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Optimal threshold of controlled attenuation parameter with MRI-PDFF as the gold standard for the detection of hepatic steatosis

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Abstract

The optimal threshold of controlled attenuation parameter (CAP) for the detection of hepatic steatosis using both M and XL probe is unknown in nonalcoholic fatty liver disease (NAFLD). Magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF) is an accurate and precise method to detect presence of hepatic steatosis and is better than CAP. Thus, the aim of this study was to evaluate the diagnostic accuracy and the optimal threshold of CAP for the detection of

hepatic steatosis as defined by MRI-PDFF 5%. This cross-sectional study included 119 adults (59% women), prospectively recruited with and without NAFLD who underwent MRI-PDFF and CAP using either M probe or XL probe when indicated within a six-month period at the NAFLD Research Center, UCSD. Mean (±standard deviation) age and BMI were 52.4 (±15.2) years and 29.9 (±5.5) kg/m^2, respectively. The prevalence of NAFLD (MRI-PDFF 5%) and MRI-PDFF 10% was 70.6% and 47.1%, respectively. The area under the ROC (AUROC) of CAP for the detection of MRI-PDFF 5% was 0.80 (95%CI:0.70–0.90) at the cut-point of 288 dB/m and of MRI-PDFF 10% was 0.87 (95%CI:0.80–0.94) at the cut-point of 306 dB/m. When stratified by IQR of CAP, we observed that an IQR below median (30 dB/m) had a robust AUROC compared to IQR above median ([0.92, 95%CI:0.85-1.00] vs. [0.70, 95%CI:0.56-0.85], p-value=0.0117), and these differences were statistically and clinically significant.

Conclusion—The cut-point of CAP for presence of hepatic steatosis (MRI-PDFF 5%) was 288 dB/m. The diagnostic accuracy of CAP for the detection of hepatic steatosis is more reliable when IQR of CAP is <30 dB/m. These novel data have implications for clinical utility of CAP in the assessment of NAFLD.

Keywords

NAFLD; hepatic steatosis; controlled attenuation parameter; MRI-PDFF

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is being recognized as one of the most prevalent causes of chronic liver disease worldwide (1, 2). In the United State, NAFLD is estimated to affect approximately one-third of the adult population and its prevalence is strongly associated with obesity, type 2 diabetes and metabolic syndrome (1, 3, 4). NAFLD is currently the second leading etiology for the indication of liver transplants in the United States (5–7) and yet early stage of NAFLD, such as simple hepatic steatosis, remains broadly underdiagnosed although it can potentially progress to NASH, leading to liver fibrosis, cirrhosis and hepatocellular carcinoma (8, 9).

Although liver biopsy is considered as the reference method for the diagnosis of NAFLD, it encounters important limitations. Its accuracy has been questioned due to sampling errors and its interpretation and quantitative scoring is limited by significant inter- and intra-observer variability (10–15). In addition, liver biopsy is an expensive and invasive procedure which limits its use for the screening of population (12). Thus, there is an increasing interest in developing non-invasive imaging techniques that can clinically assess hepatic steatosis in NAFLD. Although conventional ultrasonography is widely used as first-line assessment of hepatic steatosis, it is limited by a lack of quantitative accuracy and is operator dependent (16, 17); computerized tomography is limited by radiation exposure and inaccurate quantification of steatosis(18). Magnetic resonance imaging (MRI) such as Magnetic resonance spectroscopy (MRS) has emerged as leading noninvasive modalities for steatosis quantification in NAFLD in terms of sensitivity, specificity and reliability (18, 19). MRI that measure the proton density fat fraction (MRI-PDFF) has been proven to correlate well with MRS (20, 21) and histology-proven steatosis grade from contemporaneous liver

biopsies(22–25). However, similar to liver biopsies, MRI is expensive and not routinely accessible.

The controlled attenuation parameter (CAP) is a novel technique based on the properties of ultrasonic signals developed to quantify ultrasound attenuation during measurement of liver stiffness vibration controlled elastography acquired by the Fibroscan (26). Although CAP is less accurate than MRI-PDFF in detecting all grades of hepatic steatosis (27, 28), CAP has been shown to correlate with histological grade of hepatic steatosis in several studies (26, 29–32). Moreover, CAP allows a rapid, non-invasive, bed-side assessment of hepatic steatosis and it is less expensive and more accessible than MRI. However, the use of CAP for the diagnosis of NAFLD in routine clinical practice is limited due to the lack of optimal threshold of CAP for the detection of hepatic steatosis and the absence of indicator of the quality of CAP measurements. Recently, Karlas and colleagues performed an individual patient meta-analysis on CAP accuracy for the grading of hepatic steatosis to better define relevant threshold of CAP for the stage of hepatic steatosis. However, this study included patients with heterogeneous etiology of chronic liver diseases, mainly viral hepatitis and a minority of NAFLD. Furthermore, CAP were exclusively measured using M probe which use is limited in obese patients due to a high failure rate (33) while obesity is a frequent characteristic of NAFLD patients. The use of the XL probe equipped with CAP has been shown to reduce the failure rate in obese patients providing improvement of CAP utility for the diagnosis of NAFLD (34, 35). Studies including NAFLD patients have reported different thresholds of CAP using M and XL probe for the grade of steatosis using liver biopsy as reference (27, 36). However, to really provide a relevant quantitative threshold of CAP for the detection of hepatic steatosis, measurement using a quantitative modality should be used and non-NAFLD controls should be included." So far, the optimal threshold of CAP has not been assessed with head to head comparison with another quantitative measure of hepatic steatosis and this study will fill that gap in knowledge.

Using a well-characterized, prospective cohort of American adults with NAFLD and non-NAFLD controls, we conducted a cross-sectional analysis to evaluate the diagnostic accuracy and the optimal threshold of CAP using M and XL probe for the detection of hepatic steatosis as defined by MRI-PDFF ≥ 5%.

MATERIAL AND METHODS

Study participant and design

This was a cross-sectional analysis of participant derived consecutively from a prospective cohort aimed at assessing the diagnostic accuracy and optimal threshold of CAP to diagnose hepatic steatosis (defined as MRI-PDFF ≥ 5%) and non-NAFLD controls (defined as MRI-PDFF< 5%). We followed the Standards for Reporting of Diagnostic Accuracy STARD guidelines in this study of CAP in detecting hepatic steatosis (Supplemental Table 1). Please see supplemental methods for further details.

Study participants were recruited at the NAFLD Research Center at the University of California, San Diego (UCSD) between July 2014 and May 2017; 157 potential eligible participants were screened and 156 participants were deemed eligible for the study, 119

participants complied with the study protocol and underwent MRI-PDFF and CAP assessment within a six-month period (Supplementary Figure 1). All participants underwent a careful evaluation for other causes of hepatic steatosis and liver disease and were invited for a clinical research visit with standardized history, physical and anthropometric exam, fasting biochemical testing, transient elastography and CAP assessment at the UCSD NAFLD Research Center (20, 21, 27, 37–42), advanced magnetic resonance imaging (MRI) based phenotyping at the UCSD MR3T Research Laboratory. This study was Health Insurance Portability and Accountability Act (HIPAA) compliant, informed written consent was obtained from all patients and this study was approved by the UCSD Institutional Review Board.

Inclusion/Exclusion criteria

Inclusion criteria were as follows: at least 18 years of age, willing and able to complete all procedures and observations specified in the protocol, fully informed, and had signed the Informed Consent/Assent and Health Insurance Portability and Accountability Act provisions.

Exclusion criteria were as follows: history of significant alcohol intake within 2 years of recruitment (14 drinks/week for men or 7 drinks/week for women); any evidence of secondary causes of hepatic steatosis including nutritional, iatrogenic, or infectious etiology or HIV infection; evidence of liver diseases other than NAFLD, which include viral hepatitis (screened by positive serum hepatitis B surface antigen and hepatitis C RNA assays), autoimmune hepatitis, genetic or acquired disorders such as hemochromatosis, Wilson's disease, glycogen storage disease, alpha-1 antitrypsin deficiency, and cholestatic or vascular liver disease; evidence of decompensated liver disease (defined as Child-Pugh score > 7 points); active substance use; major systemic illnesses; contraindication(s) to MRI; pregnant or trying to be pregnant; or any other conditions believed by the principal investigator to affect patient's competence, compliance, or completion of the study.

Clinical Research Evaluation

All patients underwent a standardized clinical evaluation, detailed history, anthropometric exam, and fasting biochemical tests at the UCSD NAFLD Research Center. Detailed information from history and anthropometric exam included age, sex, height, weight, body mass index, ethnic background, vital signs were collected by a trained clinical investigator. Alcohol consumption was documented in prior clinical visit and confirmed in the research clinic using the Alcohol Use Disorders Identifications Test and the Skinner questionnaire. Other causes of liver diseases and secondary causes of hepatic steatosis such as steatogenic medications were ruled out systematically using history and biochemical tests. Biochemical tests included aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, total bilirubin, direct bilirubin, albumin, hemoglobin A1c, fasting glucose, insulin, prothrombin time, international normalized ratio, fasting lipid panel, platelet count and ferritin.

Outcome measures

The primary outcome was the presence of hepatic steatosis defined as MRI-PDFF 5%. The secondary outcome was the detection of hepatic fat content 10% defined as MRI-PDFF 10% as this threshold has been used in several therapeutic trials as inclusion criteria.

Transient Elastography and CAP measurement

Transient elastography was performed by a trained technician, blinded to clinical and MRI results, using the FibroScan® 502 Touch model (M Probe; XL Probe; Echosens, Paris, France). Detailed methods have been previously-described in references (43, 44). Briefly, TE measurement was obtained in the supine position with the right arm fully adducted by scanning the area of abdomen at the location of the right liver lobe during a 10 seconds breath hold. Participants were asked to fast at least 3 hours prior to the exam. The procedure included a minimum of 10 measurements to determine the median valid liver stiffness measurements in kilopascals (kPa) and the interquartile range (IQR). According to the manufacturer protocol, all patients were first scanned using the M probe (3.5 MHz) and when indicated by the equipment upon initial assessment, patients were re-scanned using the XL probe (2.5 MHz). The CAP value in dB/m was simultaneously measured for the assessment of liver steatosis measurements, co-localized to the valid liver stiffness measurements. All CAP data were collected prospectively. Each participant underwent two consecutives readings of LSM and CAP by the same FibroScan. Unreliable liver stiffness was defined as success rate (ratio of the number of successful measurements to the total number of acquisitions) <60% and/or number of valid measurement <10 and/or IQR/med >30%.(45)

Magnetic Resonance Imaging

MRI-PDFF Advanced magnetic resonance imaging (MRI) based phenotyping was performed at the UCSD MR3T Research Laboratory using the 3T research scanner (GE Signa EXCITE HDxt; GE Healthcare, Waukesha, WI) with all participants in the supine position. MRI-PDFF was used to measure hepatic steatosis defined as MRI-PDFF 5%. The details of the MRI protocol have been previously described in references methods (22, 23, 46, 47). The median time between MRI-PDFF and CAP was 8 days. The image analysts were blinded to all clinical and biochemical data.

Rationale for using MRI-PDFF for hepatic steatosis quantification as gold standard

MRI-PDFF was used as a gold standard for the following reasons. **First, to really provide a relevant quantitative threshold of CAP for the detection of hepatic steatosis, measurement using a quantitative modality should be used.** MRI-PDFF is a quantitative method that has been shown to be a highly precise, accurate, and reproducible non-invasive biomarker for the quantification of liver fat content (48, 49). It has been proven to correlate well with magnetic resonance spectroscopy (r2=0.99, P < 0.001) (20, 21) and histology-proven steatosis grade from contemporaneous liver biopsies (22–25). In addition, MRI-PDFF has been demonstrated to be superior to ultrasound, computed tomography and CAP for quantification of liver fat content (19, 27). Second, in the future many therapeutic trials in NAFLD will require a liver biopsy which is an invasive and expensive procedure.

Likewise MRI-PDFF is expensive, thus an optimal threshold of CAP to approximate MRI-PDFF 5% for the screening of patients with and without NAFLD would reduce the therapeutic trials cost. In addition, several trials used an MRI-PDFF 10% as inclusion criteria and thus, an optimal threshold of CAP to approximate MRI-PDFF 10% was chosen as secondary outcome. Third, to be able to assess the diagnostic accuracy of CAP for the detection of hepatic steatosis as defined by MRI-PDFF 5%, participant with NAFLD and non-NAFLD are needed and it would be unethical to perform a liver biopsy in normal participants who do not have a clinical indication of performing a liver biopsy.

Statistical Analyses

Patients' demographic data, laboratory, and imaging data were summarized with mean and standard deviation for continuous variables or median and interquartile range (IQR) and with numbers and percentages for categorical variables. Mean and frequency were compared using an independent samples t-test or Wilcoxon Rank Sum Test or Chi-square test or Fisher's Exact Test, where appropriate. The Kruskal-Wallis test was used to compare CAP and different category of hepatic fat content assessed with MRI-PDFF.

Main analyses—Receiver operating characteristic (ROC) curve analyses were used to assess the diagnostic accuracy of CAP for the detection of hepatic steatosis (MRI-PDFF 5%) and of hepatic fat content 10%. For each ROC analysis, the area under the ROC curve (AUROC), the optimal thresholds, and the following performance parameters were calculated: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The optimal threshold of each modality was determined using the Youden index.(50)

Sample size estimation—Given the previously described superiority of MRI-PDFF compared to CAP for the detection of hepatic steatosis in NAFLD biopsy-proven cohort (27), an AUROC of CAP of 0.85 (0.75–0.96) for the detection of hepatic steatosis and a correlation between MRI-PDFF and CAP approximately of 0.50, a projected sample size of 102 people are needed to assess the diagnostic accuracy of CAP for the detection of hepatic steatosis using MRI-PDFF as a gold standard with an alpha of 0.05 and a power of 0.80.

Sensitivity analyses—Sensitivity analyses were conducted to further assess the impact of covariates on the accuracy of CAP for detection of hepatic steatosis as defined by MRI-PDFF 5%. The AUROC of CAP were compared using the method by Hanley and McNeil (51).

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) or SPSS (IBM, Chicago, IL). A two-tailed p-value 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

In this prospective study, 119 participants (58.8% female) with MRI-PDFF and CAP were consecutively enrolled. The mean (± standard deviation) age and body mass index (BMI) were 52.4 (±15.2) years and 29.9 (±5.5) kg/m^2, respectively. Baseline cohort characteristics

are summarized in Table 1. CAP were assessed using either M probe (n= 82, 68.9%) or XL probe (n=37, 31.1%) when appropriate. The prevalence of NAFLD (MRI-PDFF 5%) and MRI-PDFF 10% was 70.6% (n=84) and 47.1% (n=56), respectively. A total of 156 patients were eligible for the study, although 22 patients were excluded because CAP was not performed and 15 patients were excluded because MRI-PDFF was not performed (Supplementary Figure 1).

Diagnostic accuracy of CAP for the detection of hepatic steatosis (MRI-PDFF 5%)

The distribution of CAP measurements across different category of hepatic fat content assessed with MRI-PDFF is illustrated in Figure 1. The AUROC of CAP for the detection of hepatic steatosis (MRI-PDFF 5%) was 0.80 (95%Confidence of interval (CI): 0.70-0.90) at the cut-point of 288 dB/m Figure 2A. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of CAP for the detection of hepatic steatosis (MRI-PDFF 5%) was 75.0%, 77.1%, 88.7%, 56.2% respectively Table 2.

Diagnostic accuracy of CAP for the detection of hepatic fat content 10% (MRI-PDFF 10%)

The AUROC of CAP for the detection of hepatic fat content 10% (MRI-PDFF 10%) was 0.87 (95%CI: 0.80–0.94) at the cut-point of 306 dB/m. Figure 2B. The sensitivity, specificity, PPV and NPV of CAP for the detection of hepatic fat content 10% (MRI-PDFF 10%) was 78.6%, 82.5%, 80.0%, 81.2% respectively Table 2. Additional analysis assessing the diagnostic accuracy of CAP for the detection of hepatic fat content 15% (MRI-PDFF 15%) and hepatic fat content 20% (MRI-PDFF 20%) are provided in Supplemental Table 2.

Sensitivity analyses of the performance of CAP for the detection of hepatic steatosis

When stratified by M probe or XL probe, CAP measurements were significantly higher using XL probe compared to M probe in the lower grade of hepatic fat content with a mean (+/− standard deviation) of 300.14 (+/−35.14) dB/m versus 230.25 (+/−57.7) dB/m, p = 0.005 respectively when MRI-PDFF was below 5%; and 295.0 (+/−47.00) dB/m versus 254.47 (+/−46.60) dB/m, p=0.034 when MRI-PDFF was between 5 and 10% Figure 3, Supplemental Table 3.

When stratified by IQR of CAP, the direct comparison of the AUROC of CAP for the detection of hepatic steatosis (MRI-PDFF 5%), using the Hanley and McNeil test showed that CAP measurement with IQR of CAP below median (30 dB/m) was significantly more accurate than CAP measurement with IQR of CAP above median (30 dB/m) for the detection of hepatic steatosis (MRI-PDFF 5%) with an AUROC of 0.92 (95%CI: 0.85–1.00) versus 0.70 (95%CI: 0.56–0.85), p-value=0.0117 Figure 4. In the subgroup of individuals with IQR of CAP <30 dB/m, there was no significant difference in the performance of CAP between unadjusted and adjusted model when either BMI or type 2 diabetes status was included in the models. The optimal strategy for the screening of NAFLD using CAP and IQR of CAP as validity criteria is detailed in Figure 5.

DISCUSSION

Main findings

Using a well-characterized, prospective cohort of American adults with and without NAFLD, this study demonstrates that the optimal threshold of CAP for the detection of hepatic steatosis as defined by MRI-PDFF 5% is 288 dB/m with a good diagnostic accuracy (AUROC: 0.80, 95%CI: 0.70-0.90). Furthermore, the secondary analysis shows that the optimal threshold of CAP for the detection of hepatic fat content 10% (MRI-PDFF 10%) is 306 dB/m with an AUROC of 0.87 (95%CI: 0.80–0.94) which could be integrated in future clinical trial design as inclusion criteria. The key novelty of this study is to provide estimates of the diagnostic accuracy and optimum thresholds of CAP measurements, using M or XL probes, for the detection of hepatic steatosis by an accurate, and quantitative standard using MRI-PDFF in a Western population with NAFLD and non-NAFLD controls. These novel data have important implications for the clinical utility of CAP in the assessment of NAFLD and would help developing an optimal clinical approach for non-invasive diagnosis of NAFLD. Furthermore, CAP may have utility in longitudinal follow-up of anti-steatosis therapeutic interventions in clinical routine practice. In addition, this study demonstrates that the diagnostic accuracy of CAP for the detection of hepatic steatosis is more reliable when IQR of CAP is <30 dB/m, providing reliable quality indicator that would help clinicians in interpreting the CAP measurements. Ultimately, the use of these optimal thresholds for the quantitative diagnosis of hepatic fat may modify the clinical trials design for the treatment of NAFLD and reduce their costs by reducing screen failure rates for the trials that use an MRI-PDFF of 10% or higher for inclusion into a trial. In future, patients with a certain level of CAP values may only move forward for MRI-PDFF assessment in these clinical trials thereby reducing the number of MRI scans needed to enroll patients into the trial. However, further studies are needed to determine the clinical relevance and cost-effectiveness of CAP for the diagnosis of hepatic steatosis in NAFLD.

In context with published literature

This is the first prospective study to assess the optimal threshold of CAP for the diagnosis of hepatic steatosis using M and XL probe in a in a well-characterized cohort of American adults with NAFLD and non-NAFLD controls using advanced MRI-PDFF as the gold standard. This study provides also the first estimates of the diagnostic accuracy and optimal threshold of CAP for the detection of hepatic fat content 10% which is used as inclusion criteria in therapeutic trials (NCT02912260, NCT02781584). We report a good diagnostic accuracy of CAP for the detection of hepatic steatosis in NAFLD with an AUROC of 0.80 (95%CI: 0.70–0.90) consistent with previous studies (26, 29–32). Furthermore, we have found that an IQR of CAP < 30dB/m is a quality criteria for CAP measurement which is also consistent with a recent study by Wong et al. showing the validity of CAP for the diagnosis of fatty liver is lower if the IQR of CAP is 40 dB/m using M probe in a cohort of patients with different liver diseases.(32)

In a recent study, Karlas and colleagues have proposed an optimal threshold of CAP for the detection of histological steatosis grade above S0 of 248db/m (237–261) based on an individual patient meta-analysis including heterogeneous etiology of chronic liver disease.

(31) Interestingly, the authors have identified that the etiology of the liver disease, and features highly associated with NAFLD such as diabetes and BMI needs consideration when interpreting CAP.(31) These latter observation, highlight the utmost need to assess CAP in the setting of well-characterized NAFLD cohorts. Indeed, our cohort demographical characteristics such as higher BMI (29.9 ± 5.5 kg/m^2) and higher prevalence of type 2 diabetes may have reflected a more accurate assessment of the diagnostic performances and thresholds of CAP in a Western population with NAFLD and non-NAFLD controls. Therefore, these covariates may at least partially account for the different threshold found in our study and this meta-analysis: 288 dB/m versus 248 dB/m, respectively.

Fewer studies including small cohorts have assessed the diagnostic accuracy of CAP using XL probe (34, 35, 44). The sensitivity analyses shows that CAP measurements were significantly higher using XL probe compared to M probe in the lower grade of hepatic fat content. Similarly, Chan et al. have shown significant higher value of CAP using XL probe compared to M probe in an Asian NAFLD cohort(35). Likewise, a recent study by Vuppalanchi et al. in patients with NAFLD in a multicenter setting, have reported a significant higher CAP values measured with XL probe compared to M probe in an adjusted model for BMI. In this study, only 4.2 % of the total cohort did not have NAFLD as opposed to 29.4% in the current study. In addition the liver biopsy was used as the reference standard and only a minority of patients had steatosis grade 0 (which would equate with a MRI-PDFF of less than 5%). Therefore, our study is complimentary to this previous study and provides a more robust assessment of CAP for detection of presence of hepatic steatosis at a threshold of MRI-PDFF of 5%. We believe that the reference standard that is required to establish the optimal threshold of CAP to detect presence of hepatic steatosis in the clinical practice would have to be quantitative, reproducible, and valid across the entire dynamic range of liver fat content (liver fat content typically ranges between 0.2% to 50% on MRS) rather than a subjective estimate of liver fat on an ordinal scale using histologic grade of steatosis. Although, direct comparison of the performance of CAP using XL probe compared to M probe have shown similar diagnostic accuracy (34, 35), further studies using both probes on the same patients are needed to compare CAP measurement using M and XL probe.

Hepatic steatosis is an important clinical feature in NAFLD that can progress to NASH, fibrosis, cirrhosis and hepatocellular carcinoma (8, 9). Therefore, early diagnosis and screening of hepatic steatosis before the progression to NASH and severe liver fibrosis may benefit patients at risk of NAFLD. Contrary to viral hepatitis, the impact of hepatic steatosis on accelerating the disease progression to fibrosis and cirrhosis is unclear in NAFLD. Future longitudinal studies designed to determine the prognostic significance of hepatic steatosis in long-term outcomes are needed.

Strengths and limitations

There are several notable strengths of this study including the prospectively well-characterized recruited cohort by experienced investigators at a dedicated research center that is specialized for both clinical and radiologic research in NAFLD. All participants underwent a systematic and standardized liver disease assessment to exclude for other causes of liver disease before inclusion in the study, and detailed advanced MRI of the liver.

However, we acknowledge following limitations of this study. This is a single center study conducted at a highly specialized tertiary care center using advanced MRI techniques that may not be available in other clinical center. Thus the generalizability of these findings in other clinical settings is unknown. In addition, the cross-sectional design of the study did not allow the assessment of CAP for monitoring longitudinal changes in hepatic fat content. Liver biopsy was not performed in this study as the study was designed to assessed the optimal threshold of CAP which is a quantitative biomarker for the detection of hepatic steatosis and therefore a quantitative modality should be used a gold standard. We used the most accurate non-invasive quantitative modality which has emerged as a novel standardized biomarker for assessing hepatic steatosis(52). MRI-PDFF has been proven to correlate well with magnetic resonance spectroscopy (20, 21) and histology-proven steatosis grade (22–24). Additionally, MRI-PDFF performance has been reported to be higher than histology in quantifying changes in steatosis in longitudinal studies (20, 48).

Implications for clinical care and future research

Using a prospective study, we confirmed the good diagnostic accuracy of CAP for the detection of hepatic steatosis as defined by MRI-PDFF 5% and we provided a novel optimal threshold of 288 dB/m using XL probe when appropriate in an American cohort of well-characterized individuals with NAFLD and non-NAFLD controls. The use of this new threshold, higher than previous threshold, is more accurate and would decrease the screen failure rate in clinical trials. Furthermore, the use of this optimal threshold may enable the use of CAP for non-invasive diagnosis of NAFLD in routine clinical practice. Future studies are necessary to assess the clinical utility of CAP for diagnosis of hepatic steatosis in a multicenter, longitudinal design, both in observational and intervention studies. The cost-effectiveness of utilizing CAP versus other modalities available must also be evaluated to develop optimal diagnostic strategies for diagnosing NAFLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

AUROC	area under the receiver operator characteristic curve
BMI	body mass index

| **CAP**	controlled attenuation parameter
CI	confidence interval
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
TE	transient elastography
UCSD	University of California at San Diego

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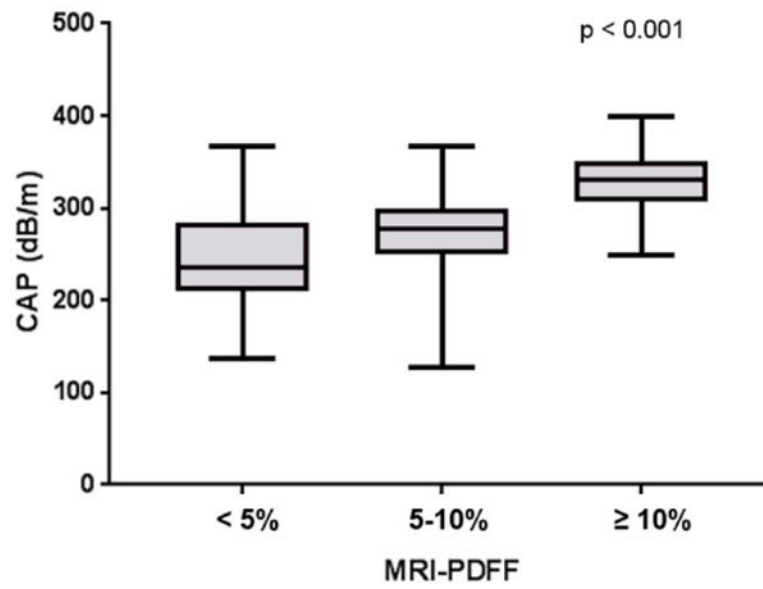
Figure 1. Distribution of CAP measurements stratified by hepatic fat content (MRI-PDFF)
CAP measurements increase with increase of liver fat content assessed by MRI-PDFF
(Kruskal–Wallis test P < 0.001): MRI-PDFF <5% n=35, MRI-PDFF 5-10% n=28, MRI-PDFF 10% n=56.
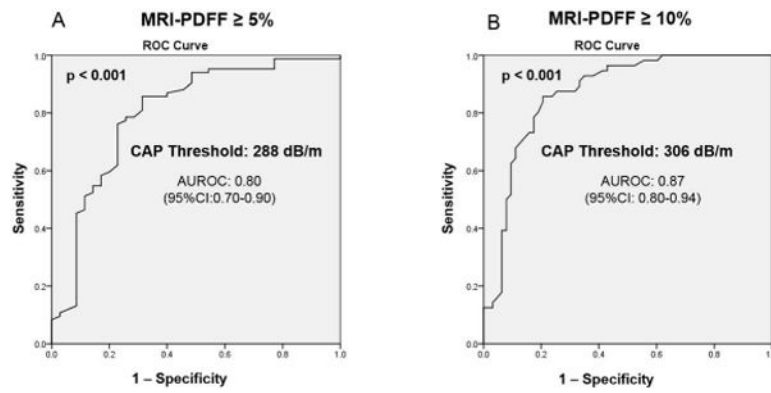
Figure 2. Diagnostic accuracy of CAP for the detection of hepatic steatosis
Receiver operating curves (ROC) and area under the ROC A. for the detection of hepatic steatosis defined by MRI-PDFF ≥ 5% B. for the detection of hepatic fat content ≥ 10% defined as MRI-PDFF ≥ 10%
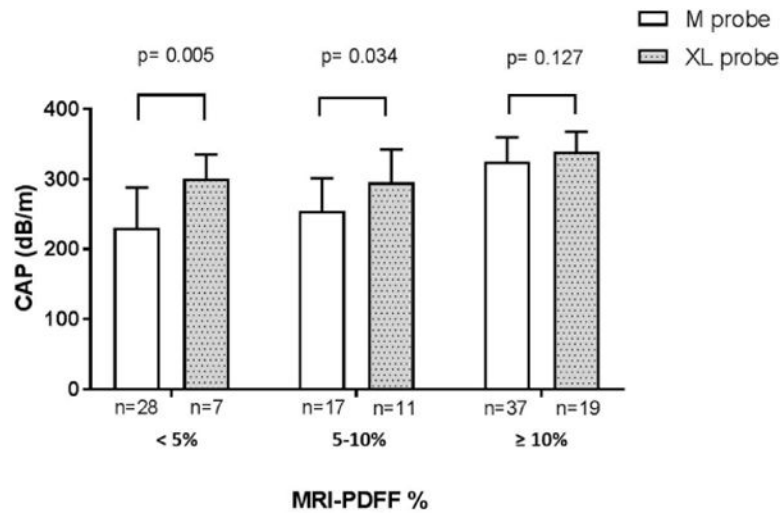
Figure 3. Higher CAP value using XL compared to M probe when MRI-PDFF < 10%
CAP measurements and standard deviation are presented using M probe (pink bar) and XL probe (blue bar) stratified by hepatic fat content assessed by MRI-PDFF. CAP measurements were significantly higher using XL probe compared to M probe in the lower grade of hepatic fat content. p-value were determined using independent two-tailed t- test.
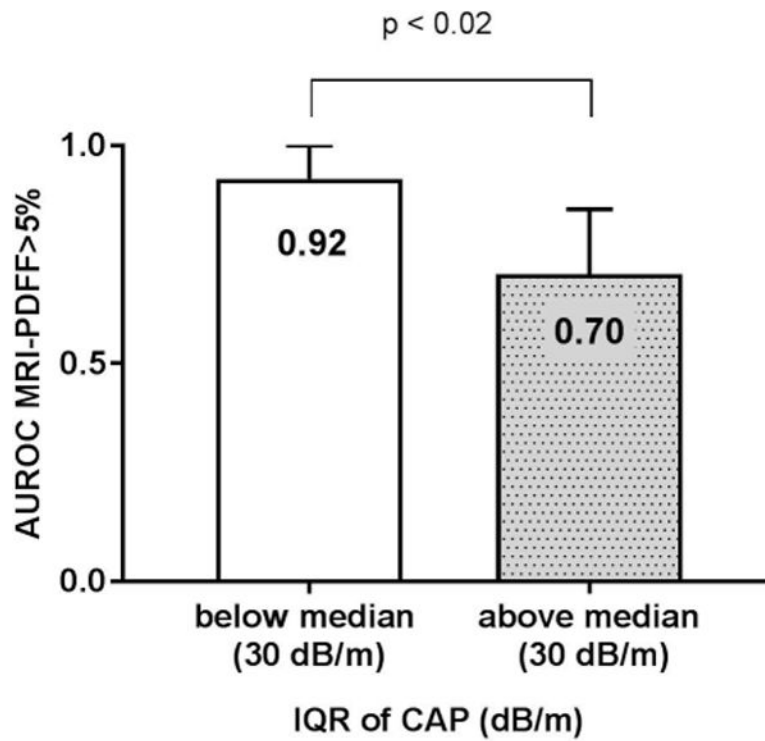
Figure 4. The diagnostic accuracy of CAP increase when IQR of CAP is <30 dB/m
Area under the receiver operating curves (AUROC) of CAP and 95 % confidence of interval for the detection of hepatic steatosis defined by MRI-PDFF 5% was significantly higher when IQR of CAP was below median (30 dB/m) n= 60 compared to AUROC of CAP when IQR of CAP n=59 was above median, p value 0.017 determined using the method by Hanley and McNeil.

Optimal strategy for the screening of NAFLD using controlled attenuation
parameter (CAP) measurement and its interquartile range (IQR) as validity criteria
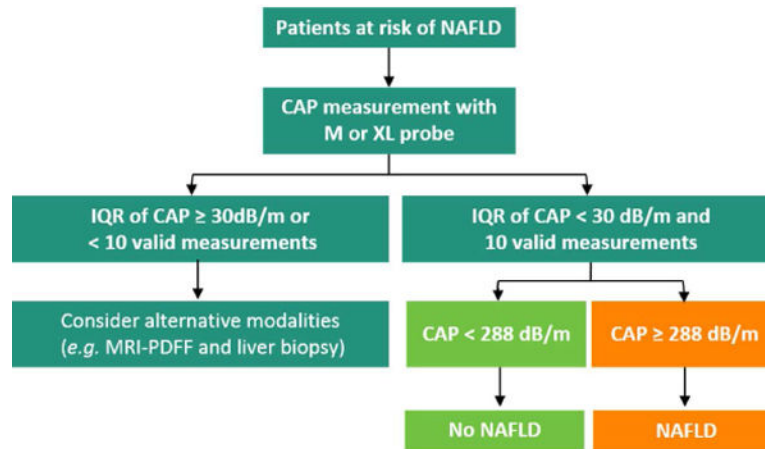
Figure 5. Optimal strategy for the screening of NAFLD using CAP measurements and its IQR as validity criteria

CAP measurements are considered valid when IQR of CAP is below 30 dB/m and 10 valid measurements are achieved. If the valid CAP measurement is below the optimal threshold the patient is considered as non-NAFLD.

Table 1

Baseline characteristics of the cohort stratified by NAFLD status

Characteristics	Total Patients (n=119)	MRIPDFF <5% (n=35)	MRIDPFF 5% (n=84)	p-value
Demographics				
Age (years)	52.4 (15.2)	50.2 (17.6)	53.3 (14.1)	0.3254
Female, n (%)	70 (58.8)	17 (48.6)	53 (62.4)	0.1424
White, n (%)	59 (51.8)	17 (48.6)	42 (53.2)	0.6508
Hispanic or Latino, n (%)	37 (32.5)	16 (45.7)	21 (28.6)	**0.0442**
Clinical				
Type 2 Diabetes, n (%)	49 (41.2)	11 (31.4)	38 (45.2)	0.1631
BMI (kg/m^2)	29.9 (5.5)	26.8 (4.9)	31.2 (5.2)	**<0.0001**
Waist circumference (cm)	101.0 (14.4)	90.8 (13.1)	105.3 (12.7)	**<0.0001**
Obesity, n (%)	52 (43.7)	8 (22.9)	44 (52.4)	**0.0031**
Biological data				
AST (U/L)	36.4 (24.7)	29.3 (13.7)	39.4 (27.7)	**0.0101**
ALT (U/L)	48.6 (39.2)	27.9 (14.2)	57.3 (43.0)	**<0.0001**
Alk P (U/L)	76.3 (33.0)	71.5 (25.7)	78.3 (35.6)	0.2478
GGT (U/L)	48.1 (53.9)	41.9 (49.9)	50.6 (55.6)	0.4630
Total Bilirubin (mg/dL)	0.7 (1.0)	1.0 (1.8)	0.5 (0.3)	0.1050
Direct Bilirubin (mg/dL)	0.2 (0.1)	0.2 (0.2)	0.2 (0.1)	0.3342
Albumin (g/dL)	4.4 (0.4)	4.4 (0.6)	4.4 (0.3)	0.5911
Glucose (mg/dl)	116.5 (45.6)	112.2 (46.4)	118.3 (45.5)	0.5104
Hemoglobin A1c (%)	6.0 (1.1)	5.8 (1.1)	6.1 (1.1)	0.2201
Insulin (U/ml)	26.9 (29.8)	14.8 (14.5)	31.4 (32.8)	**0.0025**
HOMA-R	8.1 (12.9)	3.5 (3.3)	9.9 (14.7)	**0.0027**
Triglycerides (mg/dL)	156.1 (103.6)	98.1 (34.2)	180.7 (113.2)	**<0.0001**
Total cholesterol (mg/dL)	180.9 (34.9)	171.0 (31.8)	185.1 (35.5)	**0.0479**
HDL-cholesterol (mg/dL)	49.3 (13.5)	54.9 (14.3)	47.0 (12.5)	**0.0038**
LDL-cholesterol (mg/dL)	102.7 (31.8)	96.5 (30.8)	105.4 (32.0)	0.1759
Platelet count (10^9/L)	228.0 (70.6)	207.8 (75.3)	236.3 (67.4)	**0.0468**
Prothrombin time	11.4 (2.5)	11.8 (1.8)	11.2 (2.7)	0.1878
INR	1.3 (2.3)	1.1 (0.2)	1.4 (2.8)	0.3960
Clinical Prediction Rules				
AST/ALT	0.9 (0.3)	1.1 (0.4)	0.8 (0.3)	**<0.0001**
APRI	0.5 (0.5)	0.5 (0.5)	0.5 (0.4)	0.8344
BARD, median (IQR)	2 (2)	2 (1)	2 (2)	**0.0485**
FIB-4	1.5 (1.4)	1.9 (2.1)	1.3 (0.8)	0.1471
NAFLD Fibrosis Score	−1.3 (1.7)	−1.3 (2.0)	−1.3 (1.5)	0.9887
Imaging data				

Characteristics	Total Patients (n=119)	MRIPDFF <5% (n=35)	MRIDPFF 5% (n=84)	p-value
MRI-PDFF (%)	10.8 (7.7)	2.8 (1.2)	14.1 (6.8)	**<0.0001**
Liver stiffness (kPa)				
Median, median (IQR)	6.0 (4.4)	4.5 (2.8)	6.5 (3.8)	**0.0011**
IQR, median (IQR)	0.9 (1.1)	0.6 (0.9)	1.0 (1.0)	**0.0092**
IQR/M, median (IQR)	0.2 (0.1)	0.1 (0.1)	0.2 (0.1)	0.2067
Total number of measurements	13.4 (7.0)	15.7 (11.7)	12.4 (3.2)	0.1098
Total number of valid measurement	10.2 (1.0)	10.7 (1.2)	10.0 (0.8)	**0.0079**
Success rate <60%, n (%)	11 (9.2)	4 (11.4)	7 (8.3)	0.7294
Unreliable liver stiffness *, n (%)	13 (10.9)	5 (14.3)	8 (9.5)	0.5218
CAP (dB/m)				
Median, median (IQR)	305 (80.0)	235 (75.0)	315 (52.0)	**<0.0001**
IQR, median (IQR)	30 (19.0)	32 (13.0)	28.5 (19.5)	0.0831
IQR/M, median (IQR)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	**<0.0001**
Probe size, n (%)				0.0915
Use of M probe	82 (68.9)	28 (80.0)	54 (64.3)	
Use of XL probe	37 (31.1)	7 (20.0)	30 (35.7)	

Continuous variable are expressed in mean with standard deviation in parentheses or median, unless otherwise noted as median with interquartile range (IQR) in parentheses or n (%). BMI: body mass index, Obesity was defined as BMI 30 kg/m^2, HbA1c: glycated hemoglobin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, INR: International Normalized Ratio, APRI: AST to platelet ratio, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, Alk P: Alkaline Phosphatase, MRI-PDFF: magnetic resonance imaging proton-density fat fraction, CAP: controlled attenuation parameter. Success rate was defined as the ratio of the number of valid measurements to the total number of measurements.

*Unreliable liver stiffness was defined as success rate <60% and/or number of valid measurement <10 and/or IQR/med >30%.[44]

*P-value determined by comparing characteristics of patients without NAFLD (MRI-PDFF<5%) and with NAFLD (MRI-PDFF 5%) using an independent samples t-test, Wilcoxon Two-Sample test or a Chi-Square or Fishers exact test as appropriate. Bold indicates significant P-values <0.05.

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Table 2

Diagnostic accuracy of CAP for the detection of hepatic steatosis

	AUROC (95%CI)	Cutoff (dB/m)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Primary analysis: MRI-PDFF 5%						
CAP (dB/m)						
Optimal threshold	**0.80 (0.70–0.90)**	**288**	**75.0**	**77.1**	**88.7**	**56.2**
Threshold for 100% sensitivity		128	100	0	70.6	0
Threshold for 100% specificity		369	8.3	100	100	31.2
Secondary analysis: MRI-PDFF 10%						
CAP (dB/m)						
Optimal threshold	**0.87 (0.80–0.94)**	**306**	**78.6**	**82.5**	**80.0**	**81.2**
Threshold for 100% sensitivity		250	100	38.1	58.9	100
Threshold for 100% specificity		369	12.5	100	100	56.2

MRI-PDFF: magnetic resonance imaging proton-density fat fraction, CAP: controlled attenuation parameter, PPV: positive predictive value, NPV: negative predictive value.