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Prospective Study**Prospective study comparing hepatic steatosis assessment by MRI and four ultrasound methods**

Ultrasound for hepatic steatosis assessment

Abstract**BACKGROUND**

Non-alcoholic fatty liver disease (NAFLD) is becoming a major health problem, resulting in hepatic, metabolic and cardio-vascular morbidity.

AIM

Our study aims at evaluating new ultrasonographic tools to detect and measure hepatic steatosis.

METHODS

We prospectively included 105 patients referred to our liver unit for NAFLD suspicion or follow-up. They underwent ultrasonographic measurement of liver sound speed estimation (SSE) and attenuation coefficient (AC) using Aixplorer MACH 30 (Supersonic Imagine, France), continuous Controlled Attenuation Parameter (cCAP) using Fibroscan (Echosens, France) and standard liver ultrasound with hepato-renal index (HRI) calculation. Hepatic steatosis was then classified according to MRI proton density fat fraction (PDFF). Receiver operating curve (ROC) analysis was performed to evaluate the diagnostic performance in the diagnosis of steatosis.

RESULTS

Most patients were overweight or obese (90 %) and had metabolic syndrome (70 %). One third suffered from diabetes. Steatosis was identified in 85 patients (81 %) according to PDFF. 21 patients (20 %) had advanced liver disease. SSE, AC, cCAP and HRI correlated with PDFF, with respective Spearman correlation coefficient of -0.39, 0.42, 0.54 and 0.59 ($p < 0.01$).

AUROC for detection of steatosis with HRI was 0.91 [0.83-0.99], with the best cut-off value being 1.3 (Se = 83 %, Sp = 98 %). The optimal cCAP threshold of 275 dB/m, corresponding to the recent EASL-suggested threshold, had a sensitivity of 72 % and a specificity of 80 %. Corresponding AUROC was 0.79 [0.66-0.92]. The diagnostic accuracy of cCAP was more reliable when standard deviation was < 15 dB/m with an AUC of 0.91 [0.83-0.98].

An AC threshold of 0.42 dB/cm/MHz had an AUROC was 0.82 [0.70-0.93]. SSE performed moderately with an AUROC of 0.73 [0.62-0.84].

CONCLUSION

Among all ultrasonographic tools evaluated in this study, including new-generation tools such as cCAP and SSE, hepatorenal index had the best performance. It is also the simplest and most available method as most US scans are equipped with this module.

Key Words: Non-alcoholic fatty liver disease; Ultrasonography; Steatosis assessment; MRI

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Core Tip: Among all ultrasonographic tools evaluated in this study, including new-generation systems such as continuous Controlled Attenuation Parameter and Sound

Speed Examination, hepatorenal index had the best performance. It is also the simplest and most available method as most US scans are equipped with this module. The presence of an hyperechogenic liver on US also performed well, confirming that US should remain the first-line screening tool for steatosis.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), considered as the liver manifestation of the metabolic syndrome, has become a major public health issue, affecting around 25 % of people in western societies. Its presence has been associated with an increased risk of both cardiovascular, hepatic and cancer-related morbidity (1). Therefore, identifying steatosis among individuals with increased metabolic risk is crucial for primary care.

Hepatic steatosis is the key manifestation of NAFLD and refers to the excess of fat within the hepatocytes, histologically defined by the presence of at least 5 % of hepatocytes containing fat. Histological assessment of steatosis is the gold standard for the diagnosis of liver steatosis but is an invasive procedure and cannot be performed for all patients with metabolic risk factors (2).

Ultrasound (US) is currently the first-line screening test, but several studies have shown that US is lacking the necessary sensitivity to assess mild steatosis < 20 %, particularly in obese patients with body mass index > 35 kg/m² (3–7). It is also subject to inter-observer and intra-observer variabilities (8).

Magnetic resonance imaging (MRI) has demonstrated excellent performances for the diagnosis and grading of steatosis using either spectroscopy, in-phase and opposed-phase technique or multiecho gradient sequences but this process is expensive, with limited access (9–11).

Controlled attenuation parameter (CAP) is a promising technique for steatosis assessment and grading. The interpretation of CAP values remains difficult in practice for several reasons: many cutoffs have been published, the influence of the chosen probe is still debated and solid quality criteria of measures are unavailable (12–17). A new CAP method called continuous CAP (cCAP) is emerging. The major difference with the

alternative method is that it uses ultrasound data continuously acquired during the imaging phase examination (18).

Other non-invasive techniques including B-mode image-guided US attenuation parameter or hepatorenal index have been developed in the past years (19–23).

Recently, a new US technique based on sound speed estimation (SSE) demonstrated accurate performances for the detection of steatosis. The speed of sound decreased as the fat content in liver increased. SSE could be used to detect, quantify and grade liver steatosis. However, the evaluation of steatosis was not specifically done in overweighted/obese patients suffering from NAFLD and SSE needs further investigations in this indication (24–26).

In a monocentric prospective study, we aimed at evaluating diagnosis performances of various US tools compared to MRI proton density fat fraction assessment (PDFF).

MATERIALS AND METHODS

Study participants were consecutively and prospectively recruited from the University Hospital of Clermont-Ferrand, France, from January 2021 to October 2021 by physicians of the hepatology department. Inclusion criteria were : age over 18 years, patients with known or suspected NAFLD, referred for non-invasive fibrosis evaluation using impulse elastography, with willingness and ability to participate. Exclusion criteria were clinical, laboratory, or histologic evidence of a liver disease other than NAFLD (chronic hepatitis B or C, autoimmune liver disease, excessive alcohol consumption defined by WHO criteria, Wilson's disease or other), hepatocellular carcinoma and all other liver tumors, secondary causes of liver steatosis (genetic disease, steatogenic or hepatotoxic medication use) and contraindications to MRI.

Demographic and anthropometric data were recorded. Biological data collected included platelets, prothrombin time (PT), international normalized ratio (INR), albumin, bilirubin, transaminases (aspartate aminotransferase, AST and alanine aminotransferase, ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), total cholesterol,

high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, fasting glucose, fasting insulinemia.

All participants underwent US liver examinations using the Aixplorer MACH 30® US system (Supersonic Imagine, Aix-en-Provence, France). Participants were asked to fast for at least 3 h prior to US examinations. They were positioned in the dorsal decubitus position with the right arm at maximum abduction for intercostal stretching. A 3.5 MHz abdominal curved transducer (C6-1X probe) was used. Acquisitions were performed during neutral respiratory apnea as follows: 1) right intercostal (between the 7th and 9th intercostal space) and subcostal view was considered for every patient; 2) US transducer was placed so that the hepatic capsule was parallel to the US transducer; 3) care was taken to avoid the presence of large hepatic vessels or artifacts in the image (ultrasound reflection caused by abdominal gas or by rib interposition). For hepatorenal index (HRI), the probe was placed to obtain an adequate visualization of the liver and the right kidney in a sagittal or oblique image with minimal artifacts. HRI was calculated using the region of interest (ROI) measure tool, with average brightness ratio between two ROI at least 3 mm wide placed at the same depth in hepatic parenchyma and in renal cortex (figure 1).

For each patient, 5 measures of sound speed, 5 of attenuation coefficient (AC) and 3 of HRI acquisitions were performed by the same physician. The mean values were used for statistical analysis.

Simultaneously, liver stiffness and continuous CAP (cCAP) measurements were performed using FibroScan SmartExam® (Echosens, Paris, France) by experienced operators. All patients were measured using either an M- or an XL-probe, according to the device automatically-selected probe.

A liver US was also performed by a radiologist at patient's discretion, in any radiological center, unaware of the study, in the standard clinical care of NAFLD. The presence of a hyperechogenic liver described on the US report was noted (steatosis vs. no steatosis or not mentioned).

Within the month following US examinations, all participants underwent a chemical shift- encoded liver MRI using a 3.0 Tesla MAGNETOM Vida® system

(Siemens Medical Solutions, Erlangen, Germany). A gradient echo dedicated sequence developed by the manufacturer to measure hepatic PDFF was systematically included in MRI acquisition protocols. This sequence is characterized by a low flip angle to reduce T1 bias and six echoes to correct for T2* effect. Images were acquired during a single breath hold. In and out-phases imaging was used prior to fat quantification to assess homogeneity of fat distribution. PDFF (%) estimation was obtained by placing three large regions of interest in the liver parenchyma. Steatosis was regarded as fat fraction $\geq 5.6\%$, as defined by EASL. Steatosis grading was not evaluated because correspondence between the steatosis histologic grading and PDFF value has not yet been standardized in the literature (27). Iron content was also measured using this technique.

Patients data were recorded in e-case report form (e-CRF) *via* a secure web platform (REDCap® version 9.3.7, Vanderbilt University, USA) where these data were monitored and a database extraction was performed.

The study design was approved by local ethic committee (study M210401, Clermont-Ferrand University Hospital) and informed consent was obtained for all participants.

STATISTICS

Data were expressed as descriptive statistics (mean \pm standard deviation (SD), median with IQR or number with corresponding percentage as appropriate). The normality assumption was assessed using the Shapiro-Wilk's test. Chi-Square and Student T-test were used to compare categorical and continuous variables. If normality was not ascertained, the Mann-Whitney test was used for continuous variables. Receiver operating curve (ROC) analysis was performed to evaluate the diagnostic performance of US tools compared to MRI PDFF. Optimal cutoff values were identified by maximizing the Youden index, and corresponding sensitivities, specificities, likelihood ratios (LR) were derived. Comparison of areas under receiver operating characteristic curves was made according to Hanley and McNeil. Pearson and Spearman linear correlation coefficients were used to evaluate the relationship between continuous variables, respectively when normality was assessed or not. A non-linear regression analysis was

also conducted to assess the relationship between SSE AC, cCAP, HRI and PDFF. All tests were considered statistically significant in the case of $p\text{-value} < 0.05$. Statistical analysis were performed and graphs were designed using GraphPad Prism® (v8, GraphPad Software, La Jolla, California, USA). Multivariable linear regression was used to evaluate the influence of anthropometric parameters and fibrosis severity on US measures (R Software, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical, biological and radiological characteristics of the study population

One hundred and five patients were included in this study. Main characteristics are presented in table 1. Median body mass index (BMI) was 31 kg/m². Most patients were overweight or obese (90 %) and had metabolic syndrome (70 %). One third suffered from diabetes. Steatosis was identified in 85 patients (81 %) according to PDFF. Twenty-five patients (20 %) were suspected to have advanced liver disease according to shear-wave elastography.

Mean AST and ALT were respectively 35 (± 28) U/L and 65 (± 49) U/L. Mean GGT was 120 (± 125) U/mL. Only ALT levels correlated significantly but moderately with PDFF (Spearman's $\rho = 0.4$, $p < 0.001$). One patient failed to receive Fibroscan® and HRI measurement due to poor US signal.

Demographic and anthropometric data

Sex (male)

51 (49 %)

Age (years)

56 \pm 14

BMI (kg/m²)

Overweight (%)

Obesity (%)

31 ± 6

94 (90 %)

50 (48 %)

Waist circumference (cm)*

107 ± 15

Diabetes (%)

38 (36 %)

Hypertension (%)

42 (40 %)

Metabolic syndrome (%)

73 (70 %)

Biological data

Platelets count (G/L)*

231 ± 72

AST (U/L)*

35 ± 28

ALT (U/L)*

65 ± 49

GGT (U/L)*

120 ± 125

Triglycerides (g/L)*

1.7 ± 0.93

HDL cholesterol (g/L)*

1.3 ± 0.4

Ferritin (ng/mL)*

232 ± 283

Steatosis assessment

PDFF (%)*

Steatosis on MRI (%)

15 ± 10

85 (81 %)

Fibroscan®

Technical success (%)

cCAP (dB/m)

Liver stiffness (kPa)*

Liver stiffness > 10kPa (%)

Use of M probe (%)

Use of XL probe (%)

104 (99 %)

283 ± 58

8 ± 7

21 (20 %)

83 (80 %)

21 (20 %)

Aixplorer MACH 30®

Technical success (%)

SSE (m/s)*

AC (dB/cm/MHz)*

105 (100 %)

1519 ± 22

0.48 ± 0.1

HRI*

Technical success (%)

1.43 ± 0.28

104 (99 %)

*Data are means ± SD, ⁴ BMI = body mass index, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma glutamyl transferase, PDFF = proton density fat fraction, cCAP = continuous controlled attenuation parameter, SSE = sound speed estimation, AC = attenuation coefficient, HRI = hepato-renal index.

Table 1: Characteristics of the 105 patients

Patients characteristics according to the presence of steatosis are shown in table 2. Steatotic patients had significantly higher BMI and waist circumference. As expected, metabolic syndrome was more prevalent in patients with steatosis. ¹ Mean SSE, AC and cCAP values significantly differed between non-steatotic and steatotic patients, but not liver stiffness.

Patients with steatosis (*n* = 85)

Patients without steatosis (*n* = 20)

p-value

Demographic and anthropometric data

Sex (male)

40 (47 %)

11 (55 %)

0.62

Age (years)

56 ±14

53 ± 14

0.5

BMI (kg/m²)

Normal BMI (%)

Overweight (%)

Obesity (%)

31 ±5

7 (8 %)

31 (37 %)

47 (55 %)

28 ± 6

4 (20 %)

13 (65 %)

3 (15 %)

0.0004

Waist circumference (cm)*

108 ± 14

99 ± 15

0.004

Diabetes (%)

33 (39 %)

5 (25 %)

0.3

Hypertension (%)

37 (44 %)

5 (25 %)

0.2

Metabolic syndrome (%)

65 (76 %)

8 (40 %)

0.0026

Biological data

Platelets count (G/L)*

236 ± 71

213 ± 78

0.2

AST (U/L)*

37 ± 30

27 ± 10

0.13

ALT (U/L)*

37 ± 30

49 ± 29

0.044

GGT (U/L)*

68 ± 53

116 ± 85

0.68

Triglycerides (g/L)*

1.8 ± 0.9

1.3 ± 0.9

0.0058

HDL cholesterol (g/L)*

1.3 ± 0.4

1.3 ± 0.3

0.1

Ferritin (ng/mL)*

121 ± 134

172 ± 127

0.45

Steatosis assessment

PDFF (%)*

18 ± 9

2 ± 3

< 0.0001

Fibroscan®

Technical success (%)

cCAP (dB/m)

Liver stiffness (kPa)*

Liver stiffness > 10kPa (%)

Use of M probe (%)

Use of XL probe (%)

84 (99 %)

296 ± 42

8 ± 8

19 (22 %)

65 (76 %)

20 (24 %)

20 (100 %)

246 ± 67

7 ± 5

2 (10 %)

18 (90 %)

2 (10 %)

< 0.0001

NS

Aixplorer MACH 30®

Technical success (%)

SSE (m/s)*

AC (dB/cm/MHz)*

85 (100 %)

1515 ± 22

0.5 ± 0.1

20 (100 %)

1533 ± 19

0.39 ± 0.1

0.0009

< 0.0001

HRI

Technical success (%)

1.52 ± 0.24

84 (99 %)

1.1 ± 0.18

20 (100 %)

< 0.0001

⁴
*Data are means ± SD, BMI = body mass index, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma glutamyl transferase, PDFF = proton density fat fraction, cCAP = continuous controlled attenuation parameter, SSE = sound speed estimation, AC = attenuation coefficient, HRI = hepato-renal index, NS = non-significant.

Table 2: Characteristics of steatotic and non-steatotic patients

Relationship between SSE, AC, HRI and cCAP with MRI PDFF

¹
SSE, AC, HRI and cCAP correlated with PDFF, with respective Spearman correlation coefficient of -0.39, 0.42, 0.59 and 0.54 ($p < 0.01$) (figure 2). SSE, AC, cCAP and HRI specifically displayed a significant non-linear relationship with PDFF as previously demonstrated (supplementary figure 1) (28).

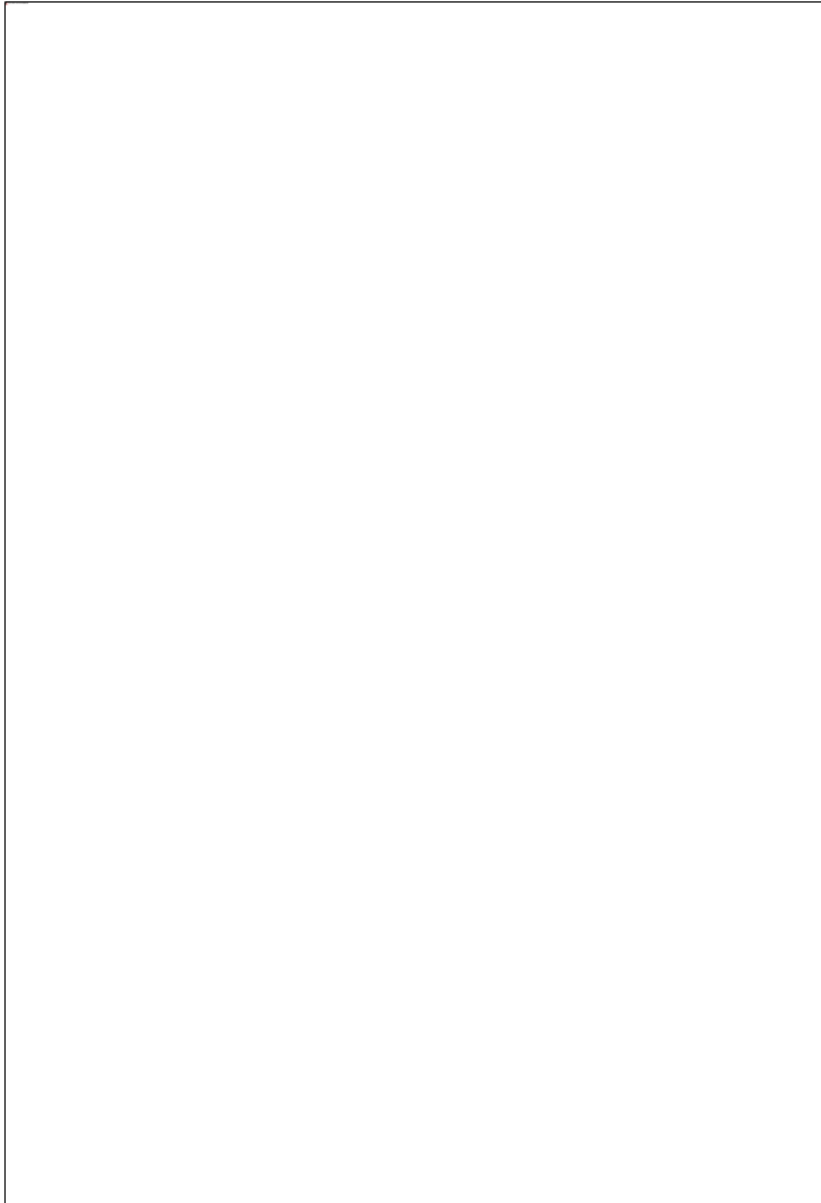


Figure 2 : Scatterplots showing linear relationship between SSE (A), AC (B), HRI (C) and cCAP (D) with MRI-PDFF using 6-echo gradient ($p\text{-value} < 0,001$). PDFF = proton density fat fraction, cCAP = continuous controlled attenuation parameter, SSE = sound speed estimation, AC = attenuation coefficient, HRI = hepatorenal index

Performances of sound speed estimation and attenuation coefficient

Intercostal SSE performed moderately for the diagnosis of steatosis with an area under curve (AUC) of 0.73 [0.62-0.84] ($P = 0.001$) (figure 4A). Using the manufacturer cutoff of 1537 m/s resulted in a sensitivity and specificity of 80 % and 45 %. The best cutoff identified in our work was 1518 m/s but performances remained modest with sensitivity and specificity of 60 % and 80 % respectively. Of note, using 5 measures of SSE compared to 3 measures did not improve performances (data not shown).

Intercostal AC performed well for the diagnosis of steatosis with an AUC of 0.82 [0.70-0.93] ($P = 0.001$) (figure 4B). The best cutoff identified in our work was 0.42 dB/cm/MHz with sensitivity and specificity of 84 % and 75 % respectively.

Performances of continuous controlled attenuation parameter

cCAP was accurate for the diagnosis of steatosis with AUC of 0.79 [0.66-0.92] but did not perform better than AC. The best cutoff identified in our work was 275 dB/m but lacked sensitivity and specificity (respectively 72 % and 80 %) (figure 4C).

As expected, using cCAP resulted in low coefficient variation (CV) with 96% of patients having a coefficient of less than 10 %. The diagnostic accuracy of cCAP was significantly improved when IQR of cCAP was < 15 dB/m with an AUC of 0.91 (95 % CI 0.83-0.98, $p < 0.01$) resulting in a sensitivity and specificity of 74 and 92 %. In this work, one third of patients had an IQR > 15 dB/m (figure 3).



Figure 3 : cCAP AUROC for the diagnosis of steatosis according to standard deviation (SD)

PDFF = proton density fat fraction, cCAP = continuous controlled attenuation parameter

Performances of hepatorenal index

HRI performed the best with an AUC of 0.91 [0.83-0.99] ($p < 0.0001$) (figure 4D). Using a cutoff set at 1.3 resulted in a sensitivity of 82 % and specificity of 98 %. In other words, only 2 patients had an increased hepatorenal gradient without having liver steatosis. The first patient had borderline steatosis (4 % on MRI) and severe fibrosis on elastography (19 kPa) which could explain the increased HRI. For the other patient, moderate iron overload may have increased hepatorenal gradient. Among the 15 false negative patients, two third had mild steatosis on MRI (defined as PDFF < 10 %).

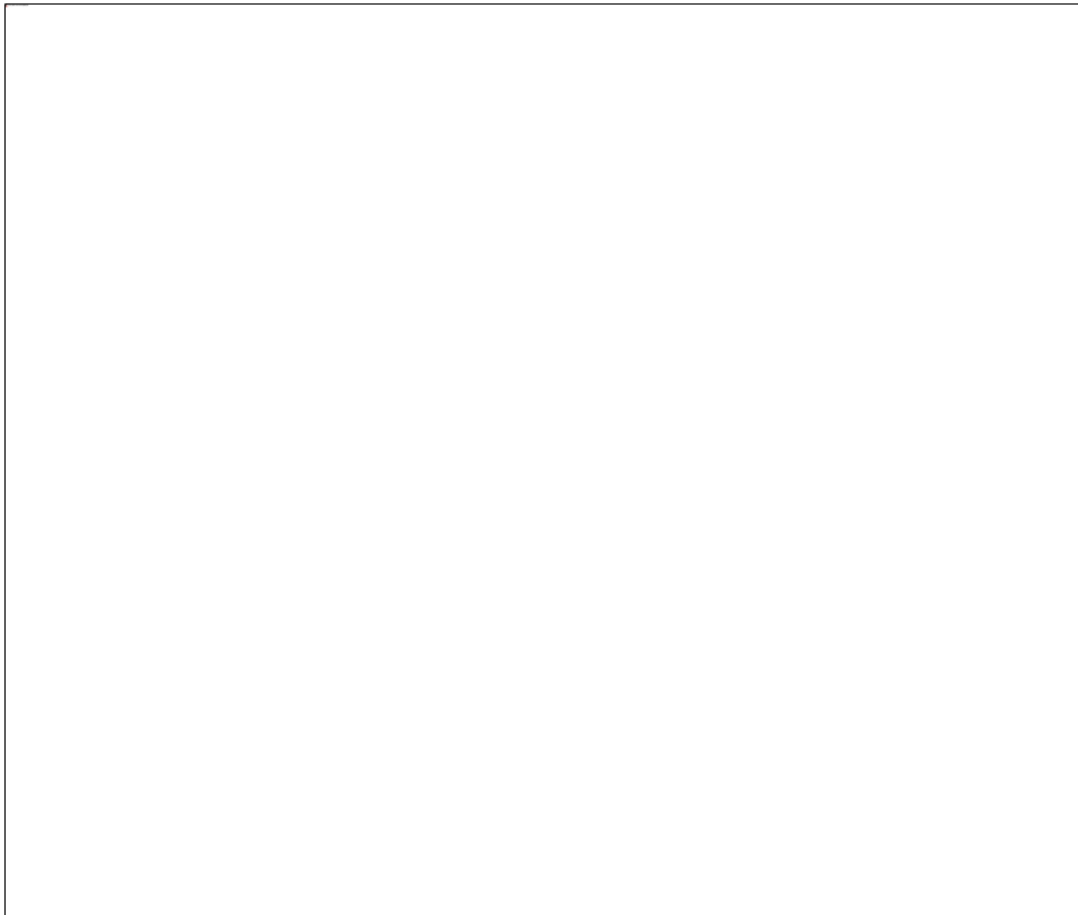


Figure 4 : ROC curve for SSE (A), AC (B), cCAP (C) and HRI (D). PDFF = proton density fat fraction, cCAP = continuous controlled attenuation parameter, SSE = sound speed estimation, AC = attenuation coefficient, HRI = hepato-renal index.

Performances of standard ultrasound

Hyperechogenic liver was described in 73/85 steatotic patients (figure 5). It showed a sensitivity of 86 % and specificity of 70 %. Among the 6 patients presenting a hyperechogenic liver on US but no steatosis on MRI, none had severe fibrosis (assessed using Fibroscan) or iron overload. Among the 12 patients with no hyperechogenic liver but steatosis on MRI, 7/12 (58 %) had mild steatosis based on PDFF. No other steatosis sign was described by radiologists.



Figure 5 : US finding according to liver steatosis based on PDFF

Intercostal or subcostal access

SSE and AC measurements were made for every patient using intercostal and subcostal view. However, if intercostal access was successful in every patient (success rate: 100 % for SSE and AC), subcostal access showed a lower success rate (94 % for SSE, 92 % for AC) and lower performances (data not shown).

Influence of BMI and severity of fibrosis

Using multivariable linear regression, we demonstrated that both HRI, cCAP, AC and SSE were associated with the presence of steatosis on MRI, independently from BMI, waist circumference elastography, iron overload and the presence of diabetes or metabolic syndrome.

DISCUSSION

Standard ultrasound is widely used as first diagnostic exam for NAFLD. Our results confirmed past studies reporting poor sensitivity for mild steatosis (3,5). Furthermore, BMI and fibrosis negatively influence US performances (6,7), and it suffers from inter- and intra-observer variability (8). Our study collected US report from various radiologists, unaware of the study, chosen at patient's discretion. Steatosis was only described according to parenchyma hyperechogenicity. No other steatosis sign, like vessels blurring, gallbladder blurring or inability to visualize the diaphragm, nor steatosis scoring system, was used by radiologist, even if it proved to improve its diagnostic performance.

Hepato-renal index calculation is a simple way to improve capabilities, as most US devices or radiology systems propose a dedicated module (21,29,30). It can be easily performed by someone already familiar with US scan evaluation. Webb *et al* proved that the known limitation of sonography to detect high grade steatosis of more than 30% of hepatocytes is resolved by HRI (31). In our study, HRI performed the best with a cut-off of 1.30. Previously described cut-off for the detection of any grade steatosis may vary in the literature from 1.22 to 1.49 (21,28,30–32), influenced by system settings and different gold standards, and thus limiting HRI reproducibility and applicability.

It was the most reliable technique in our work, permitting an objective and quantitative assessment of steatosis better than cCAP and SSE. Furthermore, B-mode guidance permits to suspect heterogenous steatosis and adapt the location of measurement, which cannot be done with cCAP.

cCAP demonstrated promising performances for diagnosis of steatosis. This confirms a pilot study, which showed that cCAP outperformed significantly conventional CAP for the diagnostic of steatosis (33). Indeed, the continuous method allows for larger volume sampling, reducing intraindividual variability and increasing correlation with MRI-PDFF. Caussy *et al* described an IQR-based validity criteria significantly improving CAP performances (34). CAP results were generally expressed as the median and interquartile range of several manually triggered sequential attenuation measurements. Individual measurements collected with the continuous CAP method being much numerous, its

results are expressed as the mean and standard deviation (SD). Thus, we proposed a quality criteria based on SD. In our work, cCAP proved to be perform significantly better for the diagnosis of steatosis when $SD < 15$ dB/m, reaching IHR measurement performances.

One main advantage of cCAP is to be combined with simultaneous fibrosis measurement, rapidly and without additional capabilities. This is of particular interest considering that the degree of fibrosis is the main prognosis factor in patients suffering from NAFLD (35). However, on a practical level, not all medical structures have access to this device. This a major issue knowing that the growing prevalence of NAFLD worldwide cannot be fully handled by tertiary-care centers.

SSE and AC measurement on Aixplorer MACH 30 system are new non-invasive tools to quantify liver fat content, which may be useful in patient follow-up or therapeutic studies (36). Using MRI-PDFF as reference, our study proved mixed performances for detection or exclusion of steatosis, with AUC ranging from 0.73 to 0.82.

SSE is a novel, understudied technique, based on the decrease of US speed as liver fat increases. Dioguardi *et al* showed that SSE could be used for the detection and quantification of liver steatosis (25). However, in this study, SSE was acquired during US exam but calculated off-site. This resulted in invalid measurements in almost one quarter of patients due to poor signal quality. Moreover, this study included patients presenting liver diseases of various etiologies, and NAFLD-patients are not the only one known to present a poor echogenicity. Ronot *et al* also reported limited performances of SSE in the diagnosis of steatosis with AUC of 0.60 (32).

AC uses the same physical principles as cCAP but is performed under B-mode visual control. Several studies demonstrated promising performances, using various devices (19,37). Nevertheless, optimal thresholds values slightly differ among different published studies, probably due to the use of different US scans and different reference standards (biopsy or MRI). A recent meta-analysis (38) explored performances of AC for the detection of any grade steatosis, compiling 11 studies and more than 1400 patients : AUC was 0.83, close to what was assessed in our work.

SSE and AC intra-individual variability with 5 measures per patient was too low to suggest any validity criteria assessing better correlation to PDFF. Using three instead of five measures did not result in significant lower performances. To be noted, even if technical success was high (99 to 100 %) with both cCAP and SSE/ AC, these last tools were the most difficult to tame as they require a stable position, the strict absence of large hepatic vessels or artifacts in the image.

We found no influence of BMI, waist circumference elastography, iron overload or presence of diabetes or metabolic syndrome on the correlation between MRI-PDFF and both HRI, cCAP, AC and SSE. Previous studies reported unsure influence (37,39).

Several scores have also been developed to detect steatosis : ¹⁰ fatty liver index (FLI), hepatic steatosis index (HIS) and NAFLD liver fat score, which combine various clinical and biological parameters (40–42). These algorithms demonstrated modest performances for the detection of steatosis and were inaccurate for the staging of steatosis (43). They do not provide add-on features compared to standard clinical and biological data and are mainly used as epidemiological tools.

One limit of this study is that AC, SSE and HRI were assessed by two different examiners. As both examiners did not perform US liver examinations for all patients, we are unable to report an interobserver comparison or concordance.

Although our sample size is quite small, this work is the first one to prospectively evaluate diagnosis performances of various new generations US tools using MRI as gold standard on an exclusively-NAFLD population. Our study population contained patients with high BMI and weight, with a low fibrosis prevalence and moderate hepatic biological abnormalities, representing NAFLD-patients in real life situations.

These results should be validated in a population with a different prevalence of steatosis and in a multicenter study.

CONCLUSION

Among all ultrasonographic tools evaluated in this study, including new-generation systems such as cCAP and SSE, hepatorenal index had the best performance. It is also the simplest and most available method as most US scans are equipped with this module. The presence of an hyperechogenic liver on US also performed well, confirming that US should remain the first-line screening tool for steatosis.

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ARTICLE HIGHLIGHTS

Research background

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, ranging from simple steatosis to aggressive hepatitis leading to liver fibrosis, cirrhosis and hepatocellular carcinoma.

Research motivation

Diagnose fatty liver disease and assess its severity during follow-up and after treatment is a key in clinical practice. Liver biopsy can deliver this information, but it is an invasive procedure with potentially severe. Therefore, non-invasive techniques were developed to stage steatosis. Ultrasound is the primary imaging modality in the assessment of patients with confirmed or suspected NAFLD.

Research objectives

We wanted to evaluate new ultrasonographic tools to detect and measure hepatic steatosis.

Research methods

105 patients underwent ultrasonographic measurement of liver sound speed estimation (SSE) and attenuation coefficient (AC) using Aixplorer MACH 30 (Supersonic Imagine, France), continuous Controlled Attenuation Parameter (cCAP) using Fibroscan (Echosens, France) and standard liver ultrasound with hepato-renal index (HRI)

¹ calculation. Hepatic steatosis was then classified according to MRI proton density fat fraction (PDFF) as gold standard.

Research results

¹ SSE, AC, cCAP and HRI correlated with PDFF, with respective Spearman correlation coefficient of -0.39, 0.42, 0.54 and 0.59 ($p < 0.01$).

AUROC for detection of steatosis with HRI was 0.91 [0.83-0.99], with the best cut-off value being 1.3 (Se = 83 %, Sp = 98 %). The optimal cCAP threshold of 275 dB/m, corresponding to the recent EASL-suggested threshold, had a sensitivity of 72 % and a specificity of 80 %. Corresponding AUROC was 0.79 [0.66-0.92]. The diagnostic accuracy of cCAP was more reliable when standard deviation was < 15 dB/m with an AUC of 0.91 [0.83-0.98].

An AC threshold of 0.42 dB/cm/MHz had an AUROC was 0.82 [0.70-0.93]. SSE performed moderately with an AUROC of 0.73 [0.62-0.84].

Research conclusions

Hepatorenal index had the best performance. It is also the simplest and most available method as most US scans are equipped with this module.

Research perspectives

Measurement quality criteria need to be defined and validated for a wider use of these techniques. Their improvement could open the way to efficient and easily accessible non-invasive steatosis grading.

7%

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