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THÈSE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en HEPATO-GASTRO-ENTEROLOGIE

Controlled Attenuation Parameter (CAP) validation as a marker of regression in liver steatosis

Validation du Paramètre d'Atténuation Controlée (CAP) comme marqueur de régression de la stéatose hépatique

MOTHE Taiana

Née le 22 juillet 1996 à Paris (XVe)

Sous la direction de Monsieur le Professeur Jérôme BOURSIER

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« Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité. Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité. J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences. Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

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J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque ».

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Liste des abréviations

CAP	Controlled Attenuation Parameter
MASLD	Metabolic dysfunction associated liver disease
PDFF	Proton density fat fraction
MRI	Magnetic resonnance imaging
MASL	Metabolic dysfunction associated steatosis
MASH	Metabolic dysfunction steatohepatitis
FDA	Food and drug administration
EMA	European medicines Agency
EASL	European association for the study of the liver
PPV	Positive predictive value
IQR	Interquartile range
ROC	Receiver operating characteristic
AUROC	Areas under the ROC curve
ROI	Region of interest
BMI	Body mass index
ASAT	Aspartate aminotransferase
ALAT	Alanine aminotransferase
GGT	Gamma-glutamyl transferase
PAL	Alkaline phosphatase
PT	Prothrombin rate
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
HCV	Hepatitis C virus
HBV	Hepatitis B virus
M	Medium
XL	Extra-large
Rs	Spearman's correlation coefficient
CI	Confidence interval
NPV	Negative predictive value
b	Baseline
fu	Follow-up
Fs	Fibroscan
SD	Standard deviation
LSM	Liver stiffness measurement
Δ	Delta

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Controlled Attenuation Parameter (CAP) validation as a marker of regression in liver steatosis

Validation du Paramètre d'Atténuation Contrôlée comme marqueur de régression de la stéatose hépatique

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ABSTRACT

Introduction : Controlled Attenuation Parameter (CAP) is an accessible tools to evaluate liver steatosis, while magnetic resonance imaging proton density fat fraction (MRI-PDFF) is the gold standard. MRI-PDFF response defined as a ≥ 30% relative decline was strongly associated with metabolic steatohepatitis (MASH) resolution without worsening fibrosis. We investigated the performance of CAP in assessing liver steatosis regression, defined as MRI-PDFF response.

Material and methods : This observational retrospective study was performed on patients from the SNIFF cohort in Angers whom underwent two liver MRIs at an interval of at least one year, from June 2013 to October 2022, and coupled with a Fibroscan evaluation with CAP. MRI-PDFF values were obtained by a « simplified » method validated in a preliminary-phase. The correlation between CAP and MRI-PDFF were analyzed. With MRI-PDFF as reference, the performance of CAP to evaluate liver steatosis regression was assessed.

Results : The « simplified » MRI-PDFF measurement method was highly correlated with the reference method (R2 = 0.9654), and applied to all patients in the study. A total of 149 patients were included. Three groups were formed according to MRI-PDFF at baseline (b) and follow-up (fu), steatosis group (bMRI-PDFF > 5%), progressor group (bMRI-PDFF < 5% and fuMRI-PDFF ≥ 5%) and no steatosis group (both MRI-PDFF < 5%). Focusing on steatosis group, there was moderate correlation between CAP and MRI-PDFF variation (Rs = 0.526, p ≤ 0,001). The AUROC of CAP to assess MRI-PDFF response was 0.74 (p = 0.001). We found an optimal threshold of Δ CAP at -8% to identify MRI-PDFF responders with sensitivity, specificity, positive and negative predictive value of 61.1%, 85.2%, 84.6% and 62.2% respectively.

Conclusion : In assessing liver steatosis regression, CAP was moderately correlated with MRI-PDFF.

INTRODUCTION

Metabolic Dysfunction Associated Liver Disease (MASLD) is defined by steatosis in more than 5% of hepatocytes on histology, or by a Proton Density Fat Fraction (PDFF) value > 5.6% measured by magnetic resonance spectroscopy or magnetic resonance imaging (MRI), after excluding secondary causes of steatosis and daily alcohol consumption ≥ 30g in men and ≥ 20g in women [1]. MASLD is the leading cause of chronic liver disease, with a rapidly increasing prevalence estimated at between 20% and 30% of the world's population [2,3]. MASLD includes two entities : liver steatosis isolated or with minimal lobular inflammation (MASL), and non-alcoholic steatohepatitis (MASH) defined by steatosis with lobular inflammation and ballooning of hepatocytes. MASH is present in around 20% of patients with MASLD, and corresponds to the aggressive form of the disease, which favors the appearance of fibrosis in the liver parenchyma, with possible progression to cirrhosis and its complications. The MAESTRO-NASH trial led to Food and Drug Administration (FDA) approval on March 14, 2024 of Resmetirom as the first molecule for the pharmacological treatment of MASH [4]. Many other therapeutic trials are underway, and the two judging criteria retained by the FDA and the European Medicines Agency (EMA) for phase 2b and phase 3 trials are: resolution of MASH without worsening of fibrosis, and improvement of fibrosis (≥ 1 stage) without worsening of MASH. These criteria are histological and therefore require liver biopsy. It is now necessary to identify markers for non-invasive diagnosis of these criteria, because once MASH therapies have been approved for use in clinical practice, it seems difficult to imagine performing a liver biopsy to assess response to treatment, considering the number of patients to be assessed and the invasive nature of the biopsy.

PDFF-MRI is now the gold standard for quantifying liver steatosis. A meta-analysis [5] suggested that a relative decline in liver steatosis ≥ 30% measured by PDFF-MRI ("steatosis response") was strongly associated with resolution of MASH without worsening fibrosis (OR:

5.5; CI 95%: 1.5-19.5), making this decline a good "surrogate marker" of treatment response, which is used in phase 2a studies of MASH therapies. In the MAESTRO-NASH trial, a relative decline ≥ 30% in MRI-PDFF was one of the strongest predictors of histological response to treatment [6]. Nevertheless, MRI remains an expensive technique with limited availability.

Fibroscan is a "point-of-care" device, available in hepato-gastroenterology practices and departments, easy to perform, with immediate results during the consultation. In addition to liver stiffness, which correlates well with the degree of hepatic fibrosis, Fibroscan includes the Controlled Attenuation Parameter (CAP), which measures the attenuation of ultrasound waves in the liver, expressed in dB/m. CAP is measured at the same time as liver stiffness, so does not extend the examination time. A value > 275 dB/m is used by the European Association for the Study of the Liver (EASL) for the detection of steatosis ≥ 5%, with high sensitivity and positive predictive value (PPV) > 90% [7]. The interquartile range (IQR) of CAP reflects its measurement variability, and its accuracy appears to decrease when its IQR exceeds 30 dB/m compared with an IQR < 30 dB/m (respective areas under the ROC curve [AUROC] of 0.92 [0.85-1.00] versus 0.70 [0.56-0.85], p=0.0117) [8]. Two prospective multicenter studies showed that CAP performance was good for the detection of steatosis ≥ 5%, with AUROCs of 0.76-0.87 (9-10). A study demonstrated the positive correlation between CAP and MRI-PDFF for the assessment of liver steatosis (r = 0.577, p < 0.0001) [11]. There are limited studies on the evolution of CAP and its performance in detecting a regression of steatosis.

The aim of this study was to investigate the performance of CAP in assessing steatosis response, compared with PDFF-MRI as the reference method.

MATERIAL AND METHODS

1. Preliminary phase : validation of the "simplified" method to measure MRI-PDFF on a population of 100 patients

The reference method to quantify hepatic steatosis with MRI-PDFF is based on an automated calculation using specialized software. The acquisition of MR images from the patients in our study did not systematically allow us to retrospectively obtain an automated PDFF measurement. It was therefore necessary first to validate a "simplified" method to measure MRI-PDFF from available sequences, which would be sufficiently reliable. The "simplified" method was carried out by an operator trained in digestive imaging, on a population of 100 patients for whom automated reference values were available. The operator was blinded to the reference values. Measurements were carried out by analyzing the signal variation according to different in-phase and out-of-phase echo times, placing three colocalized regions of interest (ROI) in the right liver, each with a minimum surface area of 500 mm^2, avoiding vessels, bile ducts, artifacts and liver lesions. Steatosis was quantified using the formula : (in-phase signal - opposite-phase signal) / 2 x in-phase signal, expressed as a percentage. The three "simplified" PDFF measurements for each MRI were then averaged, and compared with the automated reference value. Once the "simplified" method had been validated, it was applied to all patients in the study.

2. Steatosis response study

2.1. Study population

This retrospective study included patients from the University Hospital of Angers aged over 18 years, taken from the SNIFF database. All patients who underwent two liver MRIs, performed with T1 in-phase and out-of-phase sequences, at an interval of at least one year,

between June 2013 and October 2022 were included. Each MRI should be coupled with a Fibroscan evaluation with CAP measurement, performed within a maximum of three months around the MRI. There were no restrictions on the etiology of liver disease or the clinical indication for hepatic MRI and Fibroscan.

Data collected for each patient within a maximum of three months from each MRI included clinical parameters (age, gender, weight, height, waist circumference, body mass index [BMI], presence of diabetes), biological parameters (aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], gamma-glutamyl transferase [GGT], alkaline phosphatase [PAL], bilirubin, prothrombin rate [PT], platelets, albumin, blood glucose, HbA1c, total cholesterol, High Density Lipoprotein (HDL) cholesterol, Low Density Lipoprotein (LDL) cholesterol, triglycerides, ferritin) and data from non-invasive Fibroscan assessments, with information on the probe used, number of valid measurements, total number of measurements, liver stiffness and its IQR, CAP value and its IQR. The etiology of the hepatopathy leading to Fibroscan (alcohol, chronic hepatitis C [HCV] or B [HBV], MASLD, no hepatopathy, other) and the clinical indication for liver MRIs (liver disease, benign tumor, primary malignancy, secondary malignancy, bilio-pancreatic cause, abdomino-pelvic cause, other) were also collected. Histology was not available for all patients. Each patient signed a consent form for the use of his or her data in the research.

2.2. CAP measurement

CAP measurement was carried out with an M (if BMI < 30 kg/m2) or XL (if BMI ≥ 30 kg/m2) probe from the Fibroscan system (Echosens, Paris, France), at the same time as liver stiffness measurement, as recommended, by an experienced hepatology nurse specialist. For almost all examinations, 10 valid measurements were performed.

2.3. Hepatic MRIs and liver steatosis mapping

All hepatic MRIs were performed on a 1.5 Tesla MR scanner at Angers University Hospital (France). The MRI protocol systematically included in-phase and out-of-phase T1 sequences. MRI-PDFF value was quantified using the "simplified" method for the 149 patients included, on two hepatic MRIs spaced at least one year apart. When available, automated quantification of steatosis and iron was recorded.

3. Statistical analysis

Quantitative variables are expressed as mean with standard deviation or median with IQR. The Kruskal-Wallis test was used to compare the initial characteristics of different groups of patients. Correlations between variables were described using Spearman's correlation coefficient (Rs), by linear regression method. Fisher and Mann-Whitney tests were used to analyze qualitative and quantitative variables. Variations in CAP and MRI-PDFF values were obtained using the formula (follow-up value - baseline value)/baseline value x 100, to obtain a relative variation between the two measures expressed in percentage. The CAP performance in assessing liver steatosis response, defined as a relative decline ≥ 30% in MRI-PDFF, was assessed using the ROC curve. The AUROC and 95% confidence interval (CI) were used as precision indices, while the optimal threshold value for detecting steatosis response using CAP was determined with a maximum sum of sensitivity and specificity (Youden index). Statistical analyses were performed using SPSS version 22.0 software (IBM, Armonk, NY).

RESULTS

1. Preliminary study: validation of the "simplified" method to measure MRI-PDFF

The correlation between the "simplified" method to measure MRI-PDFF and the automated reference method showed strong agreement, with a linear regression equation Y = 0.7543x + 0.7284 and a coefficient of determination R^2 = 0.9654 (Figure 1).

2. Steatosis response study

2.1. Patients

A total of 149 patients (47 women and 102 men) were included in the study, with a mean age of 59 years. The initial characteristics of the patients are detailed in Table I. At baseline, 37.6% of patients were diabetic, mean body mass index (BMI) was 28.9 kg/m2, mean baseline MRI-PDFF (bMRI-PDFF) and baseline CAP (bCAP) values were 7.7% and 278 dB/m respectively, mean CAP IQR was 38.4 dB/m, mean liver stiffness was 20 kPa. Etiologies of liver disease included 25.5% alcoholic liver disease, 27.5% MASLD, 22.1% viral etiology, and 24.8% other causes. The mean interval between the two MRIs-PDFF was 1116 days, and between two Fibroscan 1165 days.

Three groups were considered : group 1 (steatosis group, n=63) included patients with a bMRI-PDFF ≥ 5%, group 2 (progressors, n=16) patients with a bMRI-PDFF < 5% but a value ≥ 5% at follow-up MRI-PDFF (fuMRI-PDFF), and group 3 (no-steatosis group, n=70) patients with a value < 5% at both MRI-PDFFs.

2.2. Definition of responder and non-responder patients on MRI-PDFF

We were particularly interested in the steatosis group (bMRI-PDFF > 5%, n=63), in order to be able to demonstrate steatosis response on fuMRI-PDFF. In this group, 50.8% of patients were diabetic, with mean bMRI-PDFF values of 16.9%, mean bCAP of 318 dB/m, mean baseline IQR CAP of 33.8 dB/m and mean baseline liver stiffness of 16.8 kPa.

Patients in the steatosis group were divided into two subgroups after fuMRI-PDFF: fuMRI-PDFF responders (n=36), defined by a relative decrease in steatosis at fuMRI-PDFF ≥ 30%, and fuMRI-PDFF non-responders (n=27) defined by a relative decline in liver steatosis < 30% (Table II).

3. CAP diagnostic performance in liver steatosis response

3.1. Correlation between CAP and MRI-PDFF

The correlation between bCAP and bMRI-PDFF values was low (n=63, Rs = 0.380, p = 0.002) (Figure 2). The correlation between fuCAP and fuMRI-PDFF values was strong (n=63, Rs = 0.623, $p \leq 0.001$) (Figure 3). There was a moderate correlation between changes in CAP (ΔCAP) and MRI-PDFF (Δ MRI-PDFF) values during follow-up (n=63 , Rs = 0.526, $p \leq 0.001$) (Figure 4). Nevertheless, in MRI-PDFF responders patients, with a median Δ MRI-PDFF value of -60.6 [-83.0 to- 38.4], there was a trend towards a decrease in Δ CAP with a median value of -10.9% [-20.2 to -0.7] (Figure 5).

3.2. Optimal treshold of CAP for assessing liver steatosis response

The AUROC of CAP for assessing liver steatosis response (MRI-PDFF responder: Δ MRI-PDFF relative decline ≥ 30%) was 0.74 (p = 0,001) (Figure 6). The optimal threshold of Δ CAP to correctly identify MRI-PDFF responders was ≤ - 8% (define CAP regressor), and the sensitivity, specificity, PPV, and NPV were 61,1%, 85,2%, 84,6%, and 62,2%, respectively.

4. Comparative group analysis

4.1. Steatosis group

In the steatosis group (n=63), baseline characteristics of patients with significant difference between responders and non-responders MRI-PDFF were ASAT, ALAT, GGT and bilirubin. Data analysis revealed a median (IQR) bCAP value at 320 dB/m (65), and a median (IQR) fuCAP value at 314 dB/m (67). Figure 7 shows the individual variation in CAP values among these patients, which was heterogeneous. Among MRI-PDFF responders patients (n=36), 22 patients were also CAP regressors (Δ CAP ≤ -8%) and 14 patients were CAP non-regressors (Δ CAP > -8%). Among MRI-PDFF non-responders (n=27), 23 patients were non-regressors CAP and 4 showed CAP regression.

4.2. Progressor group

In the progressor group (n=16) with bIRM-PDFF < 5%, data analysis showed a median (IQR) bCAP value of 261 dB/m (126). After the onset of steatosis > 5% at fuIRM-PDFF, the median (IQR) fuCAP value also increased to 330 dB/m (48) (Figure 8A). Figure 8B shows the individual variation in CAP values in these patients, with almost all patients having a fuCAP > 275 dB/m. Of these 16 patients, 7 had a bCAP > 275dB/m and 1 had a fuCAP < 275 dB/m and were therefore misclassified by CAP.

4.3. No steatosis group

In the no-steatosis group (n = 70) with both MRI-PDFF < 5%, data analysis found a median (IQR) value of bCAP and fuCAP at 247 dB/m (70) and 248 dB/m (82.75) respectively (Figure 9A). Figure 9B shows the individual variation in CAP values among these patients, which was heterogeneous. Of these 70 patients, 17 had a bCAP > 275 dB/m and 23 a fuCAP > 275dB/m, and were therefore misclassified by CAP.

DISCUSSION

This retrospective study conducted on a cohort of patients at the University Hospital of Angers showed that CAP performed moderately to assess liver steatosis regression or response defined by a relative decline ≥ 30% on PDFF-MRI, with an AUROC of 0.74 (p = 0.001) for a CAP relative variation threshold of -8%, with sensitivity, specificity, PPV and NPV of 61.1%, 85.2%, 84.6% and 62.2% respectively.

The use of a "simplified" method to measure MRI-PDFF was initially validated by showing high agreement with the automated reference method (R^2 = 0.9654). This ensured that the method could be used reliably, and was then applied to all 149 patients included in our study.

Patients were classified into three groups according to the amount of steatosis measured by bMRI-PDFF : steatosis group (patients with a bMRI-PDFF ≥ 5%), progressors group (bMRI-PDFF < 5% and fuMRI-PDFF ≥ 5%) and no steatosis group (two MRI-PDFF < 5%).

The study population included a variety of hepatopathy etiologies (ALD, MASLD, viral causes, others) as well as patients with no hepatopathy, with a higher prevalence of diabetes and obesity in the steatosis group. These comorbidities are well-known factors in the progression of liver steatosis, confirming trends observed in the literature. It should also be noted that the study population had a high mean liver stiffness of 20 kPa, reflecting a significant stage of fibrosis in a proportion of patients, which could potentially influence the interpretation of CAP measurements, as has been discussed in the literature [12]. Patients were included in this study only on the basis of the availability of two MRIs minimum one year appart and two CAPs performed within a three-month period. No selection was made on the basis of the etiology of the liver disease or the indication for MRI, the latter sometimes being performed as part of lesion assessments, or in patients with no steatosis. The selection of the CAP probe

was adapted to the patients' BMI, with the use of an M probe for patients with a BMI of less than 30 kg/m², and an XL probe for those with a BMI of 30 kg/m² or more.

In the steatosis group, 14 patients classified as MRI-PDFF responders showed no concomitant CAP regression defined by an 8% decrease in its value (false-negative CAP), and 4 patients classified as MRI-PDFF non responders showed CAP regression (false-positive CAP). In order to explore the factors likely to influence these divergences, several characteristics were analyzed in the misclassified patients. Among the 14 patients CAP false negatives, 10 had a bIMC > 30 kg/m2, 6 were diabetics, 4 had a liver tumor identified at bMRI-PDFF, 9 had a CAP IQR ≥ 30 dB/m at baseline and 4 at follow-up, mean liver stiffness was 16 kPa and 19.9 kPa at baseline and follow-up. Among the CAP false positives, all were diabetics, with high BMI > 30 kg/m2, high CAP values (mean bCAP at 365 dB/m and mean fuCAP at 296 dB/m), mean liver stiffness was 17.8 kPa and 16.8 kPa at baseline and follow-up. These divergences between CAP and fuCAP-MRI values could be influenced by the presence of diabetes, obesity, advanced hepatic fibrosis and a CAP IQR ≥ 30 dB/m, which have been identified in several studies as factors that may affect CAP accuracy [8,12-14]. A study identified high histological grade of steatosis and high CAP values as factors decreasing the diagnostic performance of CAP, and the influence of ALAT levels and inflammation on CAP values appeared negligible [13]. In a recent meta-analysis based on individual data and including 2346 patients, CAP values were influenced by etiology, diabetes, BMI, gender and ASAT [15]. Iron is a paramagnetic substance, high levels in the liver are known to limit the quantification of liver steatosis on MRI, due to the signal decrease involved [16]. We did not have hepatic MRI iron quantification for all patients, but ferritinemia levels were not particularly high in the patients misclassified by CAP in our study, and therefore did not appear to explain the discrepancies in values found between CAP and PDFF-MRI.

In the progressor group on PDFF-MRI, the results show an increase in CAP values with increasing PDFF-MRI steatosis values. These results may suggest that CAP can be used to monitor liver steatosis progression.

Few studies have investigated longitudinal changes in liver steatosis assessed by CAP and hepatic MRI-PDFF. A similar study by Wang & al. which included 45 patients with liver steatosis with 2 MRI-PDFFs performed on average 399 days apart, with CAP associated with each MRI, found that CAP was useful for estimating changes in liver steatosis, with variation in CAP value correlated with variation in MRI-PDFF (r = 0.493, p = 0.001) [17]. Our study found a better correlation (r = 0.526, p = 0.000) with a larger number of patients. Another similar study by the same author included 75 patients with MASLD to evaluate usefulness of CAP in monitoring MRI-PDFF decline of ≥ 30%, assessed with AUROC, the performance of ΔCAP in the prediction of the outcome was 0.808 (95% CI : 0.675-0.940) using ΔCAP value relative to baseline, while the ΔCAP cutoff was -15% with sensitivity, specificity, PPV and NPV at 46.2%, 90.3%, 50.0% and 88.9% respectively [18].

Stine's meta-analysis [5] suggested that a relative decline ≥ 30% in MRI-PDFF was strongly associated with resolution of MASH without worsening fibrosis. However, it may be speculated that not all patients with just slightly more than 30% regression of steatosis on MRI-PDFF may have resolution of MASH. In our study, we might suggest that CAP may misclassify patients with weak regression on MRI-PDFF, but remains effective in detecting significant regressors on MRI-PDFF.

The main limitations of our study lie in its monocentric and retrospective nature, in the absence of histological data available for all patients, as well as in the absence of selection of patients according to the etiology of the liver disease, the indication for performing MRI or Fibroscan, and the presence of initial hepatic steatosis. Furthermore, the presence of hepatic lesions, although the measurements were taken in the extra-tumoral area on MRI-PDFF,

could affect CAP values by Fibroscan, possibly affecting the reliability of the measurements of steatosis and hepatic fibrosis in some cases. These limitations highlight the need for future prospective studies with more rigorous patient selection for a more precise assessment of the performance of CAP in assessing the regression of liver steatosis.

In conclusion, these results suggest that CAP presents a moderate performance in assessing the regression of liver steatosis compared to MRI-PDFF, despite several biases and particularly the unselective inclusion criteria for patients in this study. CAP interpretation should be carried out with caution, particularly in the presence of factors that may affect its accuracy such as diabetes, BMI, advanced liver fibrosis and the IQR of the CAP ≥ 30 dB/m. CAP remains a promising tool for the assessment of liver steatosis due to its accessibility and low cost, however, it will be necessary to conduct future studies with less bias to better understand its ability to assess the regression of liver steatosis.

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Table I. Initial characteristics and comparison of 3 groups : group 1 = steatosis group (bMRI-PDFF > 5%), group 2 = progressors (bMRI-PDFF< 5% and fuMRI-PDFF > 5%) and group 3 = no steatosis (bMRI-PDFF and fuMRI-PDFF < 5%). p value determined by comparing characteristics of patients of three groups, using the Kruskal-Wallis test. $p < 0.05$ is considered significant.

Abbreviations: b for baseline; fu for follow-up. MRI-PDFF, magnetic resonance imaging–proton-density fat fraction; BMI, body mass index; MASLD, metabolic dysfunction-associated steatotic liver disease; FS, fibroscan; LSM, liver stiffness measurement; IQR, interquartile range, CAP, controlled attenuation parameter; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; PAL, alkaline phosphatase; PT, prothrombin time; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein.

Variable (unit)	Total population (n=149) Mean ± standard deviation (SD) Median [quartile]	Group 1 : steatosis (n=63)	Group 2 : progressors (n=16)	Group 3 : no steatosis (n=70)	*p*
Age (years)	59.1 ±12.3 61.5 [53.0-67.6]	59.4 ±10.2 61.3 [52.8-66.2]	64.2 ±8.1 63.5 [59.2-72.1]	57.7 ±14.4 60.8 [51.1-68.2]	0.344
Women (%)	31.5	38.1	12.5	30.0	-
Diabetics (%)	37.6	50.8	37.5	25.7	-
Weight (Kg)	80.9 ±16.8 79.0 [70.5-89.0]	87.6 ±18.2 85.0 [72.0-99.0]	86.3 ±9.0 84.5 [80.0-96.3]	73.5 ±13.7 72.0 [63.0-82.5]	0.000
Height (cm)	167.2 ±8.1 167.0 [161.0-174.0]	167.4 ±8.3 166.5 [161.0-174.0]	168.3 ±5.4 167.5 [164.3-173.1]	166.9 ±8.5 167.0 [160.0-173.3]	0.715
Waist size (cm)	103.5 ±14.5 103.0 [93.5-113.3]	109.5 ±14.1 109.0 [100.0-121.0]	109.7 ±7.3 108.0 [104.0-114.8]	96.8 ±13.2 98.0 [88.0-105.0]	0.000
bBMI (kg/m^2)	28.9 ± 5.5 28.6 [25.3-31.4]	31.2 ± 5.8 30.5 [27.2-35.2]	30.5 ± 3.2 30.9 [28.8-31.2]	26.4 ± 4.6 26.2 [22.8-29.5]	0.000
Etiology (%) Alcohol Virus MASLD Others	 25.5 22.1 27.5 24.8	 20.6 17.5 50.8 11.1	 43.8 18.8 31.3 6.3	 25.7 27.1 5.7 41.4	-

bFS probe M (%)	76.5	65.1	75.0	87.1	-
bFS total measures	14.6 ±9.8 10.0 [10.0-14.0]	12.9 ±6.8 10.0 [10.0-13.0]	15.3 ±11.4 10.0 [10.0-13.8]	16.0 ±11.4 10.0 [10.0-19.0]	0.292
bLSM (kPa)	20.0 ±17.8 13.8 [8.3-24.5]	16.8 ±14.8 11.3 [8.2-20.9]	29.3 ±21.2 21.9 [14.2-47.8]	20.8 ±18.8 14.2 [7.9-25.0]	0.041
bIQR LSM (kPa)	3.3 ±3.8 2.2 [1.1-4.4]	3.0 ±2.7 2.1 [1.0-4.3]	5.9 ±8.4 3.2 [1.2-6.5]	3.0 ±2.7 2.3 [1.2-4.2]	0.481
bCAP (dB/min)	278 ±68 278 [230-331]	318 ±48 320 [290-355]	269 ±78 261 [219-345]	244 ±62 247 [206-276]	0.000
bIQR CAP (dB/min)	38.4±24.8 32.0 [22.0-50.5]	33.8±17.0 30.0 [21.0-46.0]	41.4±22.2 34.5 [24.3-62.0]	41.2±30.2 34.0 [22.0-51.3]	0.367
bMRI-PDFF (%)	7.7 ±10.3 2.9 [0.0-13.2]	16.9 ±10.0 14.3 [8.0-22.7]	2.3 ±1.74 2.9 [0.1-3.8]	0.6 ±1.2 0.0 [0.0-0.6]	0.000
bASAT (UI/L)	50 ±39 40 [30-56]	61 ±53 50 [34-70]	40 ±12 41 [30-46]	42 ±24 34 [29-47]	0.003
bALAT (UI/L)	51 ±32 40 [27-64]	65 ±46 54 [34-81]	33 ±16 32 [21-38]	43 ±33 35 [24-49]	0.000
bGGT (UI/L)	183 ±264 104 [60-215]	219 ±345 124 [71-272]	150 ±96 124 [77-190]	160 ±202 92 [45-203]	0.099
bPAL (UI/L)	116 ±66 96 [77-132]	104 ±43 92 [78-123]	116 ±59 101 [72-138]	126 ±82 97 [76-141]	0.491
bBilirubin (µmol/L)	16 ±11 13 [9-19]	15 ±13 13 [9-17]	16 ±10 13 [9-18]	16 ±13 13 [9-20]	0.706
bAlbumin (g/L)	41.3 ±4.9 42.0 [38.3-44.5]	42.1 ±4.5 43.0 [40.0-45.0]	39.5 ±5.6 40.5 [35.8-43.0]	41 ±5 41 [38-44]	0.111
bPT (%)	86 ±21 90 [76-100]	88 ±18 91 [79-99]	74 ±26 81 [64-96]	86 ±22 91 [76-102]	0.143
bPlatelets (G/L)	178 ±72 171 [134-217]	179 ±54 170 [143-209]	142 ±50 147 [119-163]	186 ±86 186 [123-245]	0.060
bBlood sugar (mmol/L)	6.9 ±2.6 6.3 [5.1-8.2]	7.5 ±2.7 6.6 [6.0-8.9]	7.3 ±1.8 7.3 [5.5-9.0]	6.1 ±2.4 5.2 [4.9-6.6]	0.001
bHbA1c (%)	6.6 ±1.4 6.2 [5.7-7.2]	6.8 ±1.4 6.4 [5.8-7.6]	6.5 ±1.0 6.5 [5.4-7.3]	6.2 ±1.6 6.0 [5.3-6.6]	0.138

bCholesterol (mmol/L)	4.49 ±1.27 4.60 [3.53-5.25]	4.43 ±1.39 4.60 [3.50-5.45]	4.49 ±1.50 4.20 [3.10-5.95]	4.57 ±1.07 4.55 [3.61-4.93]	0.992
bHDL cholesterol (mmol/L)	1.18 ±0.41 1.12 [0.91-1.46]	1.15 ±0.43 1.10 [0.89-1.45]	1.02 ±0.30 1.03 [0.90-1.23]	1.29 ±0.39 1.20 [0.95-1.52]	0.247
bTriglycerides (mmol/L)	1.58 ±1.15 1.31 [0.98-1.80]	1.81 ±1.45 1.50 [1.19-1.92]	1.56 ±0.85 1.33 [0.96-1.96]	1.29 ±0.62 1.11 [0.83-1.60]	0.042
bFerritin (µg/L)	299 ±357 193 [81-352]	411 ±404 262 [136-498]	136 ±143 82 [26-212]	215 ±301 128 [57-237]	0.000
Δ MRI-PDFF (%)	46.3 ±238.2	-19.7 ±65.4 -32.5 [-65.3-6.6]	295.8 ±446.9 194.9 [21.6-246]	48.7 ±236.7 0.0 [0.0-0.0]	0.000
Δ CAP (%)	4.5 ±30.3	-3.2 ±19.4 -3.3 [-14.7-9.0]	33.1 ±49.9 26.8 [-0.3-65.9]	5.0 ±29.0 -2.2 [-16.4-21.6]	0.011

Table II. Baseline characteristics of patients in group 1: steatosis group (bMRI-PDFF > 5%). Non-responders MRI-PDFF = relative decline in liver steatosis at fuMRI-PDFF < 30%; responders MRI-PDFF = relative decline in steatosis at fuMRI-PDFF ≥ 30%. $p < 0.05$ is considered significant.

Abbreviations: b for baseline; fu for follow-up. MRI-PDFF, magnetic resonance imaging–proton-density fat fraction; BMI, body mass index; MASLD, metabolic dysfunction-associated steatotic liver disease; FS, fibroscan; LSM, liver stiffness measurement; IQR, interquartile range; CAP, controlled attenuation parameter; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; PAL, alkaline phosphatase; PT, prothrombin time; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein.

Variable (unit)	Group 1 : steatosis (n=63) Mean ± SD Median [quartile]	Non-responders MRI-PDFF (n=27)	Responders MRI-PDFF (n=36)	*p*
Age (years)	59.4 ±10.2 61.3 [52.8-66.2]	59.5 ±10.0 61.1 [52.1-67.5]	59.3 ±10.5 61.4 [53.2-65.9]	0.890
Women (%)	38.1	37.0	38.9	1.000
Diabetics (%)	50.8	51.9	50.0	1.000
Weight (Kg)	87.6 ±18.2 85.0 [72.0-99.0]	87.5 ±17.6 87.0 [75.0-99.0]	87.8 ±18.9 84.5 [75.0-103.8]	0.923
Height (cm)	167.4 ±8.3	167.7 ±9.1	167.1 ±7.7	0.749

	166.5 [161.0-174.0]	168.0 [160.5-175.0]	165.0 [162.3-172.5]	
Waist size (cm)	109.5 ±14.1 109.0 [100.0-121.0]	110.4 ±12.3 110.0 [102.0-119.0]	108.8 ±15.5 105.0 [98.0-121.4]	0.578
bBMI (kg/m^2)	31.2 ± 5.8 30.5 [27.2-35.2]	31.0 ± 5.6 30.5 [27.9-33.8]	31.4 ± 6.0 30.6 [26.5-36.0]	0.840
Etiology (%) Alcohol Virus MASLD Others	 20.6 17.5 50.8 11.1	 22.2 18.5 44.4 14.8	 19.4 16.7 55.6 8.3	-
bFS probe M (%)	65.1	66.7	63.9	1.000
bFS total measures	12.9 ±6.8 10.0 [10.0-13.0]	14.3 ±9.5 10.0 [10.0-13.0]	11.8 ±3.3 10.0 [10.0-12.0]	0.994
bLSM(kPa)	16.8 ±14.8 11.3 [8.2-20.9]	13.6 ±10.9 9.7 [7.3-18.1]	19.2 ±16.9 14.1 [9.3-23.0]	0.074
bIQR LSM (kPa)	3.0 ±2.7 2.1 [1.0-4.3]	2.7 ±2.3 1.7 [1.0-3.7]	3.3 ±2.9 2.5 [1.0-4.5]	0.622
bCAP (dB/min)	318 ±48 320 [290-355]	314 ±44 321 [282-346]	322 ±50 320 [298-363]	0.479
bIQR CAP (dB/min)	33.8±17.0 30.0 [21.0-46.0]	34.3±16.4 28.0 [22.0-45.0]	33.4±17.6 31.0 [20.3-52.3]	0.900
bMRI-PDFF (%)	16.9 ±10.0 14.3 [8.0-22.7]	15.5 ±9.6 13.7 [8.0-18.6]	18.0 ±10.2 15.8 [8.0-26.8]	0.338
bASAT (UI/L)	61 ±53 50 [34-70]	46 ±26 42 [27-66]	74 ±65 53 [42-72]	0.030
bALAT (UI/L)	65 ±46 54 [34-81]	54 ±37 42 [28-74]	74 ±51 63 [44-84]	0.027
bGGT (UI/L)	219 ±345 124 [71-272]	137 ±117 89 [53-209]	284 ±441 166 [88-285]	0.031
bPAL (UI/L)	104 ±43 92 [78-123]	94 ±30 93 [66-116]	112 ±50 92 [79-131]	0.310
bBilirubin (µmol/L)	15 ±13 13 [9-17]	12 ±5 11 [7-14]	18 ±16 13 [10-22]	0.041

bAlbumin (g/L)	42.1 ±4.5 43.0 [40.0-45.0]	43 ±4 42 [40-46]	41.5 ±4.8 43.0 [39.5-45.0]	0.608
bPT (%)	88 ±18 91 [79-99]	89 ±17 92 [80-99]	87 ±18 90 [78-99]	0.692
bPlatelets (g/L)	179 ±54 170 [143-209]	178 ±47 191 [141-211]	180 ±60 166 [149-209]	0.823
bBlood sugar (mmol/L)	7.5 ±2.7 6.6 [6.0-8.9]	7.0 ±2.5 6.3 [5.3-8.3]	8.0 ±2.8 6.7 [6.2-10.5]	0.128
bHbA1c (%)	6.8 ±1.4 6.4 [5.8-7.6]	6.6 ±1.3 6.0 [5.7-7.4]	6.9 ±1.4 6.7 [5.8-7.6]	0.422
bCholesterol (mmol/L)	4.43 ±1.39 4.60 [3.50-5.45]	3.93 ±1.57 4.20 [2.70-5.00]	4.80 ±1.14 4.70 [3.60-5.55]	0.085
bHDL cholesterol (mmol/L)	1.15 ±0.43 1.10 [0.89-1.45]	1.08 ±0.52 1.13 [0.59-1.40]	1.20 ±0.35 1.05 [0.90-1.52]	0.250
bTriglycerides (mmol/L)	1.81 ±1.45 1.50 [1.19-1.92]	1.41 ±0.53 1.43 [1.19-1.61]	2.10 ±1.81 1.68 [1.18-2.22]	0.121
bFerritin (µg/L)	411 ±404 262 [136-498]	361 ±381 232 [84-531]	446 ±423 297 [183-512]	0.250
Δ MRI-PDFF (%)	-19.7 ±65.4 -32.5 [-65.3-6.6]	36.1 ±60.5 14.3 [-2.3-54.5]	-63.5 ±25.5 -60.6 [-83.0—38.4]	0.000
Δ CAP (%)	-3.2 ±19.4 -3.3 [-14.7-9.0]	6.0 ±16.1 5.1 [-5.1-18.4]	-10.2 ±19.0 -10.9 [-20.1-0.7]	0.001

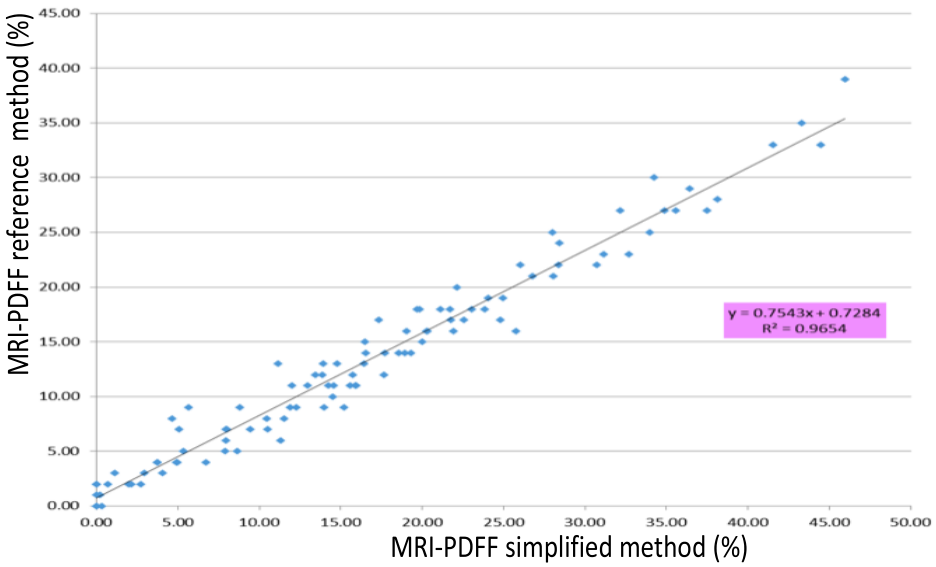


Figure 1. Preliminary study : correlation between MRI-PDFF values measured by the "simplified" method (in %) and the automated reference method (in %) on a population with an available MRI-PDFF evaluated by the reference method (n=100).

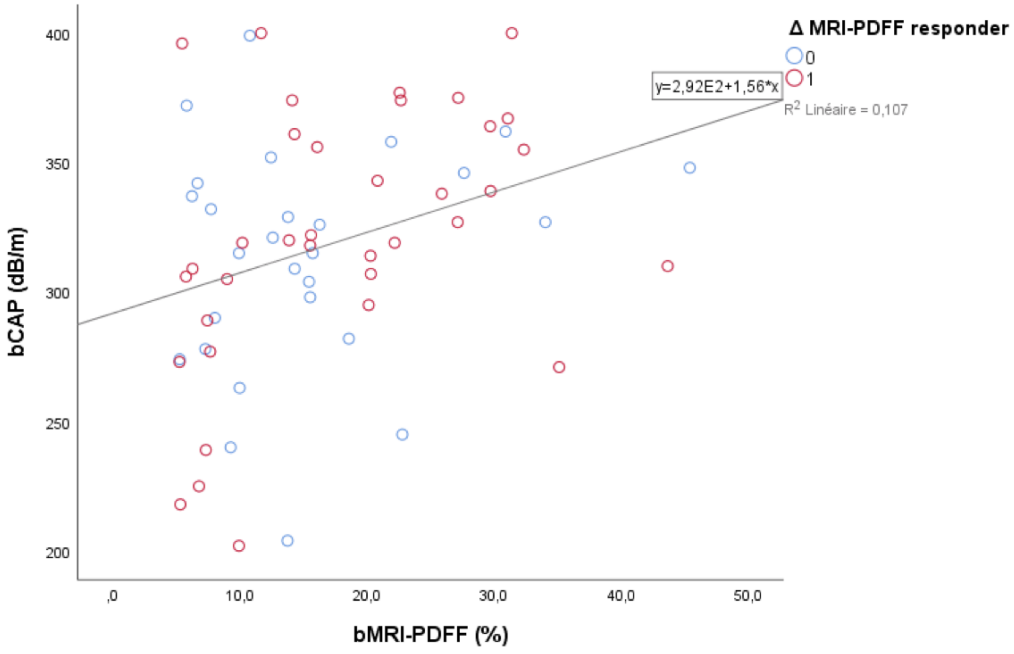


Figure 2. Correlation between bMRI-PDFF (%) and bCAP (dB/m) values in steatosis group. Rs = 0.380 (p = 0.002). 0, non-responders patient : relative decline in liver steatosis at fuMRI-PDFF < 30%; 1, responders patient : relative decline in liver steatosis at fuMRI-PDFF ≥ 30%. Abbreviations : CAP, controlled attenuated parameter; MRI-PDFF, magnetic resonance imaging–proton density fat fraction.

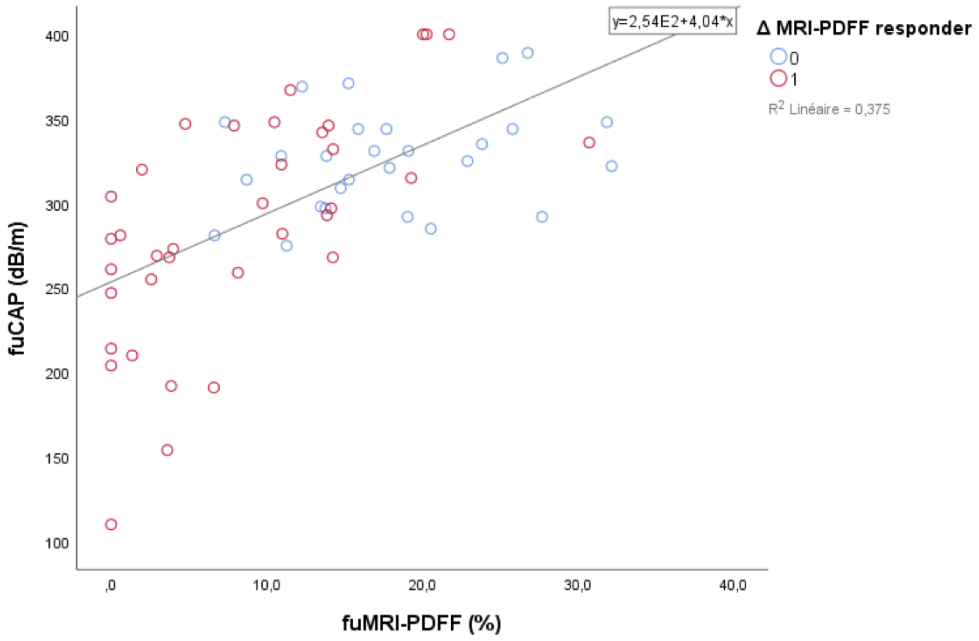


Figure 3. Correlation between fuMRI-PDFF (in %) and fuCAP (in dB/m) values in steatosis group. Rs = 0.623 ($p \leq 0.001$). 0, non-responder patient; 1, responder patient.

Abbreviations : CAP, controlled attenuated parameter; MRI-PDFF, magnetic resonance imaging–proton density fat fraction.

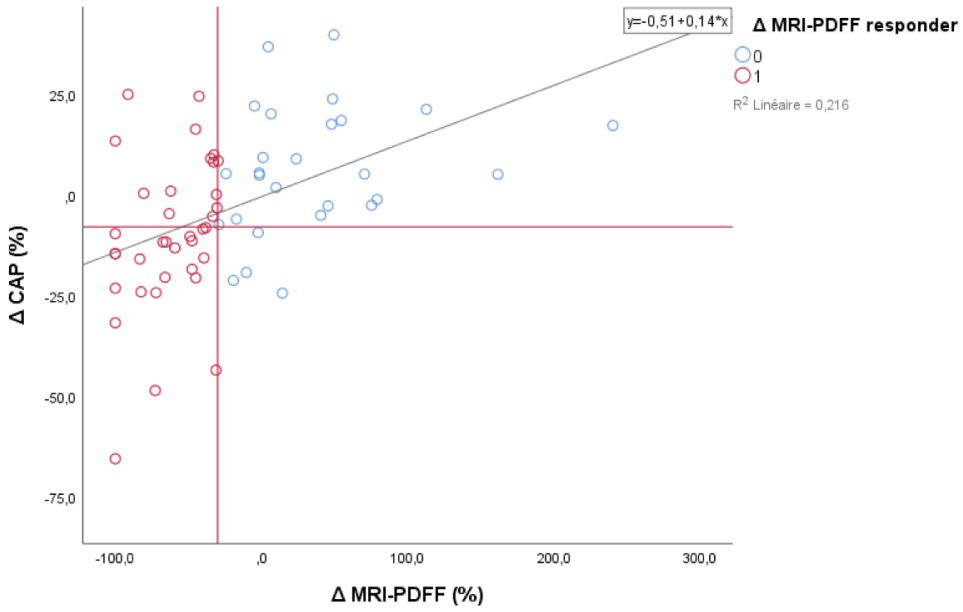


Figure 4. Correlation between Δ MRI-PDFF (%) and ΔCAP (%) relative values in steatosis group. Rs = 0.526 ($p \leq 0.001$). 0, non-responder patient; 1, responder patient. Red line for ΔCAP indicates a relative variation of -8% and for ΔMRI-PDFF indicates a relative variation of -30%

Abbreviations : CAP, controlled attenuated parameter; MRI-PDFF, magnetic resonance imaging–proton density fat fraction.

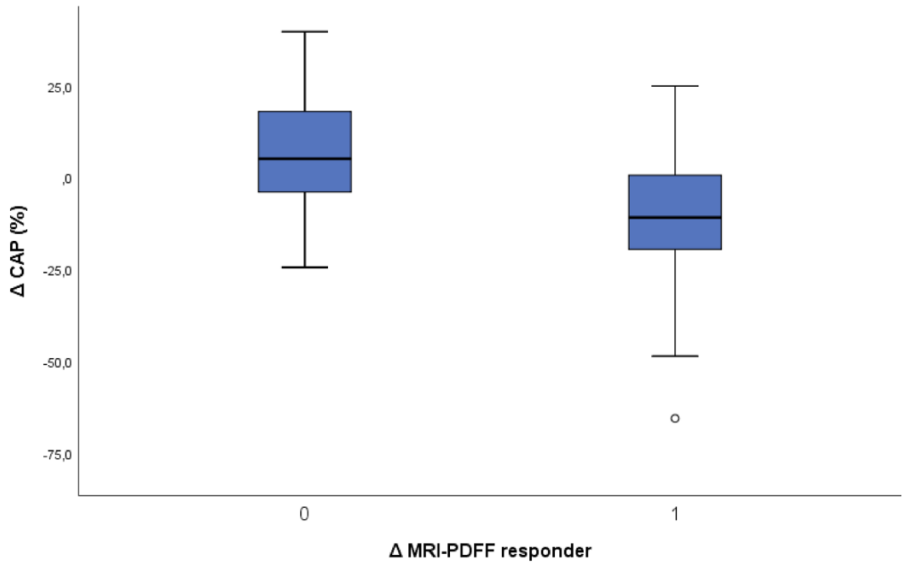


Figure 5. Boxplot of Δ CAP according to MRI-PDFF responder.

0, Δ MRI-PDFF non-responder, relative decline in liver steatosis at fuMRI-PDFF < 30%, n = 27;

1, Δ MRI-PDFF responder, relative decline in liver steatosis at fuMRI-PDFF ≥ 30%, n = 36.

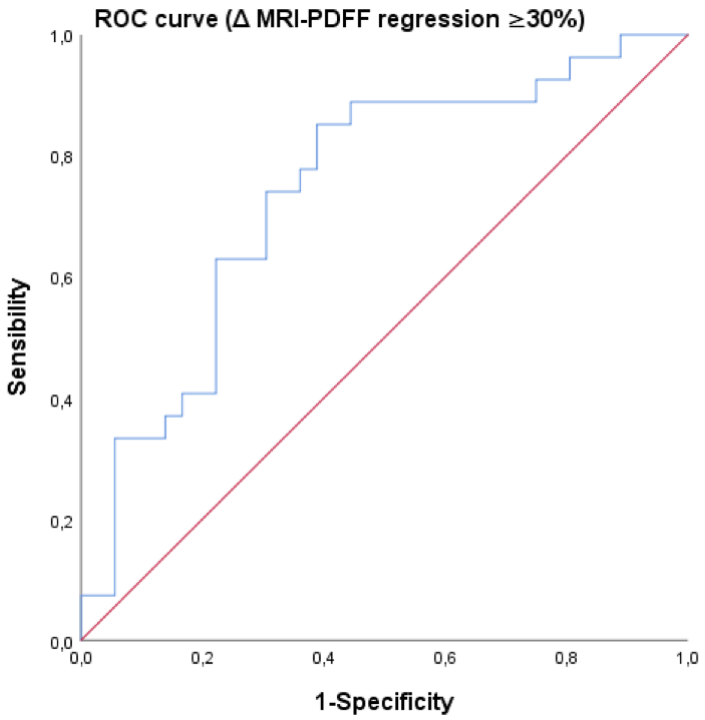


Figure 6. Diagnostic accuracy of Δ CAP for the assessment of liver steatosis response (determined by a relative decline at fuMRI-PDFF ≥ 30%) in steatosis group. ROC curve of Δ CAP for detection of liver steatosis response. AUROC = 0.74 (p = 0.001) for a cut-off at -8%.

AUROC, area under the receiver operating characteristic; CAP, controlled attenuated parameter.

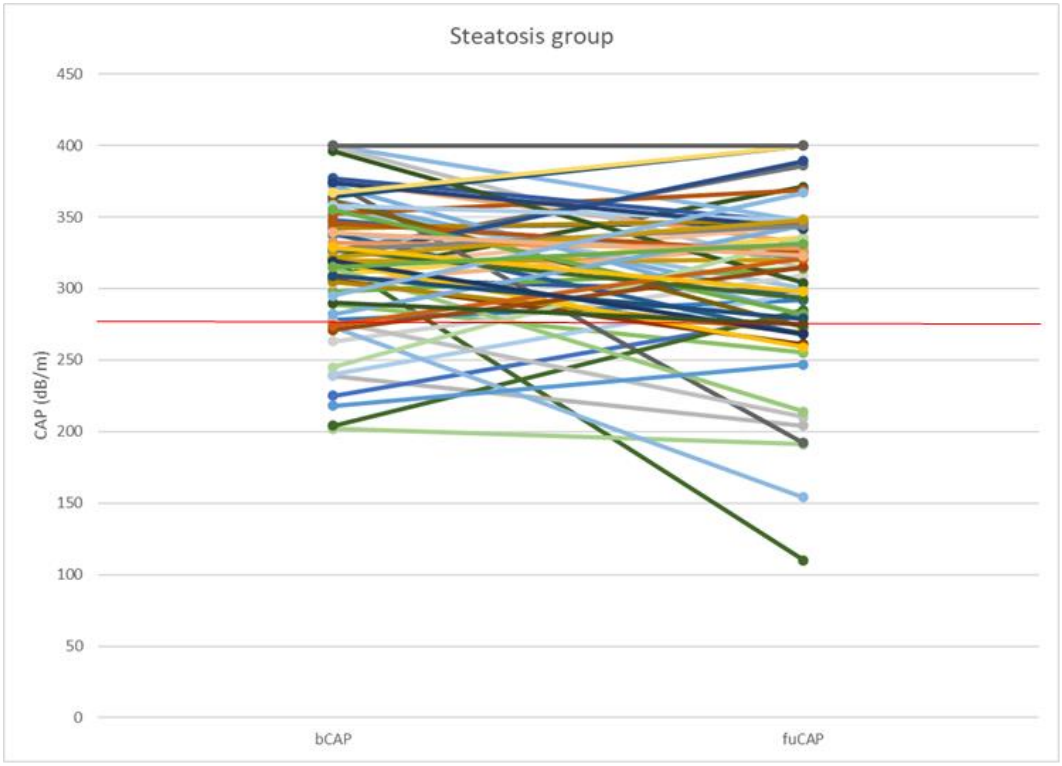


Figure 7. Individual variability of CAP values in patients in the steatosis group (n=65).

Red line: CAP value of 275 dB/m used as threshold for liver steatosis.

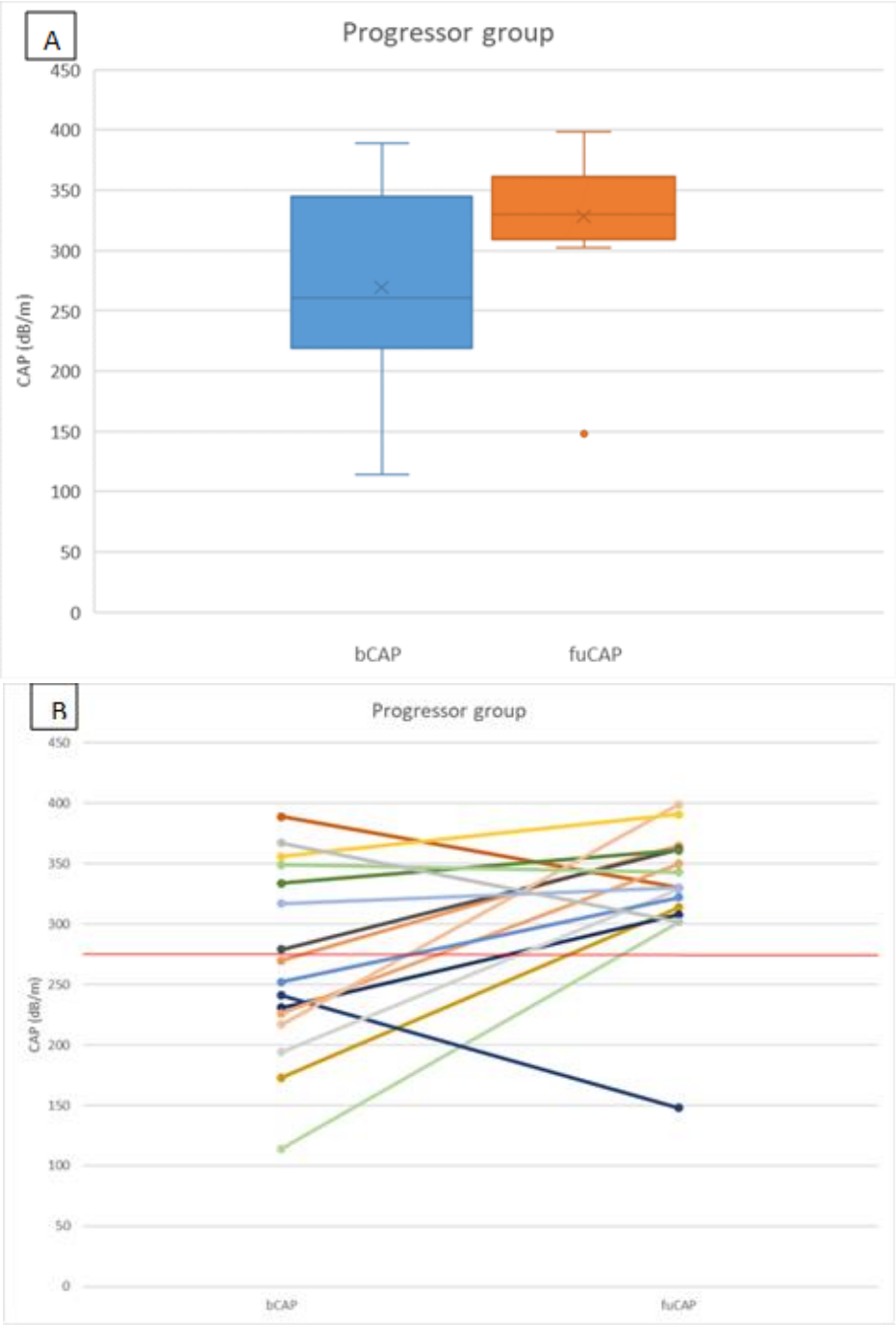
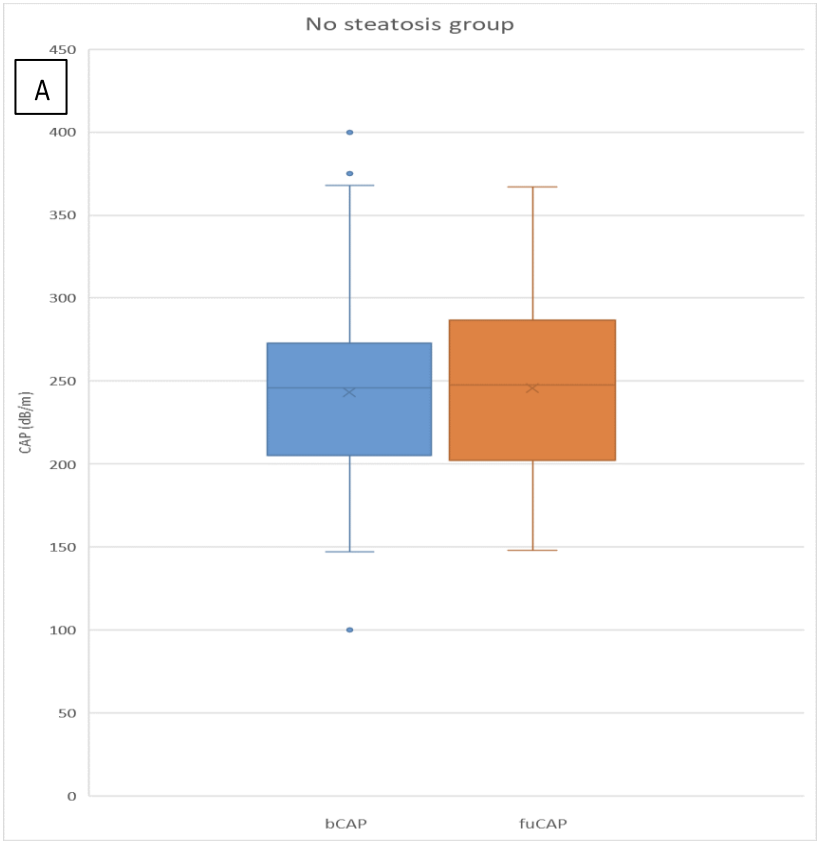


Figure 8. Progressor group (n=16) A. Boxplot of bCAP and fuCAP values. B . Individual variability of CAP values.

Red line : CAP value of 275 dB/m used as threshold for liver steatosis.



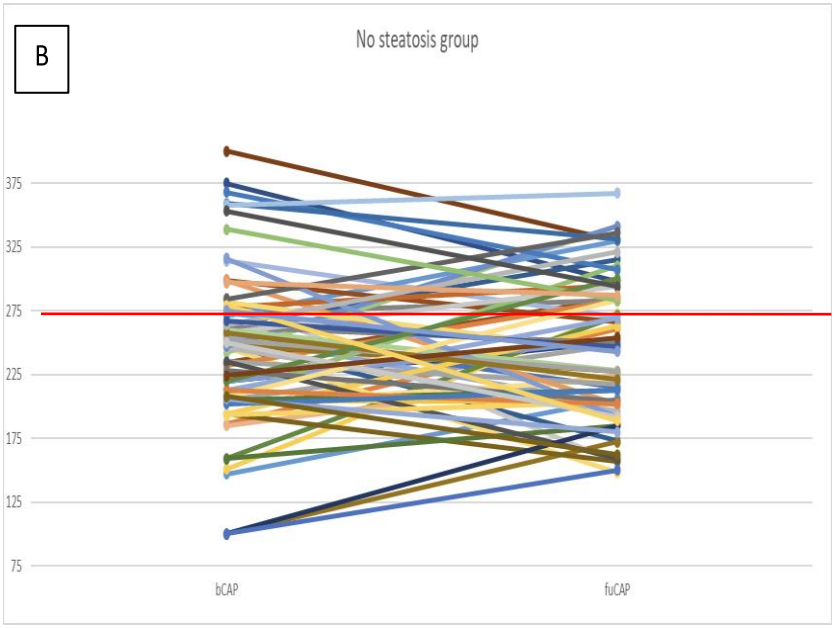


Figure 9. No steatosis group (n=70). A. Boxplot of bCAP and fuCAP values. B. Individual variability of CAP values. Red line: CAP value of 275 dB/m used as threshold for liver steatosis.

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MOTHE Taiana

Validation du Paramètre d'Atténuation Contrôlée (CAP) comme marqueur de régression de la stéatose hépatique

RÉSUMÉ

Introduction
Le paramètre d'atténuation contrôlée (CAP) est un outil accessible pour évaluer la stéatose hépatique, tandis que la teneur hépatique en graisse mesurée par IRM-PDFF est la référence. La réponse à l'IRM-PDFF, définie comme une diminution relative ≥ 30 %, a montré une forte association avec la résolution de la stéatohépatite métabolique (MASH) sans aggravation de la fibrose. Nous avons étudié la performance du CAP dans l'évaluation de la régression de la stéatose hépatique, définie par une réponse à l'IRM-PDFF.

Matériel et méthodes
Cette étude rétrospective observationnelle a été réalisée sur des patients de la cohorte SNIFF d'Angers ayant bénéficié de deux IRM hépatiques espacées d'au moins un an, entre juin 2013 et octobre 2022, couplées chacune à une évaluation par Fibroscan avec CAP. Les valeurs d'IRM-PDFF ont été mesurées par une méthode « simplifiée » validée en phase préliminaire. Les corrélations entre le CAP et l'IRM-PDFF ont été analysées. La performance du CAP pour évaluer la régression de la stéatose hépatique a été évaluée avec l'IRM-PDFF comme référence.

Résultats
La méthode de mesure « simplifiée » de l'IRM-PDFF était fortement corrélée à la méthode de référence (R^2 = 0,9654) et a été appliquée à tous les patients de l'étude. Au total, 149 patients ont été inclus. Trois groupes ont été constitués en fonction des valeurs de l'IRM-PDFF au départ (b) et au cours du suivi (fu) : le groupe stéatose (IRM-PDFF > 5%), le groupe progression (bIRM-PDFF < 5% et fuIRM-PDFF ≥ 5%) et le groupe absence de stéatose (deux IRM-PDFF < 5%). En se concentrant sur le groupe stéatose, la corrélation de la variation des valeurs de CAP et d'IRM-PDFF était modérée (Rs = 0,526, $p \leq 0,001$). L'AUROC du CAP pour évaluer la réponse à l'IRM-PDFF était de 0,74 (p = 0,001). Nous avons trouvé un seuil optimal de Δ CAP à -8% pour identifier les répondeurs à l'IRM-PDFF avec une sensibilité, spécificité, valeur prédictive positive et valeur prédictive négative de 61.1%, 85.2%, 84.6% et 62.2% respectivement.

Conclusion Le CAP était modérément corrélé à l'IRM-PDFF pour évaluer la régression de la stéatose hépatique.

Mots-clés : Paramètre d'atténuation contrôlée – CAP – IRM-PDFF – régression – stéatose hépatique

Controlled Attenuation Parameter (CAP) validation as a marker of regression in liver steatosis

ABSTRACT

Introduction
Controlled Attenuation Parameter (CAP) is an accessible tools to evaluate liver steatosis, while magnetic resonance imaging proton density fat fraction (MRI-PDFF) is the gold standard. MRI-PDFF response defined as a ≥ 30% relative decline was strongly associated with metabolic steatohepatitis (MASH) resolution without worsening fibrosis. We investigated the performance of CAP in assessing liver steatosis regression, defined as MRI-PDFF response.

Material and methods
This observational retrospective study was performed on patients from the SNIFF cohort in Angers whom underwent two liver MRIs at an interval of at least one year, from June 2013 to October 2022, and coupled with a Fibroscan evaluation with CAP. MRI-PDFF values were obtained by a « simplified » method validated in a preliminary-phase. The correlation between CAP and MRI-PDFF were analyzed. With MRI-PDFF as reference, the performance of CAP to evaluate liver steatosis regression was assessed.

Results
The « simplified » MRI-PDFF measurement method was highly correlated with the reference method (R^2 = 0.9654), and applied to all patients in the study. A total of 149 patients were included. Three groups were formed according to MRI-PDFF at baseline (b) and follow-up (fu), steatosis group (bMRI-PDFF > 5%), progressor group (bMRI-PDFF < 5% and fuMRI-PDFF ≥ 5%) and no steatosis group (both MRI-PDFF < 5%). Focusing on steatosis group, there was moderate correlation between CAP and MRI-PDFF variation (Rs = 0.526, $p \leq 0,001$). The AUROC of CAP to assess MRI-PDFF response was 0.74 (p = 0.001). We found an optimal threshold of Δ CAP at -8% to identify MRI-PDFF responders with sensitivity, specificity, positive and negative predictive value of 61.1%, 85.2%, 84.6% and 62.2% respectively.

Conclusion In assessing liver steatosis regression, CAP was moderately correlated with MRI-PDFF.

Keywords : Controlled attenuation parameter – CAP – MRI-PDFF – regression – liver steatosis

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