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(54) **NON-INVASIVE DEVICE FOR DETECTING LIVER DAMAGE**

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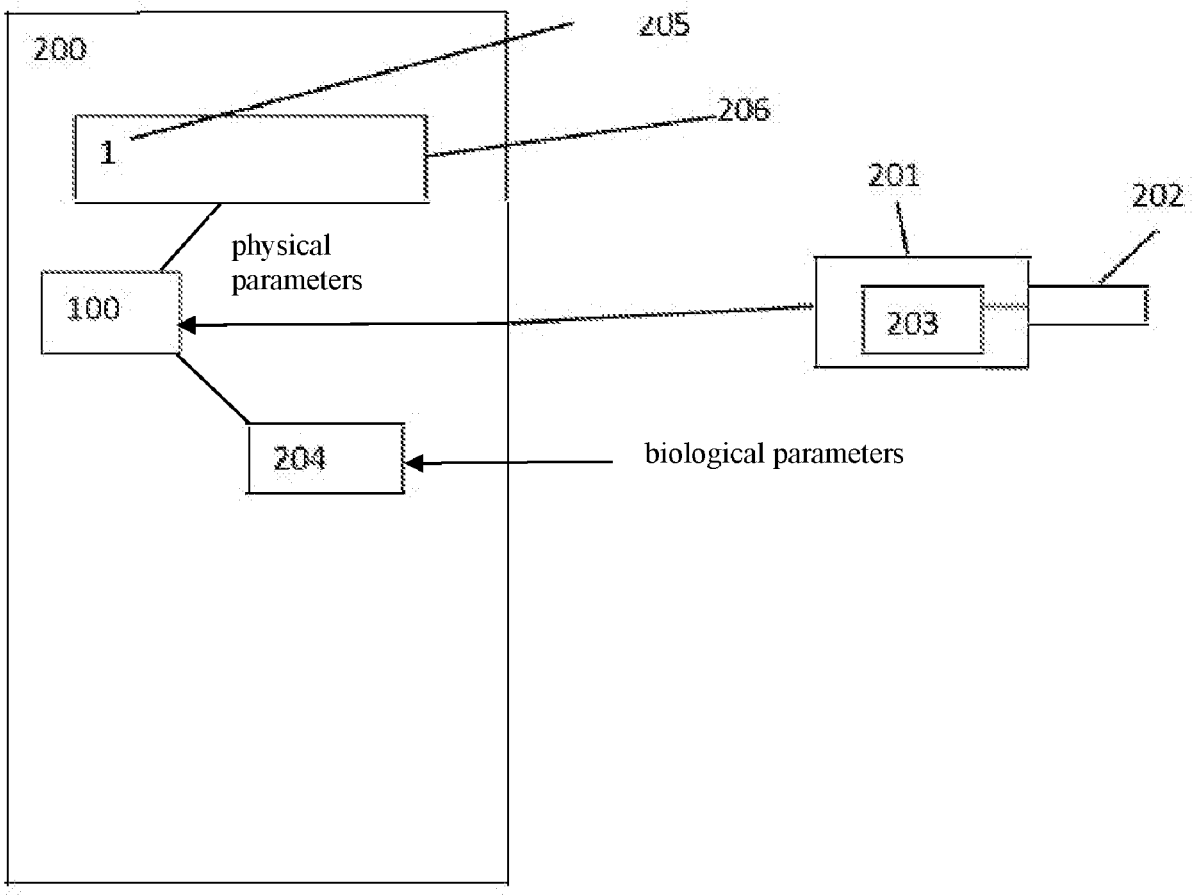
(57) **ABSTRACT**

A device calculates a score reflecting a state of liver damage, the calculating device being designed to calculate a score using the following physical parameters: a parameter corresponding to inflammation and/or fibrosis; and a parameter corresponding to steatosis.



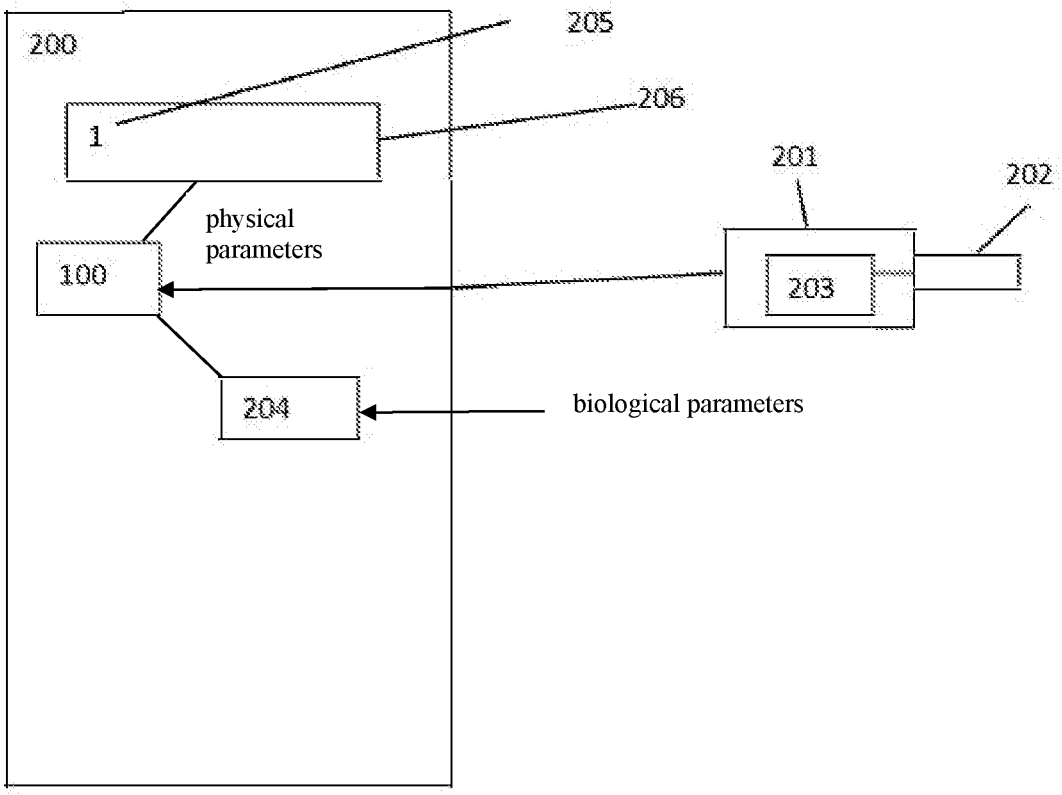


FIGURE 1

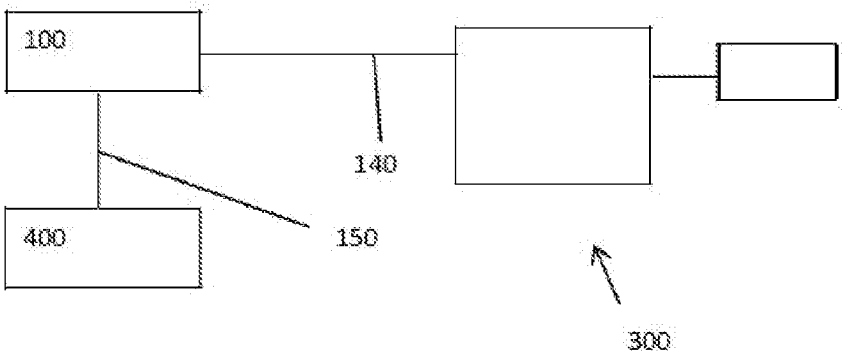


FIGURE 2

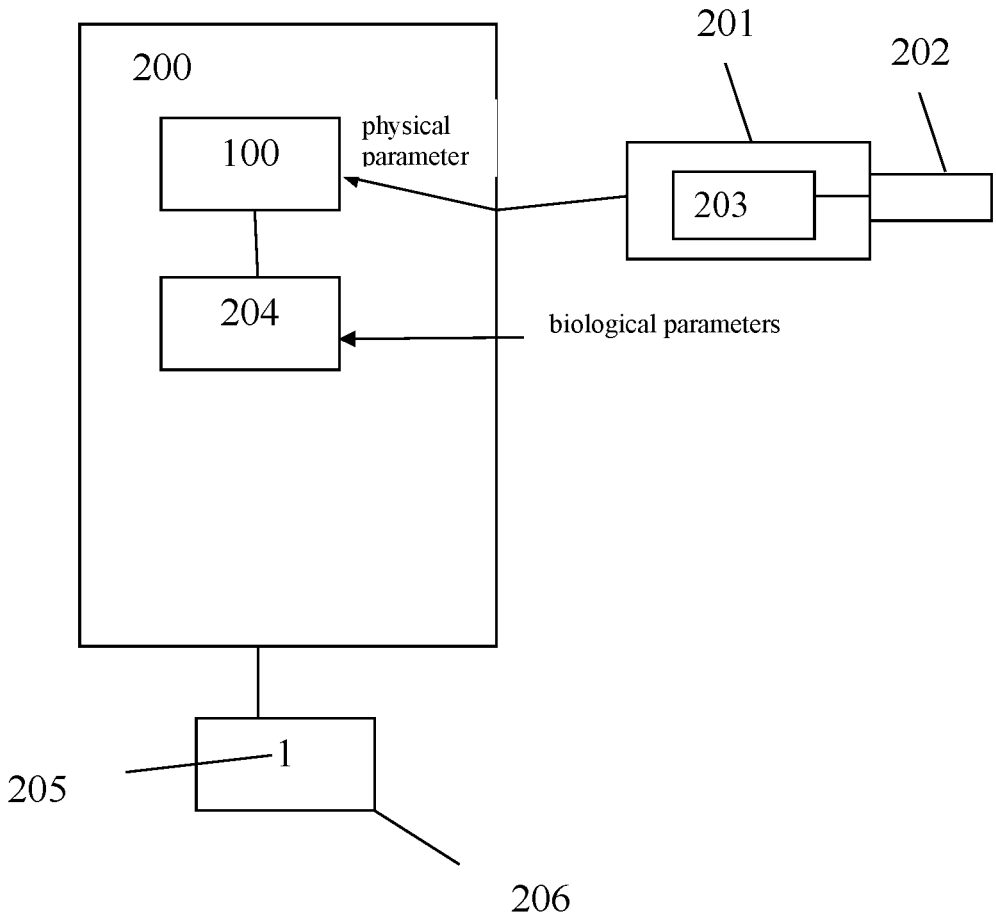

200
100
physical parameter
201
202
203
204
biological parameters
1
205
206

FIGURE 3

NON-INVASIVE DEVICE FOR DETECTING LIVER DAMAGE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This is a continuation of U.S. application Ser. No. 15/579,016, filed Dec. 1, 2017, which is the U.S. National Stage of PCT/EP2016/062392, filed Jun. 1, 2016, which in turn claims priority to French Patent Application No. 1554995, filed Jun. 2, 2015, the entire contents of all applications are incorporated herein by reference in their entireties.

TECHNICAL FIELD

[0002] The invention relates to a non-invasive device for detecting liver damage using ultrasonic waves and shear waves. Said device may be used for humans and animals and is for example intended for the detection of liver damage of ASH (Alcoholic SteatoHepatitis) or NASH (Non-Alcoholic SteatoHepatitis) type. The invention also pertains to a score reflecting liver damage.

PRIOR ART

[0003] Normally, chronic liver tissue diseases cause liver damage such as fibrosis. Fibrosis is a process of fibrous healing of liver tissue resulting from inflammation. The initially asymptomatic fibrosis may evolve into cirrhosis. The elasticity of liver tissue constitutes a marker of liver fibrosis. In order to measure and quantify the elasticity of liver tissue, it is known to use pulse elastography, as described, for example, in the patent application number FR 2843290.

[0004] This document describes an embodiment of a device according to the prior at. This device is composed of a probe provided with a vibration generator generating a low frequency elastic wave in a tissue, for example by vibration, and analysing the propagation of this low frequency elastic wave by means of high frequency ultrasonic waves transmitted and received by an ultrasonic transducer. The measurements obtained via this device make it possible to quantify the elasticity of liver tissue. This device also makes it possible to quantify the ultrasonic attenuation of tissues, as described, for example, in the patent application number FR 2949965. The quantification of ultrasonic attenuation in the liver corresponds to the amount of steatosis.

[0005] On the other hand, in humans certain diseases, for example NASH, are not necessarily linked only to the sole amount of fibrosis or to the sole amount of steatosis, and may for example associate steatosis type damage (presence of fat in the liver) and inflammation with or without fibrosis. Consequently, the stage of NASH or the evolution towards NASH cannot be diagnosed using a single parameter.

DESCRIPTION OF THE INVENTION

[0006] The present invention aims to resolve at least one of the aforesaid drawbacks of the prior art. To do so, the invention proposes a non-invasive device for detecting liver damage taking into account different parameters. The invention also proposes a score reflecting a type of liver damage.

[0007] To this end, one aspect of the invention relates to a device for calculating a score for humans or animals, said score being a quantitative or semi-quantitative evaluation of liver damage of alcoholic or non-alcoholic steatohepatitis type, said calculating device being constructed and arranged to calculate a score using the following at least physical or even biological parameters:

[0008] a parameter corresponding to inflammation and/or fibrosis,

[0009] a parameter corresponding to steatosis.

[0010] This embodiment particularly has the advantage of enabling early detection of certain types of liver damage, such as for example NASH, NASH being able to correspond to inflammation, fibrosis and steatosis. On the other hand, NAFLD (Non-Alcoholic Fatty Liver Disease) simply corresponds to steatosis. Thanks to the score, it is thus possible to differentiate patients suffering from a NAFLD type disease from patients suffering from a NASH type disease.

[0011] In one non-limiting embodiment of the device according to the invention, the score is a quantitative or semi-quantitative evaluation (for example, binary indicator) of liver damage of alcoholic or non-alcoholic steatohepatitis type.

[0012] In one non-limiting embodiment of the calculating device according to the invention, the calculating device is integrated in:

[0013] an ultrasound scanner, or

[0014] a device constructed and arranged to measure at least liver elasticity.

[0015] In one non-limiting embodiment, the device according to the invention is constructed and arranged to deliver the score concurrently with the measured physical parameters. In other words, the ultrasound scanner or the device constructed and arranged to measure at least liver elasticity measures physical parameters and the device according to the invention calculates the score while taking into account at least the measured physical parameters.

[0016] In one non-limiting embodiment of the calculating device according to the invention, the calculating device is constructed and arranged to communicate with:

[0017] a remote ultrasound scanner, or

[0018] a remote device constructed and arranged to measure at least liver elasticity.

[0019] In one non-limiting embodiment of the device according to the invention, the parameter corresponding to fibrosis is elasticity.

[0020] In one non-limiting embodiment of the device according to the invention, the parameter corresponding to steatosis is a measurement of the attenuation of ultrasonic waves, for example the parameter called CAP as described in the article Sasso, M., et al. (2010). "Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes." Ultrasound Med Biol 36(11): 1825-1835.

[0021] In one non-limiting embodiment of the device according to the invention, the parameter corresponding to steatosis is a measurement of liver tissue viscosity.

[0022] In one non-limiting embodiment of the device according to the invention, the calculating device is constructed and arranged to calculate a score using at least one additional parameter corresponding to inflammatory activity. For example, this parameter may be the transaminase value, ALAT, ASAT, GGT, liver elasticity or liver viscosity.

[0023] In one non-limiting embodiment of the device according to the invention, the calculating device is con-

structed and arranged to calculate a score using at least one additional parameter corresponding to metabolic syndrome.

[0024] In one non-limiting embodiment of the device according to the invention, the calculating device is constructed and arranged to calculate a score using at least one additional parameter of anthropomorphic type.

[0025] In one non-limiting embodiment of the device according to the invention, the calculating device is constructed and arranged to calculate a score using at least one additional parameter of biological type. The at least one biological parameter may for example be selected from the following parameters: transaminases (ASAT, ALAT), GGT, PAL, serum iron, ferritin, transferrin saturation, adipokine (for example, adiponectin, leptin, resistin), cytokine (for example, TNFa, IL6, I1_1-(3), HDL cholesterol, glycaemia, insulinemia, bilirubin, a2macroglobulin, haptoglobin, apolipoprotein A1, CK18, triglycerides, adiponectin, urea, genetic polymorphism (for example: PNPLA3, TM6SF2 polymorphism), CRP and/or leptin.

[0026] In one non-limiting embodiment of the device according to the invention, the calculating device is constructed and arranged to communicate with a device for displaying the score. The score may be displayed in the form of a numerical value, a binary indicator, a probability or a risk. This embodiment particularly has the advantage of enabling simplicity of interpretation of the analysis of the score reflecting a calculated state of liver damage.

[0027] One aspect of the invention also pertains to a score taking into account the following physical or even biological parameters:

[0028] a parameter corresponding to inflammation and/or fibrosis, and

[0029] a parameter corresponding to steatosis.

[0030] In one non-limiting embodiment, the score takes into account at least one parameter of inflammatory activity. The at least one parameter of inflammatory activity may be selected from the following parameters: the transaminase value, liver elasticity or liver viscosity.

[0031] In one non-limiting embodiment, the score takes into account at least one anthropomorphic parameter of weight, height, waist circumference, hip circumference, chest girth type or a demographic parameter of age and sex type.

[0032] In one non-limiting embodiment, the score takes into account at least one biological parameter.

[0033] The at least one biological parameter may be selected from the following parameters: transaminases (ASAT, ALAT), GGT, PAL, serum iron, ferritin, transferrin saturation, adipokine (for example, adiponectin, leptin, resistin) cytokine (for example, TNFa, IL6, I1_1-(3), cholesterol, HDL cholesterol, glycaemia, insulinemia, bilirubin, a2macroglobulin, haptoglobin, apolipoprotein A1, CK18, triglycerides, adiponectin, urea, genetic polymorphism (for example: PNPLA3, TM6SF2 polymorphism), CRP and/or leptin.

[0034] The biological parameter may be a metabolomic parameter.

[0035] In one non-limiting embodiment, the score is calculated using statistical modelling (also called statistical learning) of the type logistic regression, decision trees, Bayes classifiers, random forests, WMS, neural networks, discriminatory analysis, etc.

BRIEF DESCRIPTION OF THE FIGURES

[0036] Other characteristics and advantages of the invention will become clear from the description that is given thereof below, for indicative purposes and in no way limiting, with reference:

[0037] to FIG. **1** illustrating, in a schematic manner, a first exemplary embodiment of a device for calculating a score reflecting a state of liver damage integrated in a device constructed and arranged to measure liver elasticity,

[0038] to FIG. **2** illustrating, in a schematic manner, a second exemplary embodiment of a device for calculating a score reflecting a state of liver damage constructed and arranged to communicate with a remote ultrasound scanner.

[0039] to FIG. **3** illustrating, in a schematic manner, a third exemplary embodiment of a device for calculating a score reflecting a state of liver damage constructed and arranged to communicate with a remote ultrasound scanner.

DESCRIPTION OF THE INVENTION

[0040] FIG. **1** represents a device **100** for calculating a score reflecting a state of liver damage integrated in a device **200** constructed and arranged to measure liver elasticity.

[0041] In this non-limiting embodiment, the device **200** comprises an elastography probe **201** provided with an ultrasonic transducer **202** constructed and arranged to transmit and receive ultrasonic waves. In this embodiment, the elastography probe **201** further comprises means for generating a shear wave in the liver tissue. Said means may be an electrodynamic actuator **203** constructed and arranged to generate a low frequency wave. The device **200** is thus constructed and arranged to measure physical parameters, for example parameters which correspond to inflammation and/or fibrosis and parameters which correspond to steatosis.

[0042] As an example, a parameter linked to fibrosis may be the elasticity of the liver. This elasticity measurement constitutes a marker of the pathological state of the liver tissue.

[0043] The parameter corresponding to steatosis may be a measurement of the attenuation of ultrasonic waves in the liver tissue. Liver steatosis is an accumulation of fat in the liver. The measurement of the attenuation of the propagation of ultrasonic waves thus makes it possible to quantify steatosis.

[0044] The device **100** for calculating a score reflecting a state of liver damage is constructed and arranged to calculate a score using a parameter corresponding to inflammation of liver tissue and/or a parameter corresponding to fibrosis. In the example described, these parameters are measured using the device **200** together with the elastography probe **201** and received by the device **100**.

[0045] In the example illustrated, the device **200** also comprises a human-machine interface **204** constructed and arranged to enter metabolic syndrome marker parameters used to calculate the score.

[0046] Thus, an operator may enter, via the human-machine interface **204**, metabolic syndrome marker parameters. Metabolic syndrome is taken to mean the association of a series of health problems having in common poor corporal metabolism, it is a grouping together of risk factors more or less linked by a common origin, metabolic targets or mechanisms. This group of parameters may thereby comprise:

HDL cholesterol, triglycerides, glycaemia, arterial pressure, and/or the waist circumference.

[0047] This human-machine interface **204** is also constructed and arranged to enter biological parameters used to calculate the score. These biological parameters may be: transaminases (ALAT, ASAT), GGT, PAL, serum iron, cholesterol, HDL cholesterol, glycaemia, insulinemia, bilirubin, a2macroglobulin, haptoglobin, apolipoprotein A1, CK18, triglycerides, adiponectin, and/or leptin.

[0048] This human-machine interface **204** is also constructed and arranged to enter demographic and anthropomorphic parameters used to calculate the score. These demographic and anthropomorphic parameters are for example formed by the age, the sex, the height, the weight, the waist circumference, the hip circumference or the chest girth of an individual.

[0049] As a function of these different parameters, the calculating device **100** calculates a score using a logistic regression or any other scoring method, for example of the type decision trees, Bayes classifiers, random forests, wide margin separator (WMS) decision trees, or instead neural networks.

[0050] To this end, the calculating device **100** may be formed by one or more microprocessors constructed and arranged to execute sequences of instructions enabling the implementation of the aforesaid logistic regression or any other scoring method.

[0051] In the example illustrated of FIG. **1**, the calculated score is represented in the form of a binary indicator **205** equal to 1 and displayed on a screen **206** of the device **200**. This binary indicator **205** may be used to advise a patient to consult a specialist. For example, when the indicator is equal to 1, the patient is diagnosed as being at risk and requires a more detailed investigation or additional examinations have to be carried out. In the embodiment of FIG. **3**, the screen **206** is positioned remotely from the calculating device **100** and the device **200** that comprises the elastography probe **201**.

[0052] In contrast, when the indicator is equal to 0, the patient does not need to consult a specialist. This indicator may also be different, it may be implemented in the form of a value.

[0053] In this non-limiting embodiment, the measurements of physical parameters, the input of other parameters, the calculation of the score and the display of the score are carried out in the device **200**. Thus, this embodiment particularly has the advantage of calculating in real time the score (in other words at the place where the measurements of the physical parameters are carried out), then displaying the score enabling rapidity of analysis.

[0054] In different non-limiting examples, the device **200** may be formed by an ultrasound scanner, an MRI, or an MRI implementing magnetic resonance elastography (MRE).

[0055] In one non-limiting embodiment illustrated in FIG. **2**, the device for calculating a score reflecting a state of liver damage **100** is constructed and arranged to communicate with a remote ultrasound scanner **300**. In other words, the calculating device **100** is remote vis-a-vis the ultrasound scanner **300**. Thus, the measurements are carried out on the ultrasound scanner **300** then transmitted via a network link **140**, for example an Ethernet or Bluetooth or Wi-Fi type link, to the calculating device **100**. It is also possible to transmit other parameters, for example of anthropomorphic or demographic type, to the calculating device **100** via a computer **400**. Similarly, this computer **400** may communicate with the calculating device **100** via an Ethernet or Wi-Fi link **150**. The calculating device **100** may be materialised by one or more processors. Furthermore, the computer may be integrated in the ultrasound scanner **300**.

[0056] In this non-limiting embodiment, the score may be displayed on the ultrasound scanner **300**, on the computer **400** or both.

1.-**3**. (canceled)

4. A system for calculating a score in a patient, said score being a quantitative or semi-quantitative evaluation of liver damage of alcoholic or non-alcoholic steatohepatitis type, said system comprising:

a) one or more measurement devices including one or more ultrasound transducers and configured to carry out measurements of a first physical parameter corresponding to liver fibrosis, or liver inflammation, or both, and a second physical parameter corresponding to liver steatosis;

b) a calculating device configured to receive values of said first and second physical parameters measured by the one or more measurement devices and a value of one or more biological parameters, the one or more biological parameters including at least one transaminase (ASAT or ALAT), said calculating device including one or more processors configured to execute a sequence of instructions for determining a score parameter, based on the values of the first and second physical parameters and the one or more biological parameters, representative of liver damage in said patient,

c) a display device including a screen, the display device configured to display the score parameter determined by the calculating device, the score parameter being displayed on said screen in the form of a numerical value, a binary indicator, a probability or a risk, said score parameter providing an estimate of NASH.

5. The system of claim **4**, wherein the first physical parameter is liver stiffness or liver elasticity and the second physical parameter is ultrasonic attenuation or tissue viscosity.

6. The system of claim **4**, wherein the one or more measurement devices include an elastography apparatus, or an ultrasound scanner or both.

7. The system of claim **4**, wherein the one or more measurement devices include an elastography apparatus that is configured to carry out measurements of said first physical parameter and said second physical parameter.

8. The system of claim **4**, wherein the sequence of instructions determine the score parameter according to a logistic regression, a decision tree, a Bayes classifier, or a random forest regression.

9. The system of claim **4**, wherein the calculating device is integrated in a device that includes the one or more measurement devices and the display device.

10. The system of claim **4**, wherein the calculating device is remote from the one or more measurement devices.

11. The system of claim **4**, wherein the calculating device is adapted to communicate with the one or more measurement devices via Ethernet or Wi-Fi link to receive said values of said first and second physical parameters.

12. The system of claim **4**, wherein the display device is part of a computer that is remote from both the calculating device and the one or more measurement devices.

13. A method for calculating a score in a patient, said score being a quantitative or semi-quantitative evaluation of liver damage of alcoholic or non-alcoholic steatohepatitis type, the method comprising:

a) carrying out measurements of a first physical parameter corresponding to liver fibrosis, or liver inflammation, or both, and a second physical parameter corresponding to liver steatosis with one or more measurement devices that include one or more ultrasound transducers;

b) calculating, with a calculating device, a score parameter representative of liver damage in said patient, the score parameter being based on values of the first and second physical parameters and one or more biological parameters, the calculating device configured to receive values of said first and second physical parameters measured by the one or more measurement devices and a value of the one or more biological parameters, the one or more biological parameters including at least one transaminase (ASAT or ALAT), said calculating device including one or more microprocessors configured to execute a sequence of instructions for determining the score parameter, and

c) displaying on a screen of a display device the score parameter in the form of a numerical value, a binary indicator, a probability or a risk, said score parameter providing an estimate of NASH.

14. The method of claim **13**, wherein the first physical parameter is liver stiffness or liver elasticity and the second physical parameter is ultrasonic attenuation or tissue viscosity.

15. The method of claim **13**, wherein the one or more measurement devices include an elastography apparatus, or an ultrasound scanner or both.

16. The method of claim **13**, wherein the one or more measurement devices include an elastography apparatus that is configured to carry out measurements of said first physical parameter and said second physical parameter.

17. The method of claim **13**, wherein the sequence of instructions determine the score parameter according to a logistic regression, a decision tree, a Bayes classifier, or a random forest regression.

18. The method of claim **13**, wherein the calculating device is integrated in a device that includes the one or more measurement devices and the display device.

19. The method of claim **13**, wherein the calculating device is remote from the one or more measurement devices.

20. The method of claim **13**, wherein the calculating device is adapted to communicate with the one or more measurement devices via Ethernet or Wi-Fi link to receive said values of said first and second physical parameters.

21. The method of claim **13**, wherein the display device is part of a computer that is remote from both the calculating device and the one or more measurement devices.

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