Diagnostic Accuracy and Optimal Cut-off of Controlled Attenuation Parameter for the Detection of Hepatic Steatosis in Indian Population

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Background and aims: Ultrasound of the liver is not good to pick up mild steatosis. Controlled attenuation parameter (CAP) evaluated in transient elastography (FibroScan) is widely available in India. However, data regarding the diagnostic accuracy and optimal cut-off values of CAP for diagnosing hepatic steatosis are scarce in Indian population. MRI-PDFF is an accurate technique for quantifying hepatic steatosis. Thus, this study examined the diagnostic accuracy and optimal cut-off values of CAP for diagnosing steatosis with MRI-PDFF as reference standard.

Methods: A total of 137 adults underwent CAP and MRI-PDFF measurements prospectively. A subset of participants (n = 23) underwent liver biopsy as part of liver transplantation evaluation. The optimal cut-off values, area under the receiver operating characteristic (AUROC) curves, sensitivity, and specificity for CAP in detecting MRI-PDFF ≥5% and ≥10% were assessed.

Results: The mean age and body mass index (BMI) were 44.2 ±10.4 years and 28.3 ±3.9 kg/m², respectively. The mean hepatic steatosis was 13.0 ±7.7% by MRI-PDFF and 303 ±54 dB/m by CAP. The AUROC of CAP for detecting hepatic steatosis (MRI-PDFF ≥5%) was 0.93 (95% CI, 0.88–0.98) at the cut-off of 262 dB/m, and of MRI-PDFF ≥10% was 0.89 (95% CI, 0.84–0.94) at the cut-off of 295 dB/m. The CAP of 262 dB/m had 90% sensitivity and 91% specificity for detecting MRI-PDFF ≥5%, while the CAP of 295 dB/m had 86% sensitivity and 77% specificity for detecting MRI-PDFF ≥10%.

Conclusions: The optimal cut-off of CAP for the presence of liver steatosis (MRI-PDFF ≥5%) was 262 dB/m in Indian individuals. This CAP cut-off was associated with good sensitivity and specificity to pick up mild steatosis.

N on-alcoholic fatty liver disease (NAFLD) affects around one-fourth of the urban adult population in India.1–4 Hepatic steatosis, the earliest stage of NAFLD spectrum, remains broadly underdiagnosed and has a potential to progress to hepatic fibrosis and cirrhosis.5–7 Liver biopsy is the currently available gold standard method for diagnosis of steatosis and other NAFLD-related pathological conditions as routinely available imaging is not able to diagnose mild steatosis or non-alcoholic steatohepatitis.8,9 However, liver biopsy is invasive, needs hospitalization, and there is risk of adverse events.10 Thus, there is need of non-invasive strategies to assess hepatic steatosis and fibrosis in NAFLD. Ultrasonography is often used to diagnose NAFLD, but it is less accurate and operator dependent.11–12 Computerized tomography is limited by radiation exposure.11 Magnetic resonance imaging-based technique for quantification of hepatic steatosis is currently the non-invasive reference standard.13,14 MRI that measures proton density fat fraction (PDFF) has a good correlation with MRS and biopsy-proven steatosis grades.15–17 However, MRI-based techniques are not widely accessible.

Although not as good as MRI to detect steatosis grading,18 CAP correlates well with biopsy-proven steatosis.16,17 CAP is easily available as part of FibroScan measurement; also, it is cheaper than MRI and examination can be done in a short time. Furthermore, FibroScan used for CAP assessment also provides liver stiffness measurement (LSM) which suggests that liver fibrosis helps in management decisions. The utility of CAP in clinical practice is limited by lack of optimal cut-off values. The described CAP cut-off values differ...
depending upon the geographical region of the study population.18,23

Two Indian studies have shown CAP cut-offs in patients with NAFLD, but these studies lacked control arm (all patients were suffering from NAFLD)24 or had mixed study population (including non-NAFLD etiologies).25 Using prospective cohorts of Indian adults with and without NAFLD (controls), the current study is a cross-sectional analysis to assess diagnostic accuracy and the optimal cut-off values of CAP for detection of hepatic steatosis (defined as MRI-PDFF ≥5%).

METHODS

Participants and setting

This study was conducted between November 2018 and April 2021 at a tertiary care facility in North India. The study was approved by Ethics Committee. The patients with both FibroScan and MR-PDFF values were included from D-LIFT trial26 cohort (clinicaltrials.gov NCT03590626) and another ongoing cohort of prospective liver donors (MICR-1166/2020). The study in prospective liver donors was done to assess normal CAP and LSM values in normal liver histology cohort. We recruited 168 patients with and without NAFLD, age ≥18 years, from two cohorts. In addition to routine anthropometry measurements and biochemical investigations, each patient underwent transient elastography (TE, done by FibroScan equipment) and MRI-PDFF. In the prospective liver donor cohort, donors who had both MR-PDFF and FibroScan values were included. The exclusion criteria included hepatitis B or C positive status, significant alcohol intake (defined as >20 g/day),9 ≥5 times rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), end-stage kidney disease, congestive heart failure, pregnancy, metal implants or claustrophobia. An informed written consent was taken from all the subjects. All MR examinations were performed by an experienced MR technologist and were analyzed by a single radiologist. The FibroScan® 502 device (developed by EchoSens, Paris) was used for TE. TE was done in a fasting state of >4 h. A valid TE examination was defined as ≥10 valid LSM measurements with an interquartile range interval/median ratio <30%, and a success rate of >60%. The M probe was used for TE examinations. The XL probe was used in participants with BMI ≥30 kg/m².27 TE was performed by trained hepatologists (NSC, SD).

Sample size calculation

As described earlier, MRI-PDFF is better than CAP for the detection of hepatic steatosis. A sample size of at least 120 participants is required to assess the diagnostic accuracy of CAP (using MRI-PDFF as the standard method) for an AUROC of 0.85, correlation of 0.5 (with MRI-PDFF), alpha of 0.05, and a power of 0.90.

Statistical analysis

All statistical analyses were performed using SPSS 21 (SPSS Inc, Chicago, Illinois). The data are shown as numbers and percentages, mean ± standard deviation (parametric continuous variables) or median (25th and 75th interquartile range, for non-parametric continuous variables). Two groups were compared with chi-square test (categorical variables), Student’s t-test (parametric variables), and Kruskal-Wallis test (non-parametric variables). Receiver operating characteristic (ROC) curve analysis was used to assess the area under the curve (AUROC) and the optimal CAP cut-offs to calculate sensitivity, specificity, positive and negative predictive values. A P-value of <0.05 was taken as significant.

RESULTS

Description of the study population

Between November 2018 and March 2020, 168 participants were prospectively recruited. Eighteen patients were excluded for various reasons (n = 18) and 13 patients were excluded because of missing data (n = 13) as shown in Figure 1. Following excluded subjects, 137 participants (35.8% females) with MRI-PDFF and CAP data were finally analyzed. The mean age was 44.2 ±10.4 years. The mean body mass index was 28.3 ±3.9 kg/m². The mean MR-PDFF value was 13.0% ±7.7 and the mean CAP value was 303 ±54. The prevalence of NAFLD (defined as MRI-PDFF ≥5.0%) and MR-PDFF ≥10.0% was 83.9% (n = 115) and 58.4% (n = 80), respectively. Baseline cohort characteristics when stratified by NAFLD status are summarized in Table 1. One hundred and thirteen (82.5%) of our participants were obese, defined by BMI ≥25 kg/m². Baseline cohort characteristics when stratified by BMI status are summarized in Supplementary Table 1.

Diagnostic accuracy of CAP for detecting hepatic steatosis

The distribution of CAP measurements across different categories of hepatic fat content by MRI-PDFF is shown in Figure 2. The AUROC of CAP for the detection of ≥5.0% liver steatosis was 0.93 (95% CI, 0.88–0.98) at the cut-off of 262 dB/m (Figure 3). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 90.4%, 90.9%, 98.1%, and 64.5%, respectively (Table 2).

The AUROC of CAP for the detection of ≥10.0% steatosis was 0.89 (95% CI, 0.84–0.94) at the cut-off of 295 dB/m (Figure 3). The sensitivity, specificity, PPV, and NPV were 86.2%, 77.1%, 84.1%, and 80.0%, respectively (Table 2). For detection of ≥20% steatosis, AUROC of CAP was
0.78 (95% CI 0.69–0.87) at the cut-off of 324 dB/m, with sensitivity, specificity, PPV, and NPV of 72%, 70.5%, 35.3%, and 91.8% respectively.

**Correlations with CAP**

The correlations between the CAP and MRI-PDFF and other variables are shown in Supplementary Table 2. CAP correlated positively and significantly with MRI-PDFF ($r = 0.679$), BMI ($r = 0.390$), AST ($r = 0.323$), and ALT ($r = 0.410$). MRI-PDFF, in addition, correlated positively and significantly with triglycerides ($r = 0.326$) and GGT ($r = 0.348$), and negatively with platelets ($r = 0.1018$). The correlation between MRI-PDFF and CAP is illustrated in Supplementary Figure 1.

A total of 23 participants underwent liver biopsy also. Liver biopsy was performed within one week of MRI-PDFF and CAP measurements. The biopsy was normal in 15 prospective donors, and 8 biopsies revealed steatosis ranging from 5 to 25%.

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**Figure 1 Derivation of the study cohort.** In total, 168 participants were potentially eligible, and 18 subjects were excluded because of various reasons as shown in the figure. Among 150 eligible participants, 10 and 3 participants were excluded for missing CAP and MRI-PDFF data, respectively. A total of 137 participants were finally analyzed.

**Table 1 Baseline Characteristics of the Cohort Stratified by NAFLD Status.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total patients (n = 137)</th>
<th>MRI PDFF &lt;5.0% (n = 22)</th>
<th>MRI PDFF ≥5.0% (n = 115)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.2 (10.4)</td>
<td>38.8 (11.6)</td>
<td>45.2 (9.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>88 (64.2)</td>
<td>10 (11.4)</td>
<td>78 (88.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>49 (35.8)</td>
<td>12 (24.5)</td>
<td>37 (75.5)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3 (3.9)</td>
<td>24.3 (3.7)</td>
<td>29.1 (3.5)</td>
<td>0.000</td>
</tr>
<tr>
<td>Obesity (BMI ≥25 kg/m²), n (%)</td>
<td>113 (82.5)</td>
<td>9 (40.9)</td>
<td>104 (90.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.50 (0.4–0.8)</td>
<td>0.48 (0.3–0.7)</td>
<td>0.60 (0.5–0.8)</td>
<td>0.026</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>34 (25–46)</td>
<td>24 (20–30)</td>
<td>35 (27–49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>45 (29–69)</td>
<td>22 (15–38)</td>
<td>49 (34–74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GGT, IU/L</td>
<td>40 (27–61)</td>
<td>23 (17–30)</td>
<td>44 (32–64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>134 (50)</td>
<td>96 (10)</td>
<td>142 (52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>177 (82)</td>
<td>141 (60)</td>
<td>185 (84)</td>
<td>0.021</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>39 (9)</td>
<td>42 (9)</td>
<td>39 (9)</td>
<td>0.097</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>139 (81)</td>
<td>97 (32)</td>
<td>147 (85)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.7 (1.5)</td>
<td>13.2 (1.3)</td>
<td>13.8 (1.6)</td>
<td>0.101</td>
</tr>
<tr>
<td>TLC x 10³</td>
<td>7.6 (1.7)</td>
<td>7.6 (1.2)</td>
<td>7.6 (1.8)</td>
<td>0.992</td>
</tr>
<tr>
<td>Platelets x 10³</td>
<td>203 (68)</td>
<td>237 (52)</td>
<td>197 (70)</td>
<td>0.012</td>
</tr>
<tr>
<td>CAP, dB/m</td>
<td>303 (54)</td>
<td>230 (32)</td>
<td>316 (45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LSM, kPa</td>
<td>8.4 (4.5)</td>
<td>4.8 (1.4)</td>
<td>9.0 (4.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MRI PDFF, %</td>
<td>13.0 (7.7)</td>
<td>3.5 (0.91)</td>
<td>14.9 (7.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; FPG, fasting plasma glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; TLC, total leucocyte; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; MRI PDFF, magnetic resonance imaging-proton density fat fraction.
DISCUSSION

The current study shows that the optimal cut-off of CAP detecting hepatic steatosis (MRI-PDFF ≥5% as standard) is 262 dB/m. This value showed good diagnostic accuracy (AUROC: 0.93 (95% CI), 0.88–0.98).

In a prospective US study, using MRI-PDFF as the reference standard, the cut-off value for MRI PDFF ≥5% was 288 dB/m (AUROC 0.80). The cut-off value was 304 dB/m (AUROC 0.87) for MRI PDFF ≥10%. The CAP cut-off values are lower in this study, than the US population. This reflects differences in the population and highlights the fact that different populations should have their own cut-offs. CAP has been shown to have good diagnostic accuracy for detection of hepatic steatosis. In a meta-analysis of nine studies (n = 1297 biopsy-proven NAFLD), the mean AUROC values of CAP for diagnosing >5% steatosis was 0.96 with a 87% sensitivity. As the steatosis grade increases, the diagnostic accuracy for identifying steatosis accurately decreases. The US study also showed that the AUROC values of CAP in the diagnosis of MRI-PDFF ≥5%, ≥10%, and ≥20% was 0.80, 0.87, and 0.76, respectively. The current study also shows similar observation. Thus, CAP shows a very good accuracy for differentiating steatosis and no-steatosis, but is not so good in differentiating grades of steatosis. This important fact related to CAP can be utilized in clinical practice (diagnosing the presence or absence of hepatic steatosis) as commonly available modalities (ultrasound and computed tomography) are not good to detect mild steatosis.

Our study has several clinical implications. In a well-defined prospective cohort of NAFLD and controls, we confirm the good diagnostic accuracy of CAP for detecting hepatic steatosis and we provide an optimal cut-off of 262 dB/m for Indian population. Thus, CAP can be used as a diagnostic modality in patients with raised transaminases and normal imaging, rather than opting for a biopsy straightway. Patients with a low CAP and raised transaminases can be considered for a liver biopsy to look for alternate (other than NAFLD) causes of raised enzymes. The study also highlights the fact that cut-offs derived from other populations cannot be used as such for Indian population.

The strengths of this study include a prospective cohort and use of MR-PDFF as a reference standard. A significant number of patients were normal (normal MR-PDFF and liver biopsy), adding true controls to the data, which is missing from other Indian studies. A study from Delhi also found almost the same CAP cut-off (263 dB/m) to define ≥grade 1 steatosis; however, this study has mixed population of patients (NAFLD, viral hepatitis, and other etiologies) and MRI-PDFF was not available.

The limitations of the study include being a single center study and non-availability of liver biopsy in all subjects. Being a single center study, it represents data from North
Table 2 Diagnostic Accuracy of CAP for Detecting Liver Steatosis.

<table>
<thead>
<tr>
<th>Cut-off (dB/m)</th>
<th>AUROC (95% CI)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI PDFF ≥5%</td>
<td>0.93 (0.88–0.98)</td>
<td>90.4</td>
<td>90.9</td>
<td>98.1</td>
<td>64.5</td>
</tr>
<tr>
<td>MRI PDFF ≥10%</td>
<td>0.89 (0.84–0.94)</td>
<td>86.2</td>
<td>77.1</td>
<td>84.1</td>
<td>80.0</td>
</tr>
<tr>
<td>MRI PDFF ≥20%</td>
<td>0.78 (0.69–0.87)</td>
<td>72.0</td>
<td>70.5</td>
<td>35.3</td>
<td>91.8</td>
</tr>
</tbody>
</table>

CAP, controlled attenuation parameter; MRI PDFF, magnetic resonance imaging-proton density fat fraction; AUROC, area under receiver operating curve; PPV, positive predictive value; NPV, negative predictive value.

India. As Indian population is not homogeneous, a multicenter study will be a welcome addition to our understanding regarding the role of CAP in detecting mild steatosis.

We confirmed the good diagnostic accuracy of CAP for the detection of hepatic steatosis as defined by MRI-PDFF ≥5%. We suggest an optimal cut-off value of 262 dB/m in an Indian cohort of well-characterized individuals. This optimal cut-off of CAP may enable the utility of CAP for the diagnosis of NAFLD in routine clinical practice in India. Further studies are required to assess the clinical utility of CAP for diagnosis of liver steatosis, especially in Indian populations.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

MSK. was responsible for the study concept and design, data collection, interpretation of data, drafting of the manuscript, and approval of the final submission. NSC, DS, JSW, SD, SKM, NS and RS contributed to the patient referrals, data collection, critical revision of the manuscript, and approval of the final submission. MKS, NSC contributed to the statistical analysis, data collection, critical revision of the manuscript, and approval of the final submission. SK contributed to the data collection (MRI PDFF). NSC, SD and DS contributed to the data collection (transient elastography), critical revision of the manuscript, and approval of the final submission. MSK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICTS OF INTEREST

The authors have none to declare.

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REFERENCES


**SUPPLEMENTARY DATA**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2021.10.003.