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Comparison of transient elastography and shear wave elastography in patients with MAFLD: A single-center experience

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Abstract

Background: Metabolic-associated fatty liver disease and liver fibrosis are intimately linked to insulin resistance, type 2 diabetes, obesity, and metabolic syndrome. Transient elastography (TE) and point shear wave elastography (pSWE) were used to measure liver stiffness in patients who met the ultrasound criteria for steatotic liver diseases (SLD). This study compared two methods for estimating liver stiffness in patients with SLD, which in turn correlated with liver fibrosis.

Method: Ultrasound B-mode imaging was used to identify SLD. In total, 250 MAFLD patients were recruited. Patient characteristics, laboratory investigations, and liver stiffness measurements using TE and pSWE were assessed on the same day.

Results: In the study, 56.0% of the patients were male, with a mean age of 41.5 ± 10.7 years. The correlation between TE and pSWE was significant (Spearman's $r = 0.867$*, $p < 0.001$). The Bland-Altman Plot analysis confirmed this, with 97.5% of variations in LSM falling within 95% agreement ranges. Cohen's κ was used to assess the agreement between TE and pSWE fibrosis stages, showing almost perfect agreement (83.5% kappa agreement) and a strong association between pSWE and TE in the assessment fibrosis stages.

Conclusion: In patients with MAFLD, TE, and SWE are reliable methods for measuring liver stiffness and can be used as non-invasive screening tools for the assessment of fibrosis in SLD.

Keywords: Metabolic-associated fatty liver diseases (MAFLD), Point shear wave elastography (SWE), Transient elastography (TE), Liver stiffness measurement, Liver fibrosis, NAFLD.

What is new? What is important?

The article highlights the significance of TE and pSWE as non-invasive methods to assess liver stiffness in MAFLD patients. Liver biopsy is the gold standard method to differentiate between liver steatosis and steatohepatitis. However, it has complications and difficulties. Therefore, non-invasive tools are needed to assess liver fibrosis in MAFLD patients. TE and SWE are non-invasive, reliable, comparable, and less costly techniques for assessing liver stiffness and can be used as screening tools to detect fibrosis in MAFLD patients.

INTRODUCTION

Metabolic-associated fatty liver disease (MAFLD) is a condition characterized by hepatic steatosis on imaging or histology, without secondary causes such as alcohol consumption, chronic medication use, or hereditary disorders [1].

The inflammatory form of MAFLD, known as metabolic-associated steatohepatitis (MASH), is associated with significant inflammation and fibrosis, increasing the risk of advanced liver disease [2] [3].

MAFLD is the most common liver disease, with a global prevalence of approximately 38%. This depends on the background prevalence of the dominant risk factors: obesity and insulin resistance [4]. Egypt has one of the highest prevalences of MAFLD, affecting more than one-third of the population [5].

A liver biopsy is still the gold standard for identifying MASH and hepatic fibrosis based on histological evaluation. This procedure is invasive, expensive, restricted by its complications, such as bleeding, and challenging to perform regularly [6, 7, 8, 9].

Transient elastography (TE), an ultrasound-based technique, accurately and reproducibly detects changes in the elasticity of soft tissue, particularly liver fibrosis [10, 11].

Recently, the ultrasound-based technique known as shear wave elastography (SWE) was created with the elastography point quantification (ElastPQ) function. It measures tissue elasticity at each organ's point of interest in kilopascals (kPa) [12]. The benefits of this imaging technique are noninvasiveness, quantification, reproducibility, and operator independence [13].

The main goal of our study was to compare TE and pSWE for evaluation of liver stiffness in patients with SLD, which in turn correlated with liver fibrosis, and to assess the accuracy of both techniques' liver stiffness measurements in determining fibrosis stages and identifying risk factors for significant fibrosis (> F2) in patients with metabolic-associated fatty liver disease (MAFLD).

MATERIALS AND METHODS

From September 2020 to May 2023, the study was carried out at Menoufia University's National Liver Institute in Egypt. A total of 264 patients were included in the study; 250 met the inclusion criteria after excluding unreliable or unsuccessful TE exams. We enrolled 250 patients after obtaining their informed consent. MAFLD diagnosis is based on hepatic steatosis plus one of three criteria: overweight or obesity, presence of T2DM, or metabolic dysregulation [14]. The following criteria were used to choose our patients: Age $\geq$18 years, BMI> 25 kg/m^2 <35 kg/m^2, absence of viral hepatitis or other chronic liver illnesses such as (autoimmune hepatitis, hemochromatosis, Wilson disease), hepatocellular carcinoma, decompensated liver cirrhosis, or alcohol consumption. Patients' characteristics, laboratory data (HCV Ab, HBsAg, complete blood count, bilirubin, AST, ALT, albumin, INR, serum creatinine, HB1Ac, lipid profile: total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and triglycerides.), abdominal ultrasound, and liver stiffness measurements by transient elastography and SWE were assessed which illustrated in figure 1.

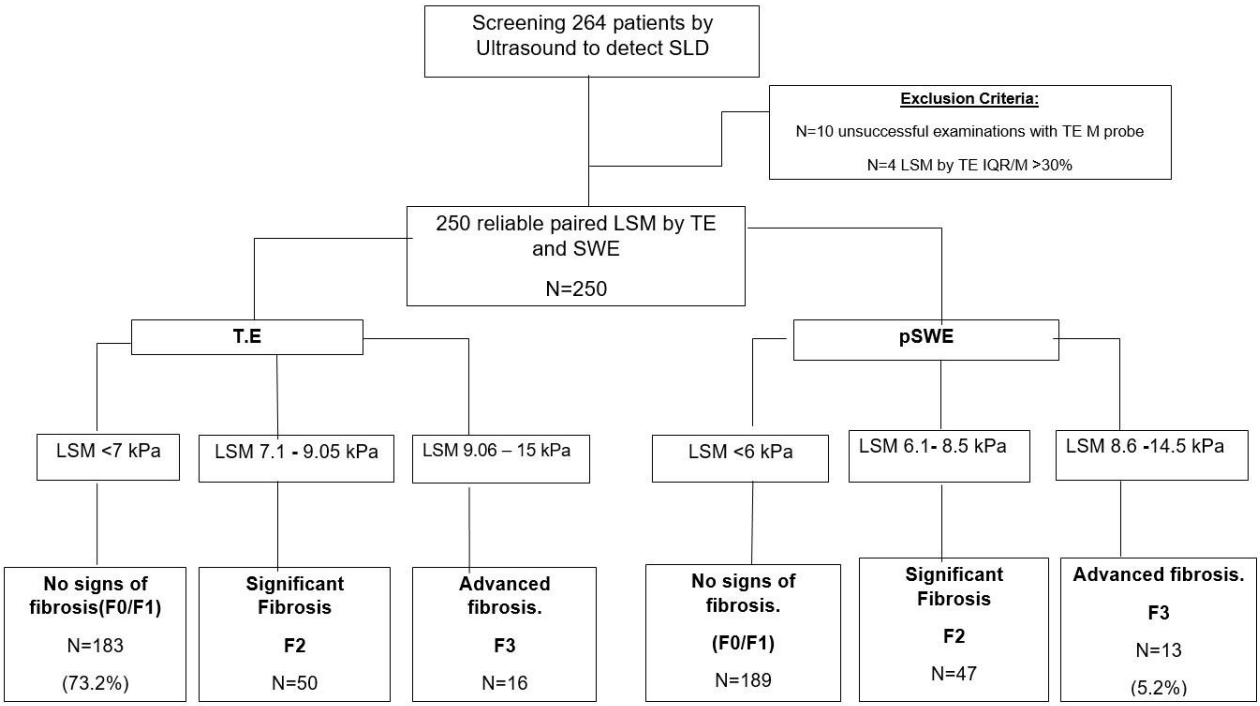

Figure 1. Study flow chart, showing the fibrosis staging by TE and PSWE, as well as best performing cutoff values.

ETHICAL APPROVAL

This study was approved by the institutional review board of the National Liver Institute, Menoufia University, and was conducted in compliance with the Declaration of Helsinki.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

IDENTIFICATION OF STEATOTIC LIVER DISEASES BY ULTRASOUND

US B-mode imaging is used to grade liver steatosis by estimating hepatic fatty infiltration extent based on liver brightness, liver-kidney contrast, intrahepatic vascular morphology, liver parenchyma, and diaphragm [15].

GRADES OF STEATOSIS

- **Absent (score 0):** Liver echotexture is normal.
- **Mild (scoring 1):** Liver echogenicity slightly increased.
- **Moderate (scoring 2):** There is a moderate rise in hepatic echogenicity and a compromised diaphragm and portal vein wall appearance.
- **Severe (score 3):** visible portal vein wall and diaphragm appearance, together with a marked rise in liver echogenicity.

LIVER STIFFNESS MEASUREMENT (LSM)

Transient elastography: Transient elastography was performed after 6 hours of fasting using the Fibroscan 502 Touch (Echosens, Paris, France) with an M probe in the right lobe of the liver. Successful examinations had ≥10 valid measurements, and reliability was determined by an interquartile range (IQR)/median for liver stiffness measurements ≤ 30% [16]. An examination was considered unsuccessful if <10 valid measurements were obtained after 30 attempts [16]. Patients who had an unsuccessful examination with the M probe were excluded from the study because the XL probe was not available at our center. That's why we did not enroll morbidly obese patients with a BMI >35 kg/m^2 in our study, using TE The liver stiffness measurement for fibrosis stages F0–F1 ranges from 2 to 7 kPa, F2 ranges from 7.5–10 kPa, F3 ranges from 10–14 kPa, and F4 is > 14 kPa [16].

Point shear wave elastography. Philips Healthcare, based in Bothell, WA, USA, used an iU22 ultrasound system to perform a liver ultrasound scan for patients. A liver ultrasound scan in B-mode is connected to an ElastPQ-equipped system, which generates shear waves. Liver stiffness was evaluated using ElastPQ with the C5-1 convex transducer. The study participants were given 10 measurement elastographic cine clips at different liver locations. The median values of LS measurements were considered reliable if 10 valid measurements were obtained [17, 18, 19]. Using pSWE for fibrosis stages, the liver stiffness measurement for F0 to F1 ranges from 2 to 6 kPa, F2 >8 kPa, F3 >9 kPa, and F4 > 11.4 kPa [20, 21].

STATISTICAL ANALYSIS

SPSS 22.0, developed by IBM/SPSS Inc., is a statistical tool used to analyze data. The study used means± standard deviation and absolute figures to represent data, and univariate and multivariate linear regression analyses were conducted to identify independent factors. The diagnostic accuracy of TE and pSWE for fibrosis stage diagnosis was evaluated using AUROC. For every stage of fibrosis, the ideal cut-off liver stiffness value is determined using the highest possible sensitivity and specificity, and an evaluation of the liver stiffness measurement's sensitivity, specificity, positive predictive value, and negative predictive value is calculated. A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1 illustrates patient characteristics and clinical data. A total of 264 patients were included in the study; 250 met the inclusion criteria after excluding unreliable or unsuccessful TE exams. The M probe was used for all patients, and none had a failed pSWE examination. Among 250 studied patients, 49 were diabetic (19.6%), and 74 were hypertensive patients (29.6%). The same operator examined each patient using TE and pSWE on the same day, resulting in 500 sets of TE and pSWE values overall.

LIVER STIFFNESS MEASUREMENT ACCORDING TO THE PRESUMED STAGE OF FIBROSIS

Median liver stiffness measurement using TE for fibrosis stages F0, F1, F2, F3, and F4 was 4.5 (3–5.7) kPa, 6.3 (5.5–7.8) kPa, 8.2(7.1–13.8)

kPa, 10.1 (8.1–14.6) kPa, and 20.9(17.3-24.5) kPa respectively. However, median liver stiffness measurement using pSWE for fibrosis stages F0, F1, F2, F3, and F4 was 4.6 (3–5.2) kPa,6.1 (5.5–8) kPa, 7.9 (7.7–10.3) kPa, 9.46 (8.2–11.1), and 18 kPa, respectively as shown in Table 2.

Table 1

Characteristics of the study population

Patient characteristics	Mean ± SD.
Age	41.5±10.7
BMI	29.93±2.62 Kg/M^2
Waist circumference	male 104.1 ± 13.91 cm female 115.6 ± 12.12 cm.
Male %	56%
Total. cholesterol (mg/dl): Normal <200	221.05 ± 59.8
Triglycerides (mg/dl): Normal (10-150)	165.53±80.74
LDL (mg/dl) : Normal (70-130)	144.92±46.97
HDL (mg/dl): Normal (40-60)	51.26±12.18
ALP (IU/L): Normal:(13-100)	88.66±21.54
AST (U/L): Normal: (0-35)	42.28±23.588
ALT (U/L): Normal:(0-35)	50.14±27.865
RBS (mg/dl):	128.4±60.466
Platelets (*10 ^{3}/UL):	262.1±51.56
Liver steatosis on ultrasound, n (%)	S0 0 (0%) S1 114 (45.6%) S2 92 (36.8%) S3 44 (17.6%)

Note: Quantitative variables are expressed as mean ± standard deviation if the distribution is normal, otherwise as median (IQR).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2

Liver stiffness measurement according to the ***presumed*** stage of fibrosis

Transient elastography	**Mean ± SD.**	**Min. – Max.**	**Median**
F0 (n=116)	4.58±0.49	3-5.7	4.5
F1 (n=66)	6.37±0.55	5.5-7.8	6.3
F2 (n=50)	8.23±0.98	7.1-13.8	8.2
F3 (n=16)	10.11±1.41	8.1-14.6	10.1
F4 (n=2)	20.9±5.09	17.3-24.5	20.9
Shear wave elastography	**Mean ± SD.**	**Min. – Max.**	**Median**
F0 (n=127)	4.60±0.67	3-5.2	4.6
F1 (n=62)	6.13±0.74	5.5-8	6.1
F2 (n=47)	7.89±0.73	7.7-10.3	7.9
F3 (n=13)	9.46±0.88	8.2-11.1	9.46
F4 (n=1)	18	18	18

CORRELATION OF LSM USING TE AND PSWE

There was a strong correlation between transient elastography LSM and shear wave elastography LSM (Spearman's r = 0.867*, p < 0.001), with a Pearson's precision of 0.901 (Figure 2).

Bland-Altman Plot analysis further supported this, showing that 97.5% of the variations in LSM between TE and pSWE were within the 95% agreement range. Patients with high LS values were observed outside of these ranges (Figure 3).

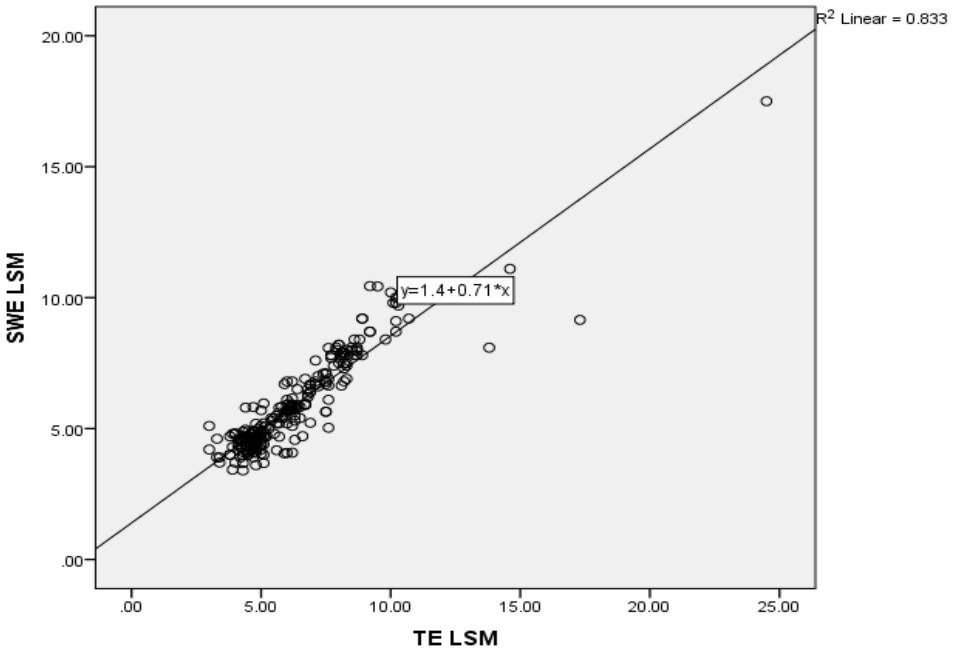

Figure 2. Correlation between transient elastography LSM and shear wave elastography LSM.

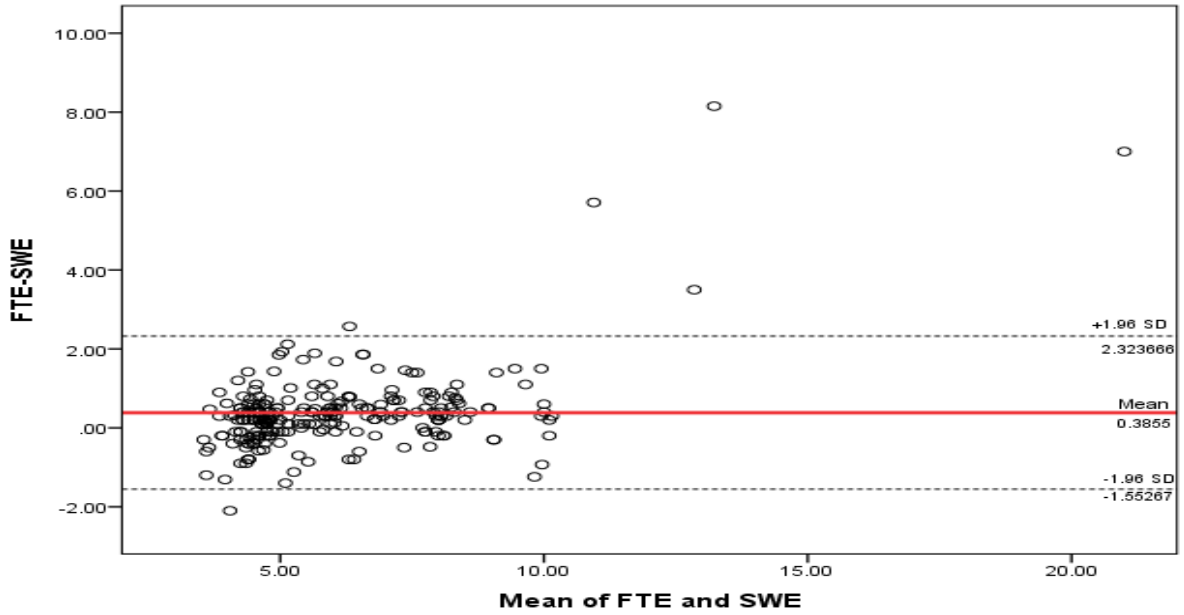

Figure 3. Bland and Altman plot of differences in measurements between transient.

Agreement between TE and pSWE LSM in the estimation of different fibrosis stages:

Cohen's κ was used to assess the accuracy of both techniques in determining fibrosis stages (F1, F2, F3, or F4) agreement based on liver stiffness measurements. The results showed almost perfect agreement between the two scans, with $\kappa = 0.835$, $p < 0.0001$ (83.5% almost perfect kappa agreement).

Correlation between the estimation of liver fibrosis stages assessed by TE & pSWE liver stiffness measurement with patient characteristics and laboratory investigation.

There was a significant positive correlation between the degree of liver fibrosis assessed by estimation of TE & SWE liver stiffness measurement with BMI, waist circumference, diabetes, dyslipidemia, liver enzymes, and platelet as shown in Table 3.

Table 3

	Early Fibrosis F0, F1 N=182	Significant Fibrosis ≥ F2 N=68	P value
Age (years)			
Min. – Max.	18 – 71	25 – 63	0.094
Mean ± SD.	40.84 ±11.43	43.1±9.22	
BMI(Kg/m^2):			
Min. – Max.	25– 38	26 – 40	**0.05**
Mean ± SD.	29.73±2.49	30.47±2.87	
Waist circumference (cm)			
Male	99.6 ± 12.4	112.09 ± 15.57	**0.001***
Female	102.4 ± 14.1	117.82 ± 11.54	
HTN			
No.	131 (72.0%)	45 (66.2%)	0.371
Yes	51 (28.0%)	23 (33.8%)	
Gender			
Female	97 (53.3%)	43 (63.2%)	0.159
Have Diabetes			
Yes	25 (13.7%)	24 (25.3%)	<0.001
T. cholesterol (mg/dl): Normal < 200			
Min. – Max.	153 – 220	149 – 425	<0.001
Mean ± SD.	225.14±45.657	276.15±57.202	
HDL (mg/dl): Normal (40-60)			
Min. – Max.	25– 81	33 – 77	**0.92**
Mean ± SD.	53.24±16.05	50.52±10.33	
LDL (mg/dl) : Normal (70-130)			
Min. – Max.	69– 256	75 –256	<0.001
Mean ± SD.	133.26±42.968	176.1±43.089	
Triglycerides (mg/dl): Normal (10-150)			
Min. – Max.	66 – 786	80 – 500	<0.001
Mean ± SD.	154.79±81.07	194.28±72.94	
AST (U/L): Normal: (0-35)			
Min. – Max.	11-86	13 – 115	<0.001
Mean ± SD.	32.97±14.014	67.57±25.78	
ALT (U/L): Normal:(0-35)			
Min. – Max.	13-117	20 – 130	<0.001
Mean ± SD.	40.75±21.14	75.28±28.22	
ALP (IU/L): Normal:(13-100)			
Min. – Max.	11-86	18 – 115	0.001
Mean ± SD.	88.68±20.39	97.82±23.21	
Albumin (g/dl): Normal : (3.5-5.5)			
Min. – Max.	4 – 5	4 – 5	**0.242**
Mean ± SD.	4.37±0.485	4.29±0.459	
Platelets			
Min. – Max.	152 –430	129 – 320	**0.001**
Mean ± SD.	266.49±51.58	232.10± 51.56	

Note: Quantitative variables are expressed as mean ± standard deviation if the distribution is normal, otherwise as median (IQR).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 4

Univariate and multivariate Logistic regression analysis for the parameters affecting significant fibrosis ≥ *F2* in MAFLD patients

	Univariate		**#Multivariate**	
	p	**OR (LL – UL 95%C.I)**	**p**	**OR (LL – UL 95%C.I)**
• **Age**	**0.139**	1.02(0.994-1.047)	**0.207**	0.975(0.938-1.014)
• **BMI**	**0.049**	1.12(1.001-1.241)	**0.154**	1.099(0.965-1.252)
• **TG**	**0.002**	1.006(1.002-1.01)	0.553	0.999(0.994-1.003)
• **LDL**	**.0000**	1.021(1.014-1.027)	0.00	1.024(1.015-1.033)
• **Diabtets Mellites**	**0.00**	3.425(1.78-6.6.577)		
• **Platelets**	**0.057**	1.004(.0999-1.009)	0.209	1.007(0.996-1.019)
• **ALT**	**0.015**	1.255(1.046 – 1.506)	0.083	1.315(0.965 – 1.793)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; LDL, low-density lipoprotein; TG, Triglyceride; OR: Odd`s ratio, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit, #: All variables with p<0.05 were included in the multivariate *: Statistically significant at p < 0.05.

According to univariate analysis, liver stiffness is related to higher BMI, hypertriglyceridemia, elevated LDL, elevated ALT, diabetes mellitus, and low platelets, as shown in Table 4.

DISCUSSION

Currently, metabolic dysfunction-associated steatotic liver disease (MASLD) is the term used to describe nonalcoholic fatty liver disease (NAFLD). Patients with hepatic steatosis who also have at least one of the five cardiometabolic risk factors are identified as having MASLD.

The term that has replaced NASH is metabolic dysfunction associated with steatohepatitis (MASH). A liver biopsy distinctly distinguishes MASH from MASLD.

Most studies evaluated the effectiveness and reliability of non-invasive tools or markers to identify MASH and predict treatment response without liver biopsy complications. To identify patients at low risk of progressive fibrosis or cirrhosis, Using TE as a non-invasive technique is recommended by the EASL clinical practice guidelines.

Evaluating MAFLD patients at high risk of progressive fibrosis or cirrhosis is an issue of debate. Consequently, assessing novel tools is crucial and pSWE is a promising tool.

In our study, we enrolled MAFLD patients who met ultrasound criteria for SLD as determined by an expert radiologist at our institute. These patients were further evaluated to determine whether they met the study's selection criteria. subsequently, liver stiffness measurements (LSM) were assessed using transient elastography and point shear wave elastography on the same day for selected patients. Consequently, the liver stiffness measurements (LSM), which had been previously reported, were correlated with liver fibrosis.

Our study showed a strong correlation between liver stiffness measurements obtained through transient elastography (TE) and point shear wave elastography (pSWE) in patients with MAFLD. This indicates that TE and pSWE are reliable, non-invasive methods for assessing liver stiffness, which correlates with liver fibrosis. The patients were categorized according to fibrosis stages based on these measurements. These fibrosis stages are: without fibrosis (F0, F1), significant fibrosis (F2), advanced fibrosis (F3), and cirrhosis (F4).

Our study has shown that liver stiffness in patients with MAFLD assessed by pSWE and TE was equally efficient in the estimation of different fibrosis stages, unlike Argalia *et al.* [17], who found that TE was considerably superior to pSWE in the assessment of fibrosis stage ≥ F2. Leong *et al.* [20] revealed that transient elastography was more accurate in diagnosing fibrosis stages ≥ F2 and ≥ F3 than pSWE. It is attributed to the study of Argalia *et al.*, and Leong *et al.* had a small number of patients, which may have affected its ability to assess MAFLD fibrosis staging. Additionally, the authors note that there was a possibility of sample bias because the histology specimens generally did not meet the required standards. According to our study, both tools were comparable in the assessment of the fibrosis stage; therefore, we recommend using whichever is available from TE and SWE.

We enrolled 250 patients, considered a large number compared to Argalia *et al.* (50 patients) and Leong *et al.* **(**100 patients). We used an M probe of TE in all patients, unlike other studies where a failed examination by the M probe was used.

Moreover, our study indicates that both techniques were comparable in the identification of all fibrosis stages, as Rosanna *et al.* [21]. These findings could be attributed to the large sample size and standardization of measurements by the M probe of TE compared to others.

Several factors may predict fibrosis progression in MAFLD. In our study, we found that higher BMI, hypertriglyceridemia, elevated LDL, elevated ALT, and diabetic mellitus were the most predictive. These two modalities are useful in screening fibrosis in high-risk groups.

MAFLD patients are often associated with several risk factors, like type 2 diabetes mellitus and obesity, which confer added risk in clinical situations. According to a meta-analysis, 17.0% of type 2 diabetic patients had advanced fibrosis, and 55.5% of diabetic patients had SLD [22]. This study assesses the predictive value of both modalities in identifying MAFLD patients with significant to advanced fibrosis before established cirrhosis. This could be a great help in the future planning of clinical trials and clinical strategies, particularly after the FDA approval of Madrigal Pharmaceuticals' first MASH drug, resmetirom, to be sold under the brand name Rezdiffra. The FDA approved the tablet drug for the treatment of MASH with significant or advanced liver fibrosis, consistent with stage F2 and F3 disease, respectively, which is considered a breakthrough in the treatment of MAFLD-associated fibrosis.

The major limitation of our study is the lack of liver biopsy so there is no gold standard for liver fibrosis assessment in this study, and this represents a very important limitation of the study. Moreover, the patients included in our study had a relatively low BMI. The proportion of patients with a BMI between 25–30 kg/m^2 in our study was 44.6%. We excluded patients with a BMI >35 kg/m^2 because we don't have the XL probe at our institute. That's why it's recommended to use the XL probe in obese patients in future studies. On the other hand, in a small number of patients with F3 and F4 fibrosis, most patients were F0 because Most of the patients included in our study were apparently healthy. Patients with a BMI greater than 35 kg/m^2 were not enrolled in our study. Nevertheless, the prevalence, severity, and genetic polymorphism of MAFLD are different in various racial groups, which influences fibrosis progression. Also, our patients had a median age of 41.5±10.7 years, which are relatively young patients, which explains why most patients had no fibrosis F0/F1.

The most important point of our study is that we recruited a large number of patients, all data were collected, and both modalities were done on the same day under the same circumstances.

In conclusion, patients with MAFLD, TE, and SWE have reliable methods for measuring liver stiffness that can be used as non-invasive screening tools for the assessment of fibrosis in SLD. Both techniques are used for monitoring treatment responses, risk stratification, and identifying high-risk patients with steatotic liver disease.

Context: Steatoza hepatică non-alcoolică (MAFLD) și fibroza hepatică sunt strâns legate de rezistența la insulină, diabetul de tip 2, obezitatea și sindromul metabolic. Elastografia tranzitorie (TE) și elastografia cu undă de forfecare punctuală (pSWE) au fost utilizate pentru a măsura rigiditatea ficatului la pacienții care au îndeplinit criteriile ecografice pentru steatoză hepatică (SLD). Acest studiu a comparat două metode de estimare a rigidității hepatice la pacienții cu SLD, care, la rândul lor, s-au corelat cu fibroza hepatică.

Metodă: Ecografie abdominală modul B a fost utilizată pentru a identifica SLD. În total, au fost recrutați 250 de pacienți cu MAFLD. Caracteristicile pacientului, investigațiile de laborator și măsurătorile rigidității hepatice folosind TE și pSWE au fost evaluate în aceeași zi.

Rezultate: 56,0% dintre pacienți au fost bărbați, cu o vârstă medie de 41,5 ± 10,7 ani. Corelația dintre TE și pSWE a fost semnificativă (r = 0,867, p < 0,001). Analiza Bland-Altman Plot a confirmat acest lucru, 97,5% dintre variațiile LSM se încadrează în intervalele de acord de 95%. Coeficientul K Cohen a fost folosit pentru a evalua acordul dintre stadiile de fibroză TE și pSWE, prezentând acord aproape perfect (acord kappa de 83,5%) și o asociere puternică între pSWE și TE în etapele de evaluare a fibrozei.*

Concluzie: La pacienții cu MAFLD, TE și SWE sunt metode de încredere pentru măsurarea rigidității hepatice și pot fi utilizate ca instrumente de screening non-invazive pentru evaluarea fibrozei în SLD.

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Funding*:* None.

Declaration of interest: All the authors declare that they have no conflict of interest.

Acknowledgments: The authors express their gratitude to Prof. Dr. Ebada Mohamed for dedicating his time to the paper evaluation.

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Received 3rd February 2024