4.07	4.29	5.98
OR 四分位 4	2.97	3.48	3.64	3.46	3.90	3.86	3.24	3.62	3.47
p 值	0.0056	0.0018	0.0013	0.0017	6.9E-4	8.7E-4	0.0025	0.0010	0.0022
95% CI 的下限	1.38	1.59	1.65	1.60	1.78	1.74	1.51	1.68	1.56
95% CI 的上限	6.42	7.61	8.02	7.50	8.56	8.54	6.93	7.81	7.69

[1195] 表20.5:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1196] sCr或UO

[1197]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	43200	60600	43500	61300	44500	62800
平均值	46900	64300	46900	65100	47700	66000
标准偏差	21100	28400	20900	28600	20600	29700
p(t-检验)		3.3E-5		1.5E-5		1.8E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n(患者)	78	72	81	69	88	62

[1198] 仅sCr

[1199]

持续期持	24	48	72

续时间(h)						
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	43500	59900	43700	60600	44500	61000
平均值	47100	64300	47200	65100	47900	65800
标准偏差	21000	28600	20900	28800	20700	29700
p（t-检验）		4.4E-5		2.0E-5		2.5E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	79	71	82	68	88	62

[1200]

[1201] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47400	65200	47400	65200	47500	64800
平均值	49400	70300	49400	70300	49600	70200
标准偏差	21000	32400	21000	32400	21100	32800
p（t-检验）		7.6E-6		7.6E-6		1.3E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	108	41	108	41	109	40

[1202]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.69	0.68	0.70	0.69	0.69	0.70	0.68	0.68	0.69
SE	0.043	0.044	0.051	0.044	0.044	0.051	0.045	0.045	0.052
p 值	1.9E-5	3.8E-5	1.2E-4	9.2E-6	1.9E-5	1.2E-4	4.0E-5	7.0E-5	2.5E-4
n 非持续组	78	79	108	81	82	108	88	88	109
n 持续组	72	71	41	69	68	41	62	62	40
截止四分	34800	34800	34700	34800	34800	34700	34800	34800	34700

[1203]

[1204]

位 2									
灵敏度	82%	82%	83%	83%	82%	83%	82%	82%	82%
特异性	32%	32%	28%	32%	32%	28%	31%	31%	28%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	64%	63%	71%	65%	65%	71%	63%	63%	70%
特异性	63%	62%	57%	63%	62%	57%	59%	59%	57%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	38%	38%	46%	39%	40%	46%	40%	40%	45%
特异性	86%	86%	82%	86%	87%	82%	85%	85%	82%
OR 四分位 2	2.14	2.07	1.87	2.25	2.17	1.87	2.05	2.05	1.79
p 值	0.051	0.063	0.18	0.042	0.051	0.18	0.076	0.076	0.21
95% CI 的下限	0.995	0.960	0.747	1.03	0.995	0.747	0.928	0.928	0.715
95% CI 的上限	4.61	4.44	4.67	4.89	4.72	4.67	4.54	4.54	4.48
OR 四分位 3	2.99	2.83	3.26	3.19	3.02	3.26	2.45	2.45	3.08
p 值	0.0012	0.0021	0.0028	7.0E-4	0.0012	0.0028	0.0086	0.0086	0.0045
95% CI 的下限	1.54	1.46	1.50	1.63	1.55	1.50	1.26	1.26	1.42
95% CI 的上限	5.81	5.49	7.06	6.23	5.88	7.06	4.78	4.78	6.68
OR 四分位 4	3.65	3.79	4.05	4.09	4.25	4.05	3.90	3.90	3.64
p 值	0.0014	0.0010	5.1E-4	5.5E-4	3.9E-4	5.1E-4	6.0E-4	6.0E-4	0.0013
95% CI 的下限	1.65	1.71	1.84	1.84	1.91	1.84	1.79	1.79	1.65
95% CI 的上限	8.10	8.42	8.90	9.09	9.46	8.90	8.48	8.48	8.02

[1205] 实施例21.使用腱生蛋白评价进入ICU的患者的肾状态:在RIFLE I或F持续

[1206] 在以下研究中招募RIFLE阶段为损伤(I)或衰竭(F)的重症监护(ICU)患者。在招募时收集每个患者的EDTA抗凝结血样(10mL)和尿样(50mL),此后在受试者住院期间,每12小时收集直到第3天,然后每24小时收集直到第7天。使用商购获得的测定试剂通过标准免疫测定来测定招募样品中的腱生蛋白。

[1207] 通过基于血清肌酸酐、排尿量或血清肌酸酐和排尿量二者的RIFLE标准评估肾状态。两个组定义为表示“持续”和“非持续”群体。“持续”表示在24、48或72小时的时间段内最小RIFLE阶段是损伤(I)或衰竭(F)的那些患者,其中持续期可从样品收集时开始直到样品

收集后24、48、72、96或168小时。“非持续”表示损伤(I)或衰竭(F)不持续并且在24、48或72小时的时间段内最小RIFLE阶段是无损伤(RIFLE 0)或具有损伤危险(R)的那些患者，其中持续期可从样品收集时开始直到样品收集后24、48、72、96或168小时。如果患者在损伤(I)或衰竭(F)后死亡或在从样品收集至样品收集后24、48、72、96或168小时的任何时间被置于肾替代疗法(RRT)，则患者视为“持续”。

[1208] 使用接收器操作特征(ROC)分析确定区分“持续”和“非持续”组的能力。

[1209] 表21.1：“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较，其中持续在样品收集后24小时内开始，并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1210] sCr或UO

[1211]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37500	57200	43800	58200	47000	58200
平均值	44000	60900	49500	61000	50100	62000
标准偏差	21400	26800	25000	26400	23900	27800
p（t-检验）		1.6E-4		0.0070		0.0058
最小值	18800	15600	17100	15600	17100	15600
最大值	123000	141000	140000	141000	140000	141000

[1212]

n（患者）	50	100	75	75	85	65

[1213] 仅sCr

[1214]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37500	57200	43500	59300	45800	58800
平均值	44300	61100	47300	62800	49700	62800
标准偏差	21500	26800	22200	27700	22800	28800
p（t-检验）		1.5E-4		2.3E-4		0.0024
最小值	18800	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	52	98	73	77	86	64

[1215] 仅UO

[1216]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47800	62000	48300	62000	48400	63200
平均值	52400	63400	52900	64300	52900	66700
标准偏差	24900	28800	24700	30900	24400	32800
p（t-检验）		0.027		0.036		0.018
最小值	17100	15600	17100	15600	17100	15600
最大值	140000	141000	140000	141000	140000	141000
n（患者）	112	37	120	29	125	24

[1217]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.70	0.70	0.62	0.64	0.67	0.61	0.63	0.63	0.63
SE	0.043	0.043	0.055	0.045	0.044	0.061	0.046	0.046	0.065
p 值	2.9E-6	3.8E-6	0.024	0.0021	8.0E-5	0.063	0.0049	0.0039	0.050

[1218]

n 非持续组	50	52	112	75	73	120	85	86	125
n 持续组	100	98	37	75	77	29	65	64	24
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	81%	82%	81%	81%	82%	79%	80%	81%	79%
特异性	38%	38%	27%	32%	33%	26%	29%	30%	26%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	59%	59%	68%	60%	62%	66%	60%	61%	67%
特异性	68%	67%	55%	60%	63%	53%	58%	58%	53%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	32%	33%	35%	32%	35%	34%	35%	36%	38%
特异性	88%	88%	78%	81%	85%	77%	82%	83%	77%
OR 四分位 2	2.61	2.78	1.57	2.05	2.20	1.34	1.67	1.88	1.31
p 值	0.013	0.0082	0.34	0.063	0.041	0.57	0.19	0.11	0.62
95% CI 的下限	1.22	1.30	0.623	0.962	1.03	0.498	0.775	0.862	0.451
95% CI 的上限	5.58	5.92	3.95	4.37	4.70	3.58	3.59	4.09	3.79
OR 四分位 3	3.06	2.99	2.58	2.25	2.82	2.17	2.04	2.17	2.24
p 值	0.0022	0.0024	0.017	0.015	0.0021	0.072	0.033	0.022	0.086
95% CI 的下限	1.50	1.47	1.18	1.17	1.45	0.932	1.06	1.12	0.893
95% CI 的上限	6.25	6.05	5.65	4.32	5.47	5.06	3.94	4.19	5.61
OR 四分位 4	3.45	3.72	1.88	2.05	3.04	1.73	2.56	2.66	1.99
p 值	0.011	0.0067	0.12	0.063	0.0060	0.22	0.015	0.011	0.15
95% CI 的下限	1.33	1.44	0.840	0.962	1.38	0.721	1.20	1.25	0.788
95% CI 的上限	8.93	9.61	4.23	4.37	6.73	4.15	5.44	5.65	5.01

[1219] 表21.2:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后48小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1220] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37400	58200	42700	59100	43800	59300
平均值	43600	60900	47100	62400	48000	63300
标准偏差	21400	26600	22700	27200	21900	28500
p（t-检验）		1.1E-4		2.9E-4		3.0E-4
最小值	18800	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	49	101	70	80	79	71

[1221]

[1222] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37400	58200	42700	59100	44300	58200
平均值	43900	61100	47000	62500	48700	62600
标准偏差	21500	26700	22500	27300	22700	28100
p（t-检验）		9.9E-5		2.3E-4		0.0011
最小值	18800	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	51	99	70	80	79	71

[1223]

[1224] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47500	64000	47700	64000	47800	64600
平均值	49900	66900	50600	68300	50700	70600
标准偏差	22100	31000	22100	32800	21900	34100
p（t-检验）		2.1E-4		2.9E-4		8.9E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	103	46	111	38	116	33

[1225]

[1226]

[1227]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.71	0.67	0.68	0.68	0.66	0.66	0.65	0.68
SE	0.043	0.042	0.050	0.043	0.043	0.054	0.045	0.045	0.056
p 值	8.2E-7	1.1E-6	6.5E-4	5.6E-5	4.4E-5	0.0025	2.5E-4	9.4E-4	0.0017
n 非持续组	49	51	103	70	70	111	79	79	116
n 持续组	101	99	46	80	80	38	71	71	33
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	81%	82%	83%	82%	82%	82%	82%	82%	82%
特异性	39%	39%	28%	34%	34%	27%	32%	32%	27%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	59%	60%	67%	62%	62%	66%	62%	61%	67%
特异性	69%	69%	57%	64%	64%	55%	61%	59%	54%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	32%	32%	39%	32%	34%	39%	35%	35%	42%
特异性	88%	88%	81%	83%	84%	79%	84%	84%	79%
OR 四分位 2	2.73	2.90	1.86	2.46	2.46	1.64	2.07	2.07	1.64
p 值	0.0096	0.0060	0.16	0.020	0.020	0.29	0.063	0.063	0.32
95% CI 的下限	1.28	1.36	0.776	1.15	1.15	0.653	0.960	0.960	0.619
95% CI	5.85	6.20	4.47	5.25	5.25	4.12	4.44	4.44	4.35

[1228]

的上限									
OR 四分位 3	3.32	3.23	2.77	3.00	3.00	2.35	2.52	2.26	2.38
p 值	0.0012	0.0013	0.0062	0.0012	0.0012	0.029	0.0059	0.015	0.036
95% CI 的下限	1.61	1.58	1.34	1.54	1.54	1.09	1.31	1.17	1.06
95% CI 的上限	6.85	6.59	5.75	5.84	5.84	5.05	4.87	4.34	5.35
OR 四分位 4	3.32	3.58	2.67	2.33	2.73	2.50	2.76	2.76	2.82
p 值	0.013	0.0085	0.012	0.033	0.013	0.024	0.0097	0.0097	0.013
95% CI 的下限	1.28	1.38	1.24	1.07	1.24	1.13	1.28	1.28	1.24
95% CI 的上限	8.61	9.26	5.75	5.07	6.04	5.53	5.95	5.95	6.44

[1229] 表21.3:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后72小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1230] sCr或UO

[1231]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37400	58200	42700	59300	43500	59300
平均值	43600	60900	46600	62600	47200	63300
标准偏差	21400	26600	22500	27100	22000	27900
p(t-检验)		1.1E-4		1.5E-4		1.4E-4
最小值	18800	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n(患者)	49	101	69	81	75	75

[1232] 仅sCr

[1233]

持续期持续	24	48	72

[1234]

时间(h)						
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37400	58200	42700	59300	43500	59300
平均值	43900	61100	46500	62700	47100	63400
标准偏差	21500	26700	22300	27200	21800	27900
p（t-检验）		9.9E-5		1.2E-4		1.0E-4
最小值	18800	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	51	99	69	81	75	75

[1235] 仅UO

[1236]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47200	64300	47500	64000	47500	64600
平均值	48600	67800	49400	68800	49600	70800
标准偏差	21200	30500	21400	31700	21200	32700
p（t-检验）		1.4E-5		2.7E-5		7.9E-6
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	98	51	105	44	110	39

[1237]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.71	0.69	0.68	0.69	0.68	0.68	0.68	0.70
SE	0.043	0.042	0.047	0.043	0.043	0.050	0.044	0.044	0.052
p 值	8.2E-7	1.1E-6	3.9E-5	1.8E-5	1.3E-5	2.4E-4	4.8E-5	3.7E-5	1.5E-4
n 非持续组	49	51	98	69	69	105	75	75	110
n 持续组	101	99	51	81	81	44	75	75	39
截止四分	34800	34800	34700	34800	34800	34700	34800	34800	34700

[1238]

位 2									
灵敏度	81%	82%	84%	83%	83%	84%	83%	83%	85%
特异性	39%	39%	30%	35%	35%	29%	33%	33%	28%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	59%	60%	69%	63%	63%	68%	63%	63%	69%
特异性	69%	69%	59%	65%	65%	57%	63%	63%	56%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	32%	32%	41%	33%	35%	41%	36%	37%	44%
特异性	88%	88%	83%	84%	86%	81%	85%	87%	81%
OR 四分位 2	2.73	2.90	2.26	2.55	2.55	2.11	2.38	2.38	2.16
p 值	0.0096	0.0060	0.067	0.016	0.016	0.11	0.026	0.026	0.12
95% CI 的下限	1.28	1.36	0.946	1.19	1.19	0.849	1.11	1.11	0.823
95% CI 的上限	5.85	6.20	5.39	5.46	5.46	5.26	5.13	5.13	5.66
OR 四分位 3	3.32	3.23	3.17	3.19	3.19	2.86	2.82	2.82	2.91
p 值	0.0012	0.0013	0.0016	7.0E-4	7.0E-4	0.0056	0.0022	0.0022	0.0072
95% CI 的下限	1.61	1.58	1.55	1.63	1.63	1.36	1.45	1.45	1.34
95% CI 的上限	6.85	6.59	6.49	6.23	6.23	6.01	5.46	5.46	6.32
OR 四分位 4	3.32	3.58	3.34	2.64	3.12	2.94	3.27	3.87	3.27
p 值	0.013	0.0085	0.0020	0.017	0.0061	0.0063	0.0035	0.0011	0.0033
95% CI 的下限	1.28	1.38	1.55	1.19	1.38	1.36	1.48	1.72	1.48
95% CI 的上限	8.61	9.26	7.16	5.83	7.02	6.38	7.25	8.74	7.23

[1239] 表21.4:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后96小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1240] sCr或UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37400	58200	42700	59100	43700	59100
平均值	43600	60900	46900	62200	47500	62800
标准偏差	21400	26600	22500	27300	22000	28000
p（t-检验）		1.1E-4		3.1E-4		2.8E-4
最小值	18800	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	49	101	68	82	74	76

[1241]

[1242] 仅sCr

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37400	58200	42700	59100	43700	59100
平均值	43900	61100	46800	62300	47400	63000
标准偏差	21500	26700	22400	27300	21800	28000
p（t-检验）		9.9E-5		2.4E-4		2.2E-4
最小值	18800	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	51	99	68	82	74	76

[1243]

[1244] 仅UO

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47500	62800	47500	62000	47500	63200
平均值	49200	65600	49700	66200	49800	67800
标准偏差	21200	31000	21400	31600	21200	32600
p（t-检验）		1.9E-4		2.5E-4		1.1E-4
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000

[1245]

n（患者）	95	54	100	49	105	44

[1246]

[1247]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.71	0.71	0.66	0.67	0.68	0.65	0.67	0.67	0.66
SE	0.043	0.042	0.048	0.043	0.043	0.049	0.044	0.044	0.051
p 值	8.2E-7	1.1E-6	8.0E-4	5.6E-5	4.4E-5	0.0019	1.4E-4	1.1E-4	0.0015
n 非持续组	49	51	95	68	68	100	74	74	105
n 持续组	101	99	54	82	82	49	76	76	44
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	81%	82%	80%	82%	82%	80%	82%	82%	80%
特异性	39%	39%	27%	34%	34%	27%	32%	32%	27%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	59%	60%	65%	62%	62%	65%	62%	62%	66%
特异性	69%	69%	58%	65%	65%	57%	62%	62%	56%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500
灵敏度	32%	32%	39%	33%	34%	39%	36%	37%	41%
特异性	88%	88%	82%	84%	85%	81%	85%	86%	81%
OR 四分位 2	2.73	2.90	1.47	2.28	2.28	1.44	2.13	2.13	1.41
p 值	0.0096	0.0060	0.34	0.031	0.031	0.38	0.051	0.051	0.42
95% CI 的下限	1.28	1.36	0.661	1.08	1.08	0.633	0.997	0.997	0.604
95% CI 的上限	5.85	6.20	3.28	4.84	4.84	3.29	4.53	4.53	3.31
OR 四分位 3	3.32	3.23	2.53	3.02	3.02	2.50	2.66	2.66	2.48
p 值	0.0012	0.0013	0.0084	0.0012	0.0012	0.011	0.0036	0.0036	0.015
95% CI 的下限	1.61	1.58	1.27	1.55	1.55	1.23	1.38	1.38	1.19
95% CI 的上限	6.85	6.59	5.06	5.88	5.88	5.07	5.15	5.15	5.16

[1248]

OR 四分位 4	3.32	3.58	2.92	2.54	3.01	2.70	3.16	3.73	2.94
p 值	0.013	0.0085	0.0056	0.021	0.0078	0.011	0.0046	0.0015	0.0063
95% CI 的下限	1.28	1.38	1.37	1.15	1.34	1.26	1.43	1.66	1.36
95% CI 的上限	8.61	9.26	6.23	5.62	6.77	5.78	6.98	8.42	6.38

[1249] 表21.5:“持续”和“非持续”组的EDTA样品中标志物水平和ROC曲线下面积(AUC)的比较,其中持续在样品收集后168小时内开始,并且肾状态通过仅血清肌酸酐(sCr)、仅排尿量(UO)或者血清肌酸酐或排尿量RIFLE标准评估。

[1250] sCr或UO

[1251]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37100	58200	41000	59900	42700	60600
平均值	42700	61000	45100	63100	45600	63700
标准偏差	21300	26400	21200	27200	20800	27700
p(t-检验)		5.2E-5		2.1E-5		1.5E-5
最小值	18800	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n(患者)	47	103	65	85	70	80

[1252] 仅sCr

[1253]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	37300	57200	41800	59100	43200	59100
平均值	43700	61100	45900	62700	46600	63300
标准偏差	21700	26500	21700	27300	21200	28000
p(t-检验)		9.7E-5		7.1E-5		6.6E-5
最小值	18800	15600	17100	15600	17100	15600

[1254]

最大值	123000	141000	123000	141000	123000	141000
n(患者)	50	100	66	84	72	78

[1255] 仅UO

[1256]

持续期持续时间(h)	24		48		72	
	非持续组	持续组	非持续组	持续组	非持续组	持续组
中值	47200	63600	47000	64000	47400	64500
平均值	48300	66200	48400	67000	48700	67800
标准偏差	20600	30600	20800	30700	20600	31500
p（t-检验）		3.7E-5		1.9E-5		1.8E-5
最小值	17100	15600	17100	15600	17100	15600
最大值	123000	141000	123000	141000	123000	141000
n（患者）	92	57	95	54	99	50

[1257]

持续期持续时间(h)	24			48			72		
	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO	sCr 或 UO	仅 sCr	仅 UO
AUC	0.72	0.71	0.68	0.71	0.69	0.68	0.70	0.68	0.68
SE	0.042	0.042	0.046	0.042	0.043	0.047	0.042	0.043	0.048
p 值	8.5E-8	8.2E-7	1.3E-4	7.3E-7	7.7E-6	7.8E-5	1.3E-6	2.5E-5	1.5E-4
n 非持续组	47	50	92	65	66	95	70	72	99
n 持续组	103	100	57	85	84	54	80	78	50
截止四分位 2	34800	34800	34700	34800	34800	34700	34800	34800	34700
灵敏度	82%	82%	81%	82%	82%	81%	82%	82%	80%
特异性	40%	40%	28%	35%	35%	28%	34%	33%	27%
截止四分位 3	52000	52000	51800	52000	52000	51800	52000	52000	51800
灵敏度	60%	60%	65%	64%	63%	67%	64%	63%	66%
特异性	72%	70%	59%	68%	67%	59%	66%	64%	58%
截止四分位 4	70700	70700	70500	70700	70700	70500	70700	70700	70500

[1258]

灵敏度	32%	32%	40%	35%	35%	41%	38%	37%	42%
特异性	89%	88%	84%	88%	86%	83%	89%	88%	83%
OR 四分位 2	3.00	3.04	1.65	2.56	2.46	1.75	2.46	2.29	1.50
p 值	0.0050	0.0043	0.22	0.015	0.019	0.18	0.020	0.033	0.33
95% CI 的下限	1.39	1.42	0.741	1.20	1.16	0.770	1.15	1.07	0.659
95% CI 的上限	6.46	6.51	3.66	5.44	5.23	3.96	5.25	4.88	3.41
OR 四分位 3	3.95	3.50	2.63	3.65	3.42	2.87	3.37	2.99	2.63
p 值	3.3E-4	7.1E-4	0.0056	2.0E-4	3.7E-4	0.0031	3.9E-4	0.0012	0.0073
95% CI 的下限	1.87	1.69	1.33	1.85	1.74	1.43	1.72	1.54	1.30
95% CI 的上限	8.38	7.23	5.21	7.22	6.73	5.77	6.60	5.81	5.35
OR 四分位 4	3.96	3.45	3.47	3.89	3.34	3.39	4.65	4.14	3.49
p 值	0.0079	0.011	0.0014	0.0021	0.0046	0.0017	4.9E-4	8.6E-4	0.0014
95% CI 的下限	1.43	1.33	1.62	1.64	1.45	1.58	1.96	1.80	1.62
95% CI 的上限	10.9	8.93	7.47	9.22	7.69	7.29	11.0	9.56	7.52

[1259] 虽然以本领域的技术人员制造和使用本发明的充分详情对其进行了描述和示例，但是在不脱离本发明的精神和范围的情况下各种替代、修改和改进应为显而易见的。本文提供的实例代表优选的实施方案，它们是示例性的，并不旨在限制本发明的范围。其中修改和其他用途将被本领域的技术人员想到。这些修改涵盖在本发明的精神内并且通过权利要求的范围进行限定。

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