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Real-time elastography "FibroScan" compared to simple non-invasive screening tools in the assessment of liver fibrosis in non-alcoholic fatty liver patients

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Abstract

Background and aim: Non-alcoholic fatty liver disease (NAFLD) and its subtype non-alcoholic steatohepatitis (NASH) are increasing worldwide. NASH is characterized by active liver inflammation with severe consequences including progressive fibrosis, cirrhosis, and eventually hepatocellular carcinoma. In Egypt, the prevalence of NAFLD diagnosed by ultrasound is about 65.3% in children and 62.7% in adults. Liver biopsy, the only reliable method of differentiating simple steatosis from NASH, has a major disadvantage of being an invasive procedure with various complications. Serum tests have limitations including non-specificity for liver inflammation and affection by clearance rates. This study aimed to assess the reliability of simple non-invasive tests for liver fibrosis (namely fibrosis-4 "FIB-4" score and NAFLD fibrosis score) in comparison with real-time elastography (RTE or FibroScan) in patients diagnosed with NAFLD.

Patients and methods: This observational prospective case–control study was conducted on 100 cases with NAFLD and 30 healthy subjects. All patients and controls were subjected to serological (FIB-4 score and NAFLD fibrosis score) and radiological (ultrasonography and RTE) assessments of liver fibrosis.

Results: In advanced FIB-4 score ≥ F3, there was a good correlation between the findings of the RTE and each of the FIB-4 scores (with a sensitivity of 90%, specificity of 93.3%, positive predictive value (PPV) of 60%, negative predictive value (NPV) of 98.8%, with a total accuracy of 93%), NAFLD fibrosis score (with a sensitivity of 52.6%, specificity of 93.8%, PPV of 66.7%, NPV of 89.4%, with a total accuracy of 86%), and grading of steatosis by ultrasound.

Conclusions: RTE is beneficial in diagnosing and assessing NAFLD, especially in advanced cases "F3 and beyond."

Keywords: NAFLD, Elastography, Liver biopsy

Introduction

Non-alcoholic fatty liver disease (NAFLD) and its subtype non-alcoholic steatohepatitis (NASH) are characterized by abnormal fat accumulation in the liver in the absence of excessive alcohol intake [1]. NAFLD and NASH are increasing worldwide, with severe consequences of NASH including progressive fibrosis, cirrhosis, and eventually hepatocellular carcinoma [2]. NAFLD is found to be an additional feature of metabolic syndrome, and the role of insulin resistance, which is a component of the metabolic syndrome, in the pathogenesis of NAFLD is supported by pathophysiologic considerations, laboratory investigations, and clinical associations

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[3]. The only reliable method of differentiating simple steatosis from NASH was liver biopsy. However; a major disadvantage of liver biopsy is that it is an invasive procedure and may be associated with various complications. As a result, it was necessary to develop accurate and non-invasive techniques to diagnose NASH and assess the histological severity of the disease [4]. Non-invasive tests of hepatic fibrosis attempt to predict the stage of hepatic fibrosis that would be seen histologically. The tests are often used to differentiate patients with significant fibrosis (F2 to F4) from those with minimal or no fibrosis (F0 to F1). There are two general categories of non-invasive tests for fibrosis: serologic panels of tests and radiologic tests [5]. Serological tests include aspartate aminotransferase to platelet ratio (APRI score), Fibrosis-4 index (FIB-4,) and others [6]. All the serum tests have limitations including non-specificity for liver inflammation and affection by clearance rates [7]. Real-time elastography (RTE = FibroScan) has emerged as the non-invasive method of reference, and it is a widely used and validated technique that measures liver stiffness based on using elastic shear waves emitted from the vibrator attached to the ultrasound transducer probe [8].

This study aimed to assess the reliability of the simple non-invasive tests for liver fibrosis (namely FIB-4 score and NAFLD fibrosis score) in comparison with RTE (FibroScan) in patients diagnosed with NAFLD.

This observational prospective case–control study was conducted on 130 subjects, classified into two groups: group I included 100 cases having NAFLD (having bright liver in ultrasound with or without elevated liver enzymes), and group II included 30 healthy subjects (with normal liver in ultrasound and normal liver enzymes) as control. Informed consent was taken after explanation and informing the patient about all procedures and types of study. The study protocol was approved by the Alexandria Faculty of Medicine Ethical Committee (AFMEC).

Inclusion criteria included adults ≥ 18 years with NAFLD based on abdominal ultrasonography examination. The exclusion criteria included other chronic liver diseases including hepatitis C, hepatitis B, or autoimmune hepatitis (AIH); patients on hepatotoxic medications; those with advanced cardiac failure with hepatic congestion; and those who could not go for FibroScan examination such as those with a BMI of ≥ 35 kg/m^2 and those with clinical and/or ultrasonographic evidence of decompensated cirrhosis and ascites.

Methods

All patients and controls were subjected to the following:

History taking: age, urban or rural residence, special habits like alcohol intake or smoking, drug history with a specific interest in steatogenic medications like methotrexate and isoniazid anti-tuberculosis, family history suggesting chronic liver disease as autoimmune hepatitis, hemochromatosis, and Wilson's disease

Clinical examination: general examination with stress on weight, height, and body mass index (BMI); cardiovascular examination; chest examination; and abdominal examination with stress on liver palpation (size, surface, consistency, and borders), spleen palpation (enlarged or not), and any stigmata of liver cell failure like flabby tremors, abnormal pattern of hair distribution, and gynecomastia

The following are the laboratory investigations:

General labs: complete blood picture (CBC), fasting blood sugar, and 2 h post-prandial (mg/dl), glycated hemoglobin [HbA1c (%)], and serum creatinine (mg/dl).

Markers of liver injury [serum alanine aminotransferase (ALT) (IU/l), serum aspartate aminotransferase (AST) (IU/l), and serum alkaline phosphatase (ALP) (U/l)].

Liver function tests [serum total and direct bilirubin (mg/dl), serum albumin (g/dl), prothrombin time, and the international normalization ratio (PT, INR)].

Hepatitis markers [HBsAg and anti-HCV-Ab using third-generation enzyme-linked immunosorbent assay technique (ELISA), anti-mitochondrial antibody (AMA), and anti-smooth muscle antibody (ASMA) for auto-immune hepatitis].

Lipid profile [total cholesterol (mg/dl), triglycerides (mg/dl), high-density lipoproteins (HDL) (mg/dl), and low-density lipoprotein (LDL) (mg/dl)].

FIB-4 Index: using this formula: {age (years) × AST (U/l)}/{platelets (10^9/l) × [sqr (ALT)]$^{-1}$} [6].

APRI score: using this formula: [{AST (U/l)/upper limit of AST normal}/platelets (10^9/l) × 100] [9].

NAFLD fibrosis score: using this formula: [−1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet (× 10^9/l) − 0.66 × albumin (g/dl)] [10].

Imaging: real-time abdominal ultrasound was done by TOSHIBA-SSA-700A (Apilo 5) for all patients and controls included in the study for the evaluation of liver (size, border, parenchymal echotexture, hepatic veins, biliary radicals, common bile duct, and focal lesions), portal vein (caliber, patency by color Doppler), spleen (size, splenic vein diameter, and collaterals), and ascites (present or not).

Assessment and grading of steatosis by ultrasound: grading of steatosis revealed by ultrasound was done according to Saadeh et al as follows:

> Grade 1: the echogenicity of the liver is just increased.
> Grade 2: echogenicity of liver obscures the echogenicity of walls of portal vein branches.
> Grade 3: echogenicity the f liver obscures the diaphragmatic outline.

Liver stiffness measurement (LSM): FibroScan (M probe and XL probe) was carried out by an experienced examiner on all patients and controls, and the median liver stiffness of the 10 successful measurements fulfilling the criteria (success rate of greater than 60% and interquartile range/median ratio of < 30%) was recorded in kPa.

Statistical analysis

The collected data were tabulated and analyzed using the SPSS version 16 software (SPSS Inc., Chicago, ILL Company). Categorical data were presented as number and percentage while quantitative data were expressed as mean ± standard deviation (S.D), median, IQR, and range. The chi-square test (X^2) or Fisher's exact test (FET) was used to analyze the categorical variables. The coordinate of correlation was assessed by the Cohen kappa test was used to assess the degree of agreement between 2 raters. Quantitative data were tested for normality using the Shapiro-Wilks test, assuming normality at $P > 0.05$. The Student t test was used to analyze the normally distributed variables among 2 independent groups. Non-parametric variables were analyzed using the Man-Whitney U test. The accepted level of significance in this work was stated at 0.05 [$P < 0.05$ was considered significant; P-value > 0.05 is non-significant (NS); P-value ≤ 0.05 is significant (S); P-value ≤ 0.001 is highly significant (HS)].

Results

The socio-demographic characters, anthropometric measurements, and basic lab findings among the studied groups are discussed in Table 1. FIB-4 scores among the studied groups are discussed in Table 2. NAFLD fibrosis score among the studied groups is discussed in Table 3. Ultrasonographic (U/S) findings among the studied groups are discussed in Table 4. Real-time elastography findings among the studied groups are discussed in Table 5.

In advanced FIB-4 score ≥ F3, there is a good correlation between the finding of the real-time elastography and the FIB-4 score, with a sensitivity of 90%, specificity of 93.3%, positive predictive value (PPV) of 60%, negative predictive value (NPV) of 98.8%, total accuracy of 93%, and certainty index (95% CI) of 0.81–1.0 ($P < 0.001$ which is highly significant). This is shown in Table 6.

Table 1 Socio-demographic characters, anthropometric measurements, and basic lab findings among the studied groups

Variable	Group I ($n = 100$)	Group II ($n = 30$)	P
Age (years), mean ± SD	47.1 ± 11.6	43.1 ± 9.9 0.086	0.086 (NS)
Sex			0.083 (NS)
Male	60 (60%)	15 (50%)	
Female	40 (40%)	15 (50%)	
DM			0.001 (HS)
Non-diabetic	71 (71%)	30 (100%)	
Diabetic	29 (29%)	0 (0%)	
Weight (kg)	94.09 ± 17.0	75.0 ± 13.22	< 0.01(HS)
Height (cm)	167.6 ± 6.16	169.1 ± 6.72	0.253(NS)
BMI (kg/m^2)	33.4 ± 5.34	26.1 ± 3.62	< 0.01(HS)
Total cholesterol (mg/dl)	236.0 ± 17.7	123.1 ± 16.6	< 0.001(HS)
HDL cholesterol	58.5 ± 8.33	86.2 ± 9.44	< 0.001(HS)
LDL cholesterol	139.5 ± 9.71	82.1 ± 11.72	< 0.001(HS)
TG (mg/dl)	161.0 ± 18.38	99.2 ± 6.82	< 0.001(HS)
AST	35.8 ± 29.4	20.0 ± 5.8	< 0.001(HS)
ALT	39.7 ± 29.8	19.1 ± 7.3	< 0.001(HS)
T. bilirubin (mg/dl)	0.72 ± 0.17	0.86 ± 0.09	< 0.031(S)
Albumin (g/dl)	4.15 ± 0.36	4.55 ± 0.43	< 0.022(S)
INR	1.00 ± 0.01	1.00 ± 0.00	1.0 (NS)
Creatinine (mg/dl)	0.90 ± 0.15	0.91 ± 0.07	0.839 (NS)
Hemoglobin (mg/dl)	13.1 ± 1.85	12.9 ± 1.52	0.48 (NS)
WBCs (cell/mm^3)	7171.4 ± 2043.91	6302.5 ± 1283.16	0.038 (S)
PLTs (× 10^3/mm^3)	241.1 ± 74.77	241.9 ± 50.90	0.76 (NS)

In advanced NAFLD fibrosis score ≥ F3, there is a good correlation between the finding of the real-time elastography and NAFLD score, with a sensitivity of 52.6%, specificity of 93.8%, positive predictive value (PPV) of 66.7%, negative predictive value (NPV)of 89.4%, total accuracy of 86%, and certainty index (95% CI) of 0.59–0.88 ($P = 0.002$ which is significant). This is shown in Table 7. The relation between the grade of fatty liver and real-time elastography is shown in Table 8. The relation between the grade of fatty liver and FIB-4 score is shown in Table 9 and Fig. 1. The relation between the grade of fatty liver and NAFLD score is shown in Table 10 and Fig. 2. FIB-4 and NAFLD fibrosis scores show a degree of agreement of 86%. This is shown in Table 11 and Fig. 3.

Discussion

In the majority of patients, NAFLD is commonly associated with metabolic comorbidities such as obesity, diabetes mellitus, and dyslipidemia. Features of metabolic

Table 2 FIB-4 score results among the studied groups

FIB-4 score	Group I ($n=100$)		Group II ($n=30$)		Total ($n=130$)		*P*
	No	%	No	%	No	%	
Stages 0–1	61	61%	29	96.7%	90	69.2%	
Stage 2	29	29%	1	3.3%	30	23.1%	
Stages 3–4	10	10%	0	0%	10	7.7%	
Total	100	100%	30	100%	130	100%	
FIB-4 score points							
Mean ± SD	1.39 ± 1.02		−0.75 ± 0.32				< 0.001(HS)
Range	0.24 to 5.08		−1.47 to −0.22				

Table 3 NAFLD fibrosis score among the studied groups

NAFLD fibrosis score	Group I ($n=100$)		Group II ($n=30$)		Total ($n=130$)		*P*
	No	%	No	%	No	%	
F0–F2	48	48%	29	96.7%	77	59.2%	
Indeterminant	36	36%	1	3.3%	37	28.5%	
F3–F4	16	16%	0	0%	16	12.3%	
Total	100	100%	30	100%	130	100%	
NAFLD score points							
Mean ± S.D	−1.74 ± 1.17		−2.75 ± 0.91				< 0.001 (HS)
Range	−4.79 to −0.06		−4.57 to −0.36				

Table 4 Ultrasonographic (U/S) findings among the studied groups

U/S finding	Group I ($n=100$)		Group II ($n=30$)		Total ($n=130$)	
	No	%	No	%	No	%
Normal liver	0	0%	30	100%	30	23.1%
Grade 1 fatty liver	48	48%	0	0%	48	36.9%
Grade 2 fatty liver	24	24%	0	0%	24	18.4%
Grade 3 fatty liver	28	28%	0	0%	28	21.5%
Total	100	100%	30	100%	130	100%

Table 5 Real-time elastography findings among the studied groups

Real-time elastography findings	Group I ($n=100$)		Group II ($n=30$)		Total ($n=130$)	
	No	%	No	%	No	%
F0	0	0%	19	63.4%	19	14.6%
F1	55	55%	7	23.3%	62	47.7%
F2	30	30%	4	13.3%	34	26.2%
F3	6	6%	0	0%	6	4.6%
F4	9	9%	0	0%	9	6.9%
Total	100	100%	30	100%	130	100%

Table 6 Degree of agreement between real-time elastography results and FIB-4 score results

Real-time elastography results	FIB-4 score results				Total	
	< F3		≥ F3			
	No	%	No	%	No	%
< F3	84	93.3%	1	10%	85	85%
≥ F3	6	6.7%	9	90%	15	15%
Total	90	100%	10	100%	100	100%

Kappa test = 0.682; $P < 0.001$ (HS); degree of agreement = 93%

Table 7 Degree of agreement between real-time elastography results and NAFLD fibrosis score results

Real-time elastography results	NAFLD fibrosis score				Total	
	< F3		≥ F3			
	No	%	No	%	No	%
< F3	76	93.8%	9	47.4%	85	85%
≥ F3	5	6.2%	10	52.6%	15	15%
Total	81	100%	19	100%	100	100%

Kappa test = 0.505; $P < 0.001$ (HS); degree of agreement = 86%

Table 8 Relation between U/S grade of fatty liver and real-time elastography results

Real-time elastography results	U/S score of fatty liver						Total		*P*
	Grade I (*n* = 48)		Grade II (*n* = 24)		Grade III (*n* = 28)				
	No	%	No	%	No	%	No	%	
< F3	48	100%	23	95.8%	14	50%	85	85%	
≥ F3	0	0%	1	4.2%	14	50%	15	15%	
Total	48	100%	24	100%	28	100%	100	100%	< 0.001 (HS)

Table 9 Relation between U/S grade of fatty liver and FIB-4 score results

FIB-4 score results	U/S score of fatty liver						Total		*P*
	Grade I (*n* = 48)		Grade II (*n* = 24)		Grade III (*n* = 28)				
	No	%	No	%	No	%	No	%	
< F3	47	97.9%	23	95.8%	20	71.4%	90	90%	
≥ F3	1	2.1%	1	4.2%	8	28.6%	10	10%	
Total	48	100%	24	100%	28	100%	100	100%	< 0.001 (HS)

syndrome are not only highly prevalent in patients with NAFLD, but components of the syndrome also increase the risk of developing NAFLD. This was found by Chalasani and his coworkers in their study and runs with our results [11–14].

Obesity (excessive body mass index [BMI] and visceral obesity) is the most common and well-documented risk factor for NAFLD. Sasaki and his colleagues and Subichin with his coworkers found in their study that the majority (> 95%) of patients with severe obesity undergoing bariatric surgery had NAFLD which was in agreement with our results where there was a good correlation between the occurrence of fatty liver and increased body weight and BMI of patients [15, 16].

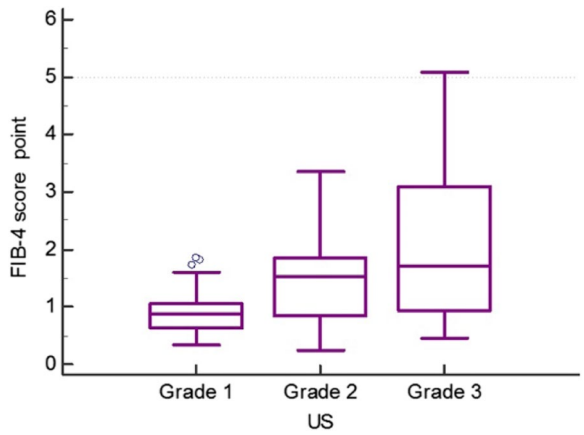

Fig. 1 Box plot showing the median and IQR of FIB-4 score according to the grade of fatty liver by ultrasound among the patients' group

Wu and his colleagues found that high serum triglyceride (TG) levels and low serum high-density lipoprotein (HDL) levels are also common in patients with NAFLD and the prevalence of NAFLD in individuals with dyslipidemia attending lipid clinics have been estimated to be 50% [17]. In agreement with that, our results revealed a good correlation between NAFLD and the increase in serum cholesterol, LDL, and TG in patients than in controls.

In a large, cross-sectional study conducted by Chalasani and his coworkers among 44,767 Taiwanese patients who attended a single clinic, the enrollees were stratified into four subgroups based on their total cholesterol to HDL cholesterol and TG to HDL cholesterol ratios. The overall prevalence rate of NAFLD was 53.76%; however, the NAFLD prevalence rate for those with the lowest total cholesterol to HDL-cholesterol and TG to HDL cholesterol ratios was 33.41%, whereas the prevalence rate in the group with the highest ratios was 78.04% [14].

Liver enzyme levels have low sensitivity and specificity and do not predict clinical outcomes and although elevated liver enzyme levels (i.e., AST and ALT levels) occur more commonly in patients with NASH compared with simple hepatic steatosis, not all patients with NASH have elevated AST or ALT levels. Even though a persistently elevated level of ALT can be associated with an increased risk of NAFLD progression, patients with advanced disease often have normal liver enzyme levels, making the identification of at-risk patients more conflicting [18]. In disagreement with that, our results documented that there was a significant increase in liver enzymes (AST, ALT) and total serum bilirubin in patients with fatty liver with a significant decrease in total serum albumin without significant change in INR between patients and controls.

Our results revealed that there was a positive correlation between NAFLD and the advanced stages in FIB-4 score. Angulo and his colleagues studied the histology of NAFLD patients and found that the most important histological feature of NAFLD associated with long-term mortality is fibrosis; specifically, zone 3 sinusoidal fibrosis plus periportal fibrosis (stage 2) to advanced (bridging) fibrosis [stage 3] or cirrhosis [stage 4], which was in agreement with our results [19].

Nobili et al. showed that liver stiffness (LS) detected by TE at more than 9 kPa was associated with a high stage of fibrosis in pathology. Yoneda et al. evaluated LS in

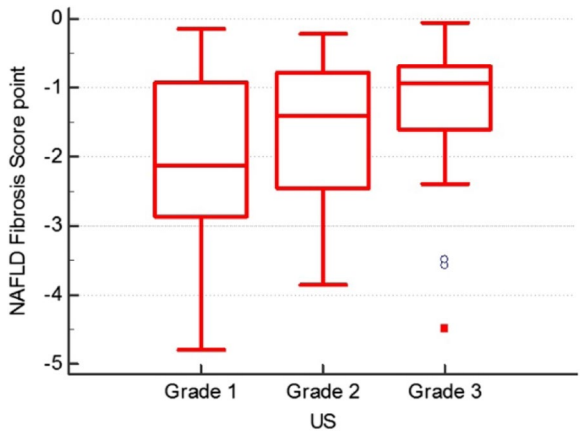

Fig. 2 Box plot showing the median and IQR of NAFLD fibrosis score according to the grade of fatty liver by ultrasound among the patients' group

Table 10 Relation between U/S grade of fatty liver and NAFLD fibrosis score results

NAFLD fibrosis score	U/S grade of fatty liver						Total		*P*
	Grade I (*n* = 48)		Grade II (*n* = 24)		Grade III (*n* = 28)				
	No	%	No	%	No	%	No	%	
< F3	47	97.9%	19	79.2%	15	53.6%	81	81%	
≥ F3	1	2.1%	5	20.8%	13	46.4%	19	19%	
Total	48	100%	24	100%	28	100%	100	100%	< 0.001 (HS)

Table 11 Degree of agreement between FIB-4 score results and NAFLD fibrosis score results

FIB-4 score	NAFLD fibrosis score				Total		*P*
	< F3		≥ F3				
	No	%	No	%	No	%	
< F3	80	98.8%	10	52.6%	90	90%	
≥ F3	1	1.2%	9	47.4%	10	10%	
Total	81	100%	19	100%	100	100%	< 0.001 (HS)

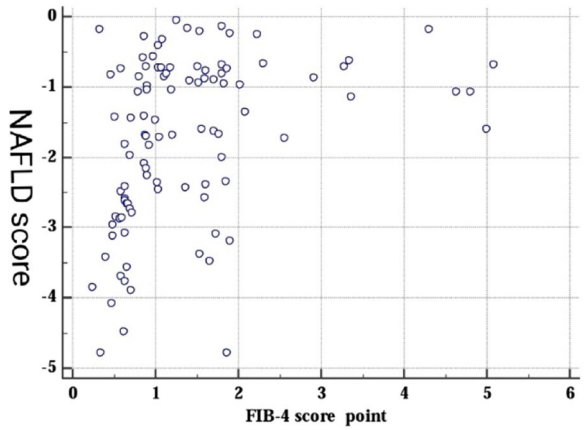

Fig. 3 Scatter graph showing a significant positive correlation (86%) between NAFLD score and FIB-4 score among the patients' group

97 NAFLD patients and observed that there was a significant correlation between METAVIR score and TE through different stages. He also concluded that using TE in detecting the level of fibrosis in NAFLD cases has high accuracy and can be a good alternative for liver biopsy in patients who cannot undergo invasive procedures, which adds to our results [20].

Cassinotto et al. demonstrated that TE can successfully identify significant fibrosis in the majority of patients. Fortunately, fibrosis is the histopathological feature most predictive of poor outcomes in NAFLD. It is also known that NAFLD patients who develop NASH are at substantially increased risk for progression of liver disease, with fibrosis progression rates that have been estimated to be one stage every 7 years, significantly higher than patients with non-NASH NAFLD. Thus, it is important to identify which patients had NASH from those with non-NASH NAFLD and to assess whether any elastography-based imaging modality can accurately discriminate those patients liable to develop NASH (based on significant fibrosis detected by TE) from those with non-NASH NAFLD which adds value to our results [21].

Patel and Sebastiani studied the various laboratory-based and radiation-based non-invasive tests (NITs) for the assessment of liver fibrosis and concluded that vibration-controlled transient elastography (VCTE) was a rapid, safe, and reproducible procedure for liver stiffness measurement (LSM) assessment that can be performed at the bedside with immediate results, and it represents a true point-of-care assessment and is the most widely used and validated technique for non-invasive imaging assessment of liver fibrosis. They also concluded that understanding the strengths and limitations of NITs would allow for more judicious interpretation in the clinical context, where NITs should be viewed as complementary to, rather than as a replacement for, liver biopsy [22].

In a recent study, Goyale et al. studied 105 adult patients with varying severity of NAFLD in a prospective, cross-sectional study. They concluded from their work that FibroScan was an accurate and accepted non-invasive tool that has shown concordance with liver biopsy results. In practice, NAFLD disease severity is usually assessed by a combination of the non-invasive clinical, biochemical, and sonographic parameters, with liver biopsy being reserved for patients with suspected progressive or advanced disease [23].

Eddowes et al. estimated the accuracy of Fibroscan vibration-controlled transient elastography liver stiffness measurement (LSMs) in assessing fibrosis in patients with suspected NAFLD in comparison with the standard-of-care liver biopsy. They found that LSM assessment achieved an area under the receiver operating characteristic curves (AUROC) values ranging from 0.80 to 0.89 for F3 and F4 cases. They concluded that LSMs by FibroScan are accurate non-invasive methods for assessing liver steatosis and fibrosis in patients with NAFLD [24]. In the current work, LSMs by FibroScan showed a good correlation with each FIB-4 score and NAFLD fibrosis score with AUROC of 0.81–1.0 and 0.59–0.88, respectively, in advanced cases ≥ F3.

Conclusions

Our results show that real-time elastography is beneficial in the diagnosis and assessment of NAFLD especially in advanced cases (F3 and beyond), with comparable efficacy but avoiding most of the drawbacks of other routine

non-invasive serological tests currently available and could be used as a routine practical method.

Limitations to the present study (field of search for upcoming studies): lack of direct correlation between RTE and liver biopsy, a limited number of the studied population.

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Authors' contributions
Afify MT and Shamseya AM designed the study. Afify MT, Shamseya AM, and Fayad HAS contributed to the data collection, data analysis, selection of patients, and drafting of the article. Elshafey MM and Fayad HAS performed the radiological examination. Afify MT and Shamseya AM critically revised the article for important intellectual content. All authors approved the final version to be published.

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Declarations

Ethics approval and consent to participate
The study protocol was approved by the Alexandria Faculty of Medicine Ethical Committee (AFMEC).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Ye JH, Chao J, Chang ML, Peng WH, Cheng HY, Liao JW et al (2016) Pentoxifylline ameliorates non-alcoholic fatty liver disease in hyperglycaemic and dyslipidaemic mice by upregulating fatty acid βoxidation. Sci Rep 6:33–42
2. Müller P, Messmer M, Bayer M, Pfeilschifter JM, Hintermann E, Christen U (2016) Non-alcoholic fatty liver disease (NAFLD) potentiates autoimmune hepatitis in the CYP2D6 mouse model. J Autoimmun 69:51–58
3. Kim JY, Lee C, Oh M, Im JA, Lee JW, Chu SH et al (2016) Relationship between non-alcoholic fatty liver disease, metabolic syndrome and insulin resistance in Korean adults: a cross-sectional study. Clin Chim Acta 458:12–17
4. Wieckowska A, Zein NN, Yerian LM, Lopez AR, McCullough AJ, Feldstein AE (2006) In vivo assessment of liver cell apoptosis as a novel biomarker of disease severity in nonalcoholic Fatty Liver Disease. Hepatology 44:27–33
5. Chou R, Wasson N (2013) Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med 158:807–820
6. Singal AG, Thomassen LV, Gretch DR, Shuhart MC (2011) Use of the AST to platelet ratio index in HCV/HIV co-infected patients. Aliment Pharmacol Ther 33:566
7. Güzelbulut F, Çetınkaya ZA, Sezıklı M, Yaşar B, Ozkara S, Övünç AO (2011) AST-platelet ratio index, Forns index, and FIB-4 in the prediction of significant fibrosis and cirrhosis in patients with chronic hepatitis C. Turk J Gastroenterol 22:279–285
8. Castera L, Forns X, Alberti A (2008) Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 48:835–847
9. Kaswala DH, Lai M, Afdhal NH (2016) Fibrosis assessment in nonalcoholic fatty liver disease (NAFLD) in 2016. Dig Dis Sci 61:1356–1364
10. Cichoz LH, Celiński K, Prozorow KB, Swatek J, Słomka M, Lach T (2012) The BARD score and the NAFLD fibrosis score in the assessment of advanced liver fibrosis in nonalcoholic fatty liver disease. Med Sci Monit 18:CR735-40
11. Byrne CD, Targher G (2015) NAFLD: a multisystem disease. J Hepatol 62(1 Suppl):S47-64
12. Golabi P, Sayiner M, Fazel Y, Koenig A, Henry L, Younossi ZM (2016) Current complications and challenges in nonalcoholic steatohepatitis screening and diagnosis. Expert Rev Gastroenterol Hepatol 10:63–71
13. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M (2016) Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 64:73–84
14. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K et al (2012) The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 55:2005–2023
15. Sasaki A, Nitta H, Otsuka K, Umemura A, Baba S, Obuchi T et al (2014) Bariatric surgery and non-alcoholic fatty liver disease: current and potential future treatments. Front Endocrinol 5:164
16. Subichin M, Clanton J, Makuszewski M, Bohon A, Zografakis JG, Dan A (2015) Liver disease in the morbidly obese: a review of 1000 consecutive patients undergoing weight loss surgery. Surg Obes Relat Dis 11:137–141
17. Wu KT, Kuo PL, Su SB, Chen YY, Yeh ML, Huang CI et al (2016) Nonalcoholic fatty liver disease severity is associated with the ratios of total cholesterol and triglycerides to high-density lipoprotein cholesterol. J Clin Lipidol 10:420-425.e1
18. Wilkins T, Hepburn I, Schade RR (2013) Nonalcoholic fatty liver disease: diagnosis and management. Am Fam Physic 88:35–42
19. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P et al (2015) Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 149:389–97.e10
20. Nobili V, Vizzutti F, Arena U, Abraldes JG, Marra F, Pietrobattista A et al (2008) Accuracy and reproducibility of transient elastography for the diagnosis of fibrosis in pediatric nonalcoholic steatohepatitis. Hepatology 48:442–448
21. Cassinotto C, Boursier J, de Lédinghen V, Lebigot J, Lapuyade B, Cales P et al (2016) Liver stiffness in nonalcoholic fatty liver disease: a comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology 63:1817–1827
22. Patel K, Sebastiani G (2020) Limitations of non-invasive tests for assessment of liver fibrosis. JHEP Rep 2(2):100067
23. Goyale A, Jain A, Smith C, Papatheodoridi M, Misas MG, Roccarina D et al (2021) Assessment of non-alcoholic fatty liver disease (NAFLD) severity with novel serum-based markers: a pilot study. PLoS ONE 16(11):e0260313. https://doi.org/10.1371/journal.pone.0260313
24. Eddowes PJ, Sasso M, Allison M, Tsochatzis E, Anstee QM, Sheridan D et al (2019) Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology 156:1717–1730

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