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Assessment of hepatic fibrosis and steatosis by vibration-controlled transient elastography and controlled attenuation parameter versus non-invasive assessment scores in patients with non-alcoholic fatty liver disease

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is regarded as the most common liver disease in the twenty-first century, and a condition leaving individuals at increased risk of extra-hepatic morbidity. Liver biopsy has long been regarded as the gold standard for diagnosis and prognostication of patients with NAFLD. However, due to its invasive nature and potential complications (e.g., bleeding), other methods for non-invasive laboratory and radiological assessment of hepatic steatosis and fibrosis in NAFLD have evolved and include scores such as AST/Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4) score, NAFLD fibrosis score (NFS), and fatty liver index (FLI), in addition to radiological methods such as transient elastography (TE), which is a well-validated non-invasive ultrasound-based technique for assessment of hepatic fibrosis. Recently, novel development of controlled attenuation parameter (CAP) in TE allowed simultaneous assessment of hepatic steatosis. This provided a chance to assess both hepatic fibrosis and steatosis in the same setting and without any unwanted complications. This study aimed at assessing the role of TE and CAP versus other non-invasive assessment scores for liver fibrosis and steatosis in patients with NAFLD.

Results: This study included 90 patients diagnosed with NAFLD based on abdominal ultrasonography, body mass index, and serum liver enzymes. All patients were assessed with TE and non-invasive scores (APRI score, FIB-4 score, NFS, and FLI). There was a highly significant positive correlation between fibrosis and steatosis grades assessed by TE and other non-invasive respective scores. Both TE and CAP achieved acceptable sensitivity and specificity compared to other non-invasive assessment methods.

Conclusions: TE with CAP can be used as a screening method for patients suspected with NAFLD or patients without a clear indication for liver biopsy. CAP allows a non-invasive method of assessment of hepatic steatosis in patients with NAFLD.

Keywords: Fatty, Liver, Elastography, Fibrosis, Steatosis, Attenuation

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Background

Non-alcoholic fatty liver disease (NAFLD) is regarded as the most common liver disease in the twenty-first century [1], a growing risk factor for hepatocellular carcinoma (HCC), a leading indication for liver transplantation [2], and a condition leaving individuals at increased risk of extra-hepatic morbidity and mortality [3].

Over the past 2 decades, NAFLD has grown from a relatively unknown disease to the most common cause of chronic liver disease in the world. In fact, 25% of the world's population is currently thought to have NAFLD [4]. The clinical spectrum of NAFLD ranges from a relatively benign fatty infiltration to non-alcoholic steatohepatitis (NASH) that can progress to liver cirrhosis, liver cell failure, or HCC [5]. NAFLD is also associated with an increased risk of mortality due to liver disease and cardiovascular disease. The distinction of different forms of NAFLD is important in the clinical management of patients due to very different prognoses. Furthermore, liver fibrosis has emerged as the strongest predictor of long-term outcomes in patients with NAFLD [6].

The evaluation of liver fibrosis severity has become the main issue to verify the prognosis of NAFLD patients, and liver biopsy has long been regarded as the gold standard in this aspect. However, histological interpretation of liver biopsy is subject to micro-inhomogeneity, sampling errors, presence of un-fragmented cores, and observer variability among pathologists. Moreover, the invasive nature of this procedure in addition to its potential life-threatening complications such as bleeding, hematoma, and pain necessitated the identification of alternative non-invasive tools to replace liver biopsy in diagnosis and prognostication of NAFLD patients [7].

Non-invasive laboratory and radiological assessment methods for hepatic steatosis and fibrosis in NAFLD have evolved during the past decade, and these methods may be able to overcome the limitations of liver biopsy. These methods include scores such as AST/platelet ratio index (APRI) score, fibrosis-4 (FIB-4) score, NAFLD fibrosis score (NFS), and fatty liver index (FLI), in addition to radiological methods such as transient elastography (TE), which is an ultrasound-based technique and considered as one of the most extensively used and well-validated non-invasive methods for assessment of hepatic fibrosis [8].

Presently, non-invasive assessment of hepatic fibrosis may be conducted using both combined biochemical markers such as cytokeratin 18 (CK18) and specific devices such as TE [9]. Liver stiffness measurement (LSM) by TE (FibroScan, Echosens, Paris) uses ultrasound-based technology for quantitative assessment of hepatic fibrosis. It has been shown to be sufficiently accurate to predict the fibrosis stage in NAFLD patients [10].

Vibration-controlled transient elastography (VCTE) measures the speed of a mechanically induced shear wave using pulse-echo ultrasonic acquisitions in a much larger portion of the tissue, approximately 100 times more than a liver biopsy core. However, prior studies evaluating the performance of VCTE in NAFLD have been limited by medium (M) size probes with an ultrasound probe frequency of 3.5 MHz to measure LSM at a depth of 2.5 and 6.5 cm from the skin. LSM assessed by VCTE has been shown to be an easy to perform, non-invasive test to reliably estimate the degree of liver fibrosis in patients with NAFLD [11].

The newer version of VCTE had several features that not only overcome its prior limitations, but also enhance its role as a diagnostic tool in the evaluation of patients with NAFLD. It is currently approved by the regulatory authorities to measure a 3.5 MHz ultrasound coefficient of attenuation, known as the controlled attenuation parameter (CAP).

CAP is a new technology based on the principle of the ultrasonic attenuation of transient elastography depending on the viscosity [fat] of the medium [liver] and the distance of propagation of the ultrasonic signals into the liver, providing a useful method for the quantitative detection of liver fat content and is considered a better assessment method for hepatic steatosis. Compared with ultrasound, this technology improves the sensitivity and specificity for the diagnosis of fatty liver and can be used for universal screening, diagnosis, and follow-up in NAFLD patients [12].

While LSM is measured in kilopascals (KPa), CAP is measured in decibels per meter (dB/m) and reflects the decrease in the amplitude of ultrasound signal in the liver [13]. Therefore, a higher CAP is reflective of the higher degree of steatosis. CAP is displayed only when LSM is valid, as it is only computed from the ultrasound signals used for acquiring LSM. The shear wave speed with an estimation of stiffness and CAP currently allows for simultaneous assessment of both liver fibrosis and steatosis [14].

This study aimed at the evaluation of the role of TE and CAP in the assessment of both liver fibrosis and steatosis in comparison to other non-invasive assessment scores such as APRI, FIB-4, NFS, and FLI in patients with NAFLD.

Methods

This study included 90 patients with NAFLD recruited from the outpatient clinics of Ain Shams University Hospitals and Theodor Bilharz Research Institute over a 6-month period from June to December 2019. All participants provided written informed consent prior to enrollment. Written consents were approved by the ethical committee of both institutions.

All patients were subjected to thorough history taking and clinical examination with special emphasis on the presence of risk factors, previous history, signs or symptoms, or complications of chronic liver disease or viral hepatitis. All patients with causes of liver disease other than NAFLD (e.g., viral hepatitis, hepatocellular carcinoma, Wilson's disease, and hemochromatosis) were excluded. Physical measurements were done and included:

- Body mass index (BMI): weight (kg)/height (m)² (normal: < 25)
- Waist circumference (WC): measured horizontally at the level of the navel without compressing the skin. (Normal: males 78:94 cm, females 64:80 cm).

Routine laboratory investigations were done for all patients participating in the study, including complete blood count, liver function tests, renal function tests, lipid profile, blood glucose levels, thyroid function tests, and coagulation profiles.

Pelviabdominal ultrasound was done to all patients using the Philips Envisor C HD device. Measurements were performed after overnight fasting with the patient in a supine position with emphasis on measuring the span of the right hepatic lobe in the mid-clavicular line on oblique view and classified as shrunken (< 11 cm), average (11–15 cm), or enlarged (> 15 cm). Hepatic texture as regards fat infiltration was also noted.

The diagnosis of NAFLD in recruited patients depended on high BMI, abnormalities in liver enzymes, detection of hepatic steatosis on pelviabdominal ultrasonography, features of metabolic syndrome, and non-invasive assessment scores for hepatic fibrosis, e.g., FIB-4, APRI, NFS, and hepatic steatosis, e.g., FLI [15].

VCTE was done for all patients using FibroScan 502 (Echosens, Paris, France) device using two probes: M+ and XL+, which was available at the participating institutions, for measuring LSM and CAP.

All studies were performed by a dedicated study coordinator using standardized protocols as provided by the manufacturer. Two scans were performed during the same visit several minutes apart by the same coordinator (intra-operator assessment) or by a second coordinator (inter-operator assessment) in a subset of participants. Only patients with 10 valid measures were included, and poor results were excluded from the analysis. According to the manufacturer's instructions, in addition to previous studies, the stages of fibrosis (F0: 1–6, F1: 6.1–7, F2: 7–9, F3: 9.1–10.3, and F4: \geq 10.4) were defined in kPa [15, 16]. Moreover, steatosis stages (S0: < 215, S1: 216–252, S2: 253–296, S3: > 296) were defined in dB/m [17].

Fibrosis and steatosis scores were also calculated for each patient using standardized equations (APRI [18], FIB-4 [19], NFS [20], and FLI [21]).

The results were tabulated and statistically analyzed using computer software (SPSS version 25 for Windows, SPSS Inc., Chicago, IL). Descriptive statistics included mean and standard deviation for quantitative variables, in addition to number and percentage for qualitative variables. Correlation between dependent and independent variables was done using Pearson's and Spearman rank correlation coefficients. Diagnostic accuracy was assessed through sensitivity, specificity, and accuracy using receiver operator characteristics (ROC) curve. Significance levels were determined based on the level of probability (p) where $p < 0.05$ indicated a significant difference and $p < 0.001$ indicated a highly significant difference.

Results

This cross-sectional study included 90 adult patients (Table 1) with NAFLD, divided into 62 females (68.9 %) and 28 males (31.1 %), aging 18–72 years (mean age 45.53 ± 11.5), who have either abnormal serum transaminases or GGT levels, or steatosis at ultrasonography, or have one or more of the following features of metabolic syndrome:

- Fasting blood glucose greater than 110 mg/dl or a previous diagnosis of diabetes mellitus.
- BMI of 27 or higher or WC greater than 102 cm in males and 88 cm in females.
- Blood pressure greater than 130/85 or current anti-hypertensive treatment.
- Triglyceride levels greater than 150 mg/dl or current use of fibrates.
- HDL-cholesterol lower than 40 mg/dl (males) and 50 mg/dl (females).

There was a highly significant positive correlation between fibrosis grades assessed by TE and other non-invasive scores and lab parameters (APRI, FIB-4, NFS), ALT, AST, and gamma-glutamyl transferase (GGT), in addition to a highly significant negative correlation between fibrosis grades and platelet count (Table 2).

As regards grades of hepatic steatosis, there was a statistically significant positive correlation with BMI, WC, FLI, and presence of diabetes mellitus, in addition to a highly significant positive correlation with lab parameters such as ALT, AST, GGT, cholesterol, and triglycerides. Detailed correlation and regression results are summarized in Table 3.

Evaluation of the diagnostic accuracy of TE showed that the best cut-off value for fibrosis detection by TE (LSM) vs. APRI, FIB-4, and NFS scores is overall average 5.2 which fulfills the highest sensitivity, specificity, and accuracy (85.30%, 47.70%, and 85.48%, respectively, AUC 0.742). Detailed results are summarized in Table 4.

Table 1 Basic patients' demographic data and characteristics

Parameter	N (%) / mean \pm SD
Gender	
Male	28 (31.1%)
Female	62 (68.9%)
Age (years)	45.53 \pm 11.5 (Range: 18-72)
BMI (Kg/m ²)	35.59 \pm 5.77
WC (cm)	109.44 \pm 11.54
Diabetes mellitus	
Yes	47 (52.2%)
No	43 (47.8%)
Fibrosis grade	
F0	52 (57.78%)
F1	20 (22.22%)
F2	16 (17.78%)
F4	2 (2.22%)
Steatosis grade	
S0	11 (12.2%)
S1	18 (20.0%)
S2	31 (34.4%)
S3	30 (33.3%)
Overall LSM	8.61 \pm 1.48
APRI	10.74 \pm 7.29
FIB-4	0.92 \pm 0.56
NFS	- 1.61 \pm 2.922
FLI	57.8 \pm 7.73

On the other hand, evaluation of the diagnostic accuracy of CAP showed that the best cut-off value for steatosis detected by CAP vs. FLI score is 220.5 which fulfills the highest sensitivity, specificity, and accuracy (86.00%, 65.0%, and 85.65%, respectively). Detailed results are summarized in Table 5.

Discussion

NAFLD is regarded as the most common liver disease in the twenty-first century, and it is present if at least 5% of the liver weight is fat without excess alcohol consumption or secondary causes of fat accumulation in the background. Approximately 25% of adults around the world have NAFLD, and the prevalence is still increasing.

The majority of patients in this study had no or mild liver fibrosis [F0: 52 (57.78%), F1: 20 (22.22%)], while 16 patients showed moderate fibrosis [F2: 16 (17.78%)], and only 2 patients showed advanced fibrosis [F4:2 (2.22%)]. These results come against the results of another study done by Fallatah and his colleagues assessing the role of FibroScan compared to other non-invasive assessment scores in 122 Saudi patients with NAFLD. In his study,

there was a high percentage of patients showing advanced liver fibrosis by FibroScan [F4: 40 (32.8%)]. These contradicting results can be possibly attributed to demographic differences between patient populations of the two studies, where there is a high prevalence of metabolic syndrome and type 2 diabetes mellitus in the Saudi population, explaining the high prevalence of advanced NAFLD-related liver fibrosis [16].

On the other hand, our results agree with Fallatah et al. study which concluded that there was a significant positive correlation between LSM detected by TE as compared to APRI and FIB-4 results ($r = 0.51$, $r = 0.50$, $p < 0.001$) [16]. This also agrees with Sumida et al. who compared the results of 6 non-invasive markers of liver fibrosis based on data from 576 biopsy-proven NAFLD patients and found the sensitivity and specificity of FIB-4 score for the diagnosis of significant fibrosis was 90% and 64%, respectively, with diagnostic accuracy 87.1% (AUROC 0.871) [22]. Our study also goes with Boursier et al. who found the diagnostic accuracy of FIB-4 score for the diagnosis of significant fibrosis was 70.4% (AUROC 0.704) [23].

Moreover, the current study showed that there was statistically highly significant correlation between NFS score and LSM by TE ($r = 0.60$, $r = 0.53$, $p < 0.001$), which goes with results of another study done by Samy and colleagues who evaluated 60 patients with NAFLD and assessed fibrotest, NFS, FIB-4 score, and LSM by TE in the detection of liver fibrosis depending on liver biopsy and showed there was a statistically significant association between fibrosis and NFS value [24].

We also found that there is statistically highly significant negative correlation between platelet count and LSM by TE ($r = - 0.81$, $r = 0.70$, $p < 0.001$), and this agree with Fallatah et al. who found a strong negative correlation between platelet count and stiffness, as thrombocytopenia in liver disease is associated with advanced fibrosis and even cirrhosis [16].

Moreover, there was a highly significant statistical correlation between ALT, AST, and LSM measured by TE ($r = 0.54$, $r = 0.52$, $p < 0.001$ and $r = 0.52$, $r = 0.59$, $p < 0.001$, respectively), which agrees with Fabrellas and his colleagues who evaluated 215 subjects with metabolic risk factors without known liver disease identified randomly from a primary care center. A control group of 80 subjects matched by age and sex without metabolic risk factors was also studied. CAP and LSM were assessed using TE and found that there was a good statistical correlation between liver transaminases and increased LSM, suggestive of liver fibrosis [25].

As regards GGT, the current study showed a highly significant statistical correlation between GGT and LSM by TE ($r = 0.60$, $r = 0.87$, $p < 0.001$), which goes in accordance with other study done by Mansour et al. who

Table 2 Correlation and regression between fibrosis grades by TE and different non-invasive parameters for liver fibrosis

Relations		Correlation and regression	P value
APRI	Fibrosis value	$r = 0.76$	0.0001
	Fibrosis grade	$r = 0.73$	0.0001
	Regression	Fibrosis value = $3.242 + 0.233$ (APRI)	0.0001
FIB-4	Fibrosis value	$r = 0.69$	0.0001
	Fibrosis grade	$r = 0.64$	0.0001
	Regression	Fibrosis value = $3.221 + 2.732$ (FIB-4)	0.0001
NFS	Fibrosis value	$r = 0.53$	0.0001
	Fibrosis grade	$r = 0.60$	0.0001
	Regression	Fibrosis value = $5.530 + 0.161$ (NFS)	0.0001
Platelet counts	Fibrosis value	$r = -0.70$	0.0001
	Fibrosis grade	$r = -0.81$	0.0001
	Regression	Fibrosis value = $11.922 - 0.020$ (platelet counts)	0.0001
ALT	Fibrosis value	$r = 0.52$	0.0001
	Fibrosis grade	$r = 0.54$	0.0001
	Regression	Fibrosis value = $2.698 + 0.101$ (ALT)	0.0001
AST	Fibrosis value	$r = 0.59$	0.0001
	Fibrosis grade	$r = 0.52$	0.0001
	Regression	Fibrosis value = $1.670 + 0.130$ (AST)	0.0001
GGT	Fibrosis value	$r = 0.60$	0.0001
	Fibrosis grade	$r = 0.87$	0.0001
	Regression	Fibrosis value = $2.045 + 0.113$ (GGT)	0.0001

analyzed 108 patients with NAFLD and found a statistically significant correlation between GGT and LSM by TE ($r = 0.242$, $p < 0.05$) [26].

As regards liver steatosis grades, the current study showed that most patients had marked hepatic steatosis as demonstrated by CAP [S2: 31 (34.4%), S3: 30 (33.3%)], while the rest showed mild steatosis [S0: 11 (12.2%), S1: 18 (20%)]. This comes against the results of another study by de Lédinghen and his colleagues which concluded that the majority of patients showed no or mild steatosis [S0: 58 (51.8%), S1: 21 (18.8%)], while the rest of the patients showed more advanced steatosis grades [S2: 16 (14.3%), S3: 17 (15.2%)]. The discrepancy in the results between the two studies can be attributed to differences in the study population, where in his study, the mean BMI of patients was 26 kg/m^2 , while in our current study, the patients had mean BMI of 35.59 ± 5.77 . It is clear from this data that the patients in the current study had higher mean body weight and thus are expected to be more liable to hepatic steatosis [17].

We also found that there is a statistically highly significant correlation between FLI and steatosis measured by CAP ($r = 0.60$, $r = 0.53$, $p < 0.001$), and this revealed that FLI has a high discriminatory power in the diagnosis of NAFLD. This result agrees with Motamed and his colleagues who analyzed 5052 subjects and found that there

was a significant positive high correlation observed between serum FLI and NAFLD (AUC = 0.8656, 95% CI 0.8548–0.8764) which was also confirmed by binary regression, to the point that a one-unit increase in FLI led to a 5.8% increase in the chance of developing NAFLD and showed good predictive performance in the diagnosis of NAFLD [27]. Additionally, this agrees with Dehnavi et al. who analyzed 212 patients with NAFLD and found that FLI was significantly associated with NAFLD (OR = 1.062, 95%CI 1.042–1.082, $p < 0.001$), and that mean FLI, BMI, WC, TG, and GGT were all significantly higher in NAFLD patients than in non-NAFLD participants, and that a one unit increase in FLI elevated the chance of developing NAFLD by 6.2% [28].

We also found that there is a statistically significant correlation between GGT and steatosis measured by CAP ($r = 0.60$, $r = 0.53$, $p < 0.001$) which goes with the findings of Dehnavi et al. who concluded that there is a statistically significant correlation between GGT and steatosis (AUC = 0.66, 95%CI = 0.58–0.75, $p < 0.001$) [28]. This also agrees with Motamed et al. who found that there was a significant positive high correlation was observed between serum GGT and NAFLD (AUC = 0.6927, 95% CI 0.6772–0.7081), $p < 0.0001$) [27].

We also found that there is a highly significant statistical correlation between TG and serum cholesterol as

Table 3 Correlation and regression between steatosis grades by CAP and different non-invasive parameters for liver steatosis

Relations		Correlation and regression	P value
FLI	Steatosis value	$r = 0.26$	0.012
	Steatosis grade	$r = 0.44$	0.0001
	Regression	Steatosis value = $251.005 + 2.006$ (FLI)	0.012
BMI	Steatosis value	$r = 0.54$	0.028
	Steatosis grade	$r = 0.59$	0.004
	Regression	Steatosis value = $246.676 + 0.447$ (BMI)	0.019
WC	Steatosis value	$r = 0.62$	0.036
	Steatosis grade	$r = 0.59$	0.024
	Regression	Steatosis value = $222.269 + 0.369$ (WC)	0.003
ALT	Steatosis value	$r = 0.56$	0.0001
	Steatosis grade	$r = 0.57$	0.0001
	Regression	Steatosis value = $188.947 + 2.445$ (ALT)	0.0001
AST	Steatosis value	$r = 0.50$	0.0001
	Steatosis grade	$r = 0.52$	0.0001
	Regression	Steatosis value = $184.903 + 2.488$ (AST)	0.0001
GGT	Steatosis value	$r = 0.58$	0.0001
	Steatosis grade	$r = 0.56$	0.0001
	Regression	Steatosis value = $218.29 + 0.46$ (GGT)	0.0001
TG	Steatosis value	$r = 0.56$	0.0001
	Steatosis grade	$r = 0.58$	0.0001
	Regression	Steatosis value = $205.268 + 0.357$ (TG)	0.0001
Serum cholesterol	Steatosis value	$r = 0.64$	0.0001
	Steatosis grade	$r = 0.78$	0.0001
	Regression	Steatosis value = $114.586 + 0.721$ (cholesterol)	0.0001
DM	Steatosis value	$r = 0.46$	0.026
	Steatosis grade	$r = 0.49$	0.002
	Regression	Steatosis value = $257.766 + 10.118$ (diabetes or not)	0.041

compared to steatosis measured by CAP ($r = 0.56$, $r = 0.58$, $p < 0.001$, and $r = 0.64$, $r = 0.78$, $p < 0.001$, respectively). This agrees with Kwok et al. who examined 1918 patients with CAP and LSM and found that increased CAP ≥ 222 dB/m was associated with higher body weight, BMI, WC, TG, fasting plasma glucose, and ALT. It was also associated with lower HDL cholesterol [13].

We also found that there is a statistically significant correlation between BMI and WC in comparison to steatosis grades and values obtained by CAP ($r = 0.54$, $r = 0.59$, $p < 0.028$, and $r = 0.59$, $r = 0.62$, $p < 0.036$, respectively), and this agrees with Dehnavi et al. who found that there is a highly significant correlation between BMI and WC and steatosis grades and values ($p < 0.001$) [28].

Table 4 Sensitivity, specificity, and accuracy for fibrosis by TE (LSM) and non-invasive assessment scores

Items	Fibrosis by LSM vs. APRI	Fibrosis by LSM vs. FIB-4	Fibrosis by LSM vs. NFS	Average
Best cut-off (KPa)	4.50	6.95	4.10	5.20
Area under the curve (AUC)	0.788	0.917	0.742	0.838
Sensitivity	85.70%	85.00%	86.00%	85.30%
Specificity	50.00%	52.00%	47.00%	47.70%
Accuracy	85.50%	85.52%	85.47%	85.48%
95% CI	0.67–0.91	0.85–0.98	0.64–0.85	0.76–0.92
P value	0.0001	0.0001	0.0001	0.0001

Table 5 Sensitivity, specificity, and accuracy for steatosis by CAP and non-invasive assessment scores

Items	Steatosis by CAP vs. FLI score
Best cut-off (dB/m)	220.50
Area under the curve (AUC)	0.782
Sensitivity	86.00%
Specificity	65.00%
Accuracy	85.65%
95% CI	0.65–0.91
P value	0.001

The current study also found that there was a statistically significant correlation between DM and steatosis grades and values obtained by CAP ($r = 0.46$, $r = 0.49$, $p < 0.026$), which goes with Kwok et al. who found that there is a significant positive high correlation observed between serum fasting blood glucose and steatosis and that around 32–62% of diabetic patients were found to have NAFLD [13].

We also found that the best cut-off value for fibrosis detection by TE (LSM) vs. NFS is 4.10 KPa, which fulfills the highest sensitivity, specificity, and accuracy (Table 4). A study by Samy and his colleagues found that, depending on liver biopsy, the sensitivity, specificity, and accuracy of NFS to detect liver fibrosis are good, with AUROCs of 0.94. For mild fibrosis, the sensitivity, specificity, and accuracy of NFS was 89.47%, 90.24%, and 94.7%, respectively. On the other hand, the sensitivity, specificity, and accuracy of NFS in cases of severe liver fibrosis were found to be 100%, 89.8%, and 98.1%, respectively [24].

We also found that the best cut-off value for fibrosis detection by TE (LSM) vs. FIB-4 score is 6.95 KPa, which fulfills the highest sensitivity, specificity, and accuracy (Table 4). This also agrees with the results obtained by Samy et al. who concluded that, depending on liver biopsy, the sensitivity, specificity, and accuracy of FIB-4

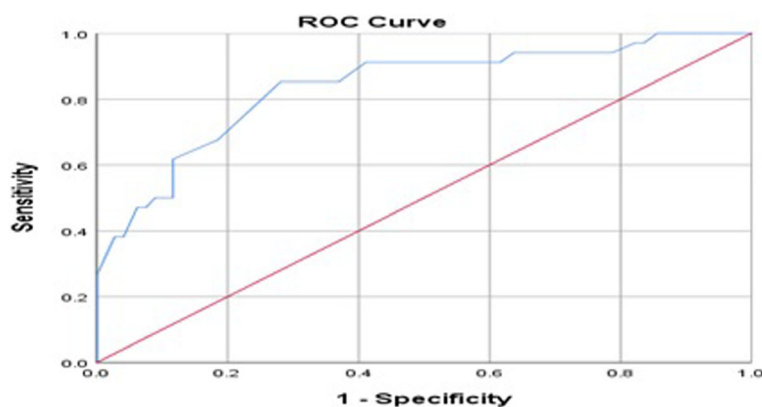
score to detect liver fibrosis are good, with AUROCs of 0.992 (94.7%, 97.6%, and 99.2%, respectively) [24]. Similarly, another study by Sumida et al. found the sensitivity and specificity of the FIB-4 score for the diagnosis of significant fibrosis was 90% and 64%, respectively, with diagnostic accuracy 87.1% [22].

Our results show that the best cut-off value for fibrosis detection by TE (LSM) vs. APRI score is 4.5 KPa, which fulfills the highest sensitivity, specificity, and accuracy (Table 4). This agrees with Kolhe et al. who analyzed histological and clinical data of 100 consecutive urban slum-dwelling patients with NAFLD and showed that APRI had sensitivity, specificity, accuracy, PPV, NPV, and AUROC of 85.2%, 87.7%, 95%, 58.33%, 96.05%, and 0.95, respectively, with a statistically high significant correlation between APRI and biopsy-proven fibrosis [29].

Our study shows that the best cut-off value for fibrosis detection by TE (LSM) vs. APRI, FIB-4, and NFS scores has an overall average of 5.2 Kpa, which fulfills the highest sensitivity, specificity, and accuracy (85.30%, 47.70%, and 85.48%, respectively, AUC 0.742) (Fig. 1). Similarly, Önerhag and his colleagues who included 144 patients with biopsy-proven NAFLD showed that FIB-4-index had the highest NPV (91%) and APRI the highest PPV (71%). The AUROC for FIB-4-index, NFS, and APRI acceptably predicted advanced fibrosis with values between 0.81 and 0.86 [30].

Our study results are close to Hashemi et al. who performed a meta-analysis that enrolled the literature published about LSM detected by TE for the diagnosis and staging of NAFLD and found the sensitivity and specificity of FibroScan in the detection of fibrosis to be 87.5% and 78.4%, respectively [31]. This also agrees with Boursier et al. who evaluated the diagnostic accuracy of LSM by TE in a cross-sectional study including 452 NAFLD patients; found that its accuracy was 83.1% [23].

Our study also agrees with Aykut et al. who compared the diagnostic performances of three different non-

**Fig. 1** ROC denoting the best cut-off value of LSM, which fulfills the highest sensitivity and specificity

invasive methods including TE for the detection of liver fibrosis in a total of 88 patients with biopsy-proven NAFLD and found the diagnostic accuracy 90.2% [32].

Our results show that the best cut-off value for steatosis detection by CAP vs FLI score is 220.5 dB/m, which fulfills the highest sensitivity, specificity, and accuracy (Table 5) (Fig. 2). Motamed et al. also showed that FLI showed good performance in the diagnosis of NAFLD with accuracy equal to 86.56% (AUC = 0.8656) and revealed that FLI has a high discriminatory power in the diagnosis of NAFLD [27]. This could be somewhat anticipated due to the fact that FLI is composed of four quantities related to NAFLD, including BMI, WC, GGT, and TG. A high BMI or WC, the main obesity indices, is considered an essential risk factor for NAFLD, and the prevalence of NAFLD substantially increases in obese individuals.

Similarly, Dehnavi et al. investigated the relationship between FLI and NAFLD based on logistic regression and their findings revealed a highly significant positive relationship between FLI and NAFLD, so that even a one unit increase in FLI elevated the chance of developing NAFLD by 6.2% (OR = 1.062, 95%CI 1.042–1.082, $p < 0.001$). Even after adjusting for confounding factors such as sex, age, diastolic blood pressure (DBP), FBS, ALT, and LDL, the logistic regression analysis showed a significant positive association between FLI and NAFLD (OR = 1.059, 95%CI 1.035–1.083, $p < 0.001$) [28].

These findings go also with Siddiqui et al. who performed a prospective study of 393 adults with NAFLD

who underwent VCTE within 1 year of liver histology analysis and found that the CAP value is positively associated with severity of hepatic steatosis and the cross-validated AUROC is 76% for classifying patients with $\geq 5\%$ steatosis on histology [33]. This also goes with Eddowes et al. who evaluated 450 patients and assessed the diagnostic accuracy of CAP and LSM against liver biopsy and found that CAP by TE is accurate non-invasive methods for assessing liver steatosis in patients with NAFLD with an AUROC of 0.87 (95% CI 0.82–0.92), sensitivity of 0.80, and specificity of 0.83 [34].

Conclusions

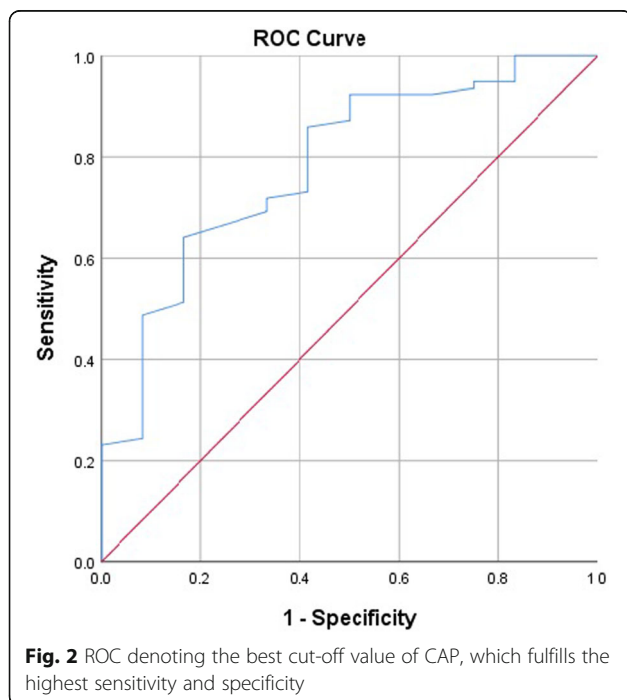
- TE including LSM and CAP has the advantages of being a simple, non-invasive, inexpensive, painless, and operator/machine-independent method and displays good application prospects.
- Our study shows a highly significant positive correlation between LSM by TE and other non-invasive assessment scores of liver fibrosis (APRI, FIB-4, and NFS), in addition to ALT, AST, and GGT.
- Moreover, our study shows a highly significant positive correlation between hepatic steatosis measurement as obtained by CAP and other parameters, including BMI, WC, FLI, presence of diabetes mellitus, ALT, AST, GGT, cholesterol, and triglycerides.
- The best cut-off value for liver fibrosis detection by TE (LSM) vs. APRI, FIB-4, and NFS scores is overall average 5.2, which fulfills the highest sensitivity, specificity, and accuracy (85.30%, 47.70%, and 85.48%, respectively, AUC 0.742).
- On the other hand, the best cut-off value for steatosis detected by CAP vs. FLI score is 220.5 which fulfills the highest sensitivity, specificity, and accuracy (86.00%, 65.0%, and 85.65%, respectively).
- The possibility of concomitant assessment of liver fibrosis (using LSM) and of steatosis (using CAP) makes TE a promising non-invasive tool for assessing and quantifying both steatosis and fibrosis in patients with NAFLD.

Abbreviations

APRI: AST/platelet ratio index; AUC: Area under the curve; BMI: Body mass index; CAP: Controlled attenuation parameter; CK18: Cytokeratin 18; CI: Confidence interval; dB/m: Decibels/meter; FIB-4: Fibrosis-4 score; FLI: Fatty liver index; GGT: Gamma-glutamyl transferase; HCC: Hepatocellular carcinoma; HDL: High-density lipoproteins; KPa: Kilopascals; LSM: Liver stiffness measurement; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; NFS: NAFLD fibrosis score; ROC: Receiver operator characteristics; TE: Transient elastography; TG: Triglycerides; VCTE: Vibration-controlled transient elastography; WC: Waist circumference

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Authors' contributions

EB formulated the research idea, AM prepared the study design, shared in the interpretation of collected data, and shared in the revision of the manuscript. SB collected the research data. ME shared in interpretation and analysis of collected data. AA drafted the manuscript. AE revised and proofread the manuscript draft and shared in data analysis. The authors read and approved the final manuscript.

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Availability of data and materials

All data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All subjects involved in the study signed an informed written consent to participate. This study was performed in accordance with the standards of the ethical research committee of Ain Shams University (reference number: not applicable).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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