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Real Time Elastography in Patients with Chronic Hepatitis C: Assessment of Hepatic Fibrosis Using Liver Fibrosis Index

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Abstract

Background: Real time elastography (RTE) is a recent non-invasive method for hepatic fibrosis assessment. Multiple methods of quantitative evaluation using RTE have been proposed; yet, no sufficient studies are present to allow for its use in routine clinical practice.

Aim: To assess the reliability of liver fibrosis index (LFI), as a new method of quantitative analysis of hepatic fibrosis in chronic hepatitis C patients.

Patients and Methods: Sixty patients with chronic hepatitis C and scheduled for liver biopsy were enrolled. RTE was performed to all patients in addition to a group of twenty health volunteers. LFI measurements were compared to liver biopsy. Patients were also subjected to routine blood tests and conventional abdominal ultrasonography.

Results: LFI highly correlated with the stage of hepatic fibrosis (r=0.746, p<0.001). LFI had high diagnostic accuracy for F≥3 (AUROC 0.96, sensitivity 94%, and specificity 93%), and for F≥2 (AUROC 0.93, sensitivity 84.6%, and specificity 85.4%), meanwhile it showed a lower accuracy for F≥1 (AUROC 0.87, sensitivity 83%, and specificity 71.4%).

Conclusion: Real time elastography can be a reliable tool for hepatic fibrosis assessment in patients with chronic hepatitis C, being able to differentiate absence and mild fibrosis from advanced fibrosis and cirrhosis.

Key Words: *Hepatic fibrosis – Chronic hepatitis C – Real time Elastography – Liver fibrosis index.*

Introduction

FOR many years, liver biopsy (LB) was considered as the gold standard to evaluate hepatic fibrosis. However, due to its many limitations, LB is now regarded as the best standard reference [1]. Sampling error and interobserver variability are major limitations [2]. Besides, being an invasive method, with rare but significant complications such as bleeding and mortality, has made itunsuitable for frequent monitoring [3]. Because of these disadvantages and under the fact that absolute staging of hepatic fibrosis has become less important with the new trend to treat all chronic hepatitis C (CHC) patients, owing to the new drug regimens, the international guidelines recommended that non-invasive methods for hepatic fibrosis assessment can be used in routine clinical practice [4-6], with LB reserved for cases where there is uncertainty or potential additional etiologies. Noninvasive methods currently available rely on two different concepts: A 'biological' aspect based on serum biomarkers of fibrosis, and a 'physical' aspect involving liver stiffness measurement [7].

The rational for liver stiffness (elasticity) measurement was based on the simple basic concept that the hardness of the liver tissue is related to the degree of liver fibrosis as noted on palpation [8]. At the present, ultrasound elastography has two known types: Shear-wave elastography and Real-time tissue elastography (RTE) [9]. Shear-wave based techniques including Transient elastography (TE), Acoustic Radiation Force Impulse Imaging (ARFI) and Shear Wave Elastography (SWE) measure the propagation of shear wave induced within the tissues to estimate liver stiffness [10], however, RTE is technically different as it compares and analyses echo signals before and after compression [8], then the relative strain of tissues is displayed as a colored strain image (elastogram) overlying the B-mode image [10]. Strain images show a progressively increasing patchy pattern as fibrosis progresses [11], however, to increase objectivity, different methods of elastogram analysis have been developed to retrieve a semi-quantitative estimate of hepatic fibrosis [12].

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The usefulness of RTE for assessing hepatic fibrosis is well established in literature **[11,13]**; however, variable results have been reported about the performance of the different quantitative methods **[14]**, which can limit the recommendation for RTE use in clinical practice **[15]**. Quantitative methods in literature included the Liver Fibrosis Index (LFI), Elasticity Index (EI) and Elastic Ratio (ER). Fujimoto et al., reported high correlation between the LFI and the stage of hepatic fibrosis (r=0.68, p<0.001) in CHC patients, with a high ability to differentiate each stage **[16]**. Also, in a recent meta-analysis by Hong et al. **[14]**, the overall AUROC of LFI for F≥2, F≥3, and F4 were 0.79, 0.94, and 0.85, respectively. So in this study, we aimed to assess the reliability of LFI in evaluating hepatic fibrosis in CHC patients through comparing the results to LB as the reference standard.

Patients and Methods

Patients:

At the National Hepatology Institute and along the year 2014, Fifty-four clinically diagnosed patients as CHC were prospectively enrolled in this study, who were scheduled for LB before receiving treatment. Their characteristics are summarized in (Table 1). The median age was 46 years; with the range being 21-65 years old and male/female were 28/26. The histopathological stages of hepatic fibrosis were: F0 in 21 subjects (1 patient and 20 controls), F1 in 27 subjects, F2 in 9 subjects, F3 in 13 subjects and F4 in 4 subjects. Steatosis was noted in 33 patient (61%).

Table (1): Characteristics of the studied patients.

Patients number	54	
Sex:	Male: 28(51.9%) Female: 26(48.1%)	
Age (median, range)	46 (21-65) years	
BMI (mean ± SD)	26 (±4.1) Kg/m^2	
ALT (median, range)	51 IU/l (9-316)	
AST (median, range)	45 IU/l (8-236)	
Platelet count (mean ± SD)	217.7±71.15 (x10^4/µl)	
APRI (median, range)	0.512 (0.089-3.8)	
Fibrosis stage:	No.	%
F0	1	1.9
F1	27	50
F2	9	16.7
F3	13	24.1
F4	4	7.4
Histological activity:		
A1	38	70.4
A2	9	16.7
A3	3	5.6
Not available	4	7.4
Steatosis	33	61

All these patients were anti-hepatitis C virus and hepatitis C virus RNA positive. We excluded co-infection with other viruses such as hepatitis B virus and other liver diseases such as biliary cirrhosis. Other exclusion criteria were: any contraindication for LB, decompensated cirrhosis or presence of hepatic focal lesions. Twenty healthy volunteers were also enrolled; all had average BMI, normal blood tests, and no signs of fatty liver on ultrasonography. In all subjects, conventional abdominal ultrasound and RTE were performed prior to LB, and all of them provided consent prior to the procedures.

Blood laboratory assessment was carried out at enrollment including CBC, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, albumin and blood coagulation profile. The APRI index, as a serum marker of hepatic fibrosis, was calculated as follows: AST (xupper limit of normal range) x100/platelet count (10^9/L). The upper limit of normal of AST for women was 35 IU/mL and 50 IU/mL for men.

Methods:

1- L*iver histology:*

US-guided LB was performed using a semi-automatic true-cut needle (16 G) under local anesthesia. The specimen lengths ranged from 10 to 25mm and the sections were stained with hematoxylin and eosin, and Masson trichrome staining. All biopsy specimens were analyzed by two experienced pathologists blinded to the results of RTE. Liver fibrosis staging and activity grading were evaluated according to the METAVIR scoring system **[16]**: Fibrosis: F0=No fibrosis; F1=Portal fibrosis without septa; F2=portal fibrosis with few septa; F3=Numerous septa without cirrhosis; and F4=Cirrhosis, and inflammatory activity: A0=No histologic necro-inflammatory activity; A1=Mild activity; A2=Moderate activity; and A3=Severe activity.

2- *Real time elastography:*

RTE was performed before liver biopsy using HI VISION Preirus (Hitachi Medical Corp., Japan) with a EUP-L52 linear probe (3-7 MHz).Internal compression and relaxation induced by heart beat was used to obtain the strain images. After examination in the B-mode, the ultrasound mode was switched to RTE and liver was scanned from the right intercostal space to measure tissue elasticity within the right hepatic lobe, at approximately the same site of LB. The ROI (2.5x2.5cm) for RTE was set inside liver parenchyma, at a depth of more than 1cm from the surface of the liver to avoid reflection artifacts. Attempts to avoid regions with

large vessels or shadowing from ribs were also done, the best RTE images devoid of artifacts were chosen for analysis. Position of the analysis area for histogram measurement was set widely but avoiding artifacts. Analysis of RTE image features were automatically performed with computer software. This software converts the selected analysis area into a 256-step grayscale image, plots the strain histogram, and binarizes the RTE image, to extract 9 image features. Multiple regression analysis was then performed to calculate the LFI using the following equation: LFI = "–0.00897 x MEAN – 0.005 x SD+0.0232 x %AREA + 0.0253 x COMP + 0.775x SKEW – 0.28x KURT + 2.08x ENT + 3.04 x IDM + 40.0x ASM – 5.54". Examples of liver RTE images and LFI measurements are shown in Figs. (1-3). As can be seen, the image patchiness and the LFI increased as the F stage of fibrosis increased.

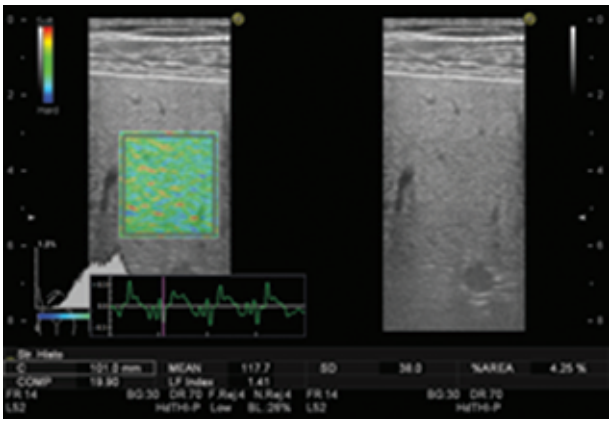


Fig. (1): Example of liver RTE image and result of LFI (F0 stage): The color-coded elastogram shows a diffuse soft pattern, characterized by a homogeneous light-green image. LFI: 1.41.

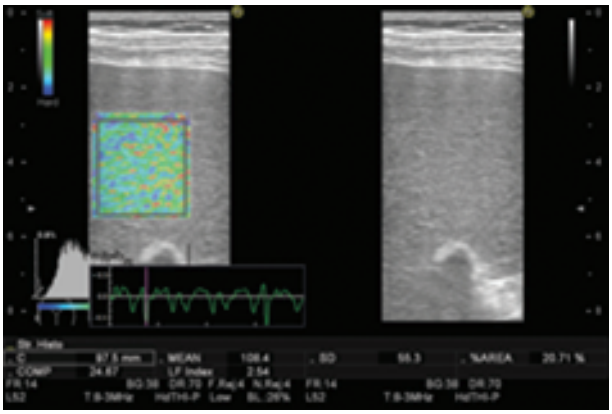


Fig. (2): Example of liver RTE image and result of LFI (F2 stage): The color-coded elastogram shows an intermediate pattern, characterized by a mottled image with blue spots on a light-green background. LFI: 2.54.

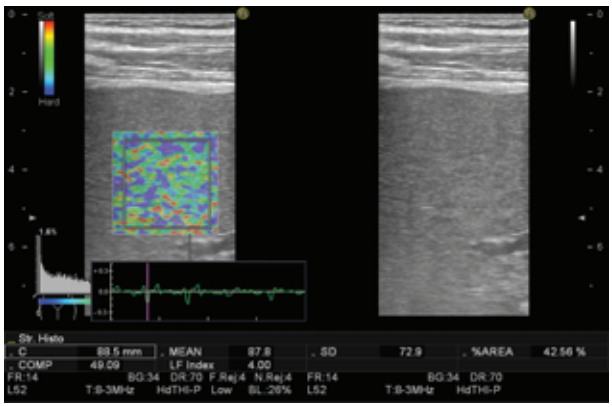


Fig. (3): Example of liver RTE image and result of LFI (F3 stage):The color-coded elastogram shows the hard pattern, characterized by image patchiness of green, and blue. LFI: 4.

3- *Statistical analysis:*

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using One Way ANOVA with post-Hoc pairwise comparisons in normal data and Kruskal Wallis test with post-Hoc pairwise comparisons in non-normal data. Correlation between various variables was done using Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off values. *p*-values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 (2006) for Microsoft Windows.

Results

Relationship between the LFI and Histologic Fibrosis Stage: The Spearman's correlation coefficient showed a high correlation between the LFI and the stage of liver fibrosis (r=0.746, p<0.001). The median LFI in patients with F0, F1, F2, F3, and F4 were 1.6, 2.1, 2.46, and 4, respectively. LFI showed a stepwise increase with increasing the histologic severity of fibrosis. F1 did not show a statistically significant difference in LFI from F2 stage, the same was observed for F3 and F4 stages, whereas for all other combinations of stages, LFI significantly differed with the stage of liver fibrosis (p<0.001).

Figure (4) shows the ROC analysis. The overall AUROC for F0 versus F1-4, F0-1 versus F2-4, and F0-2 versus F3-4 were 0.876, 0.935 and 0.964, respectively. When the cutoff value of LFI was set

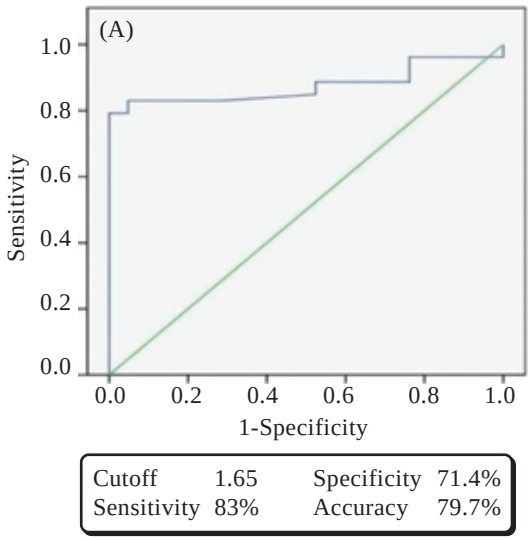
to 1.65 for F0 versus F1-4, the sensitivity, specificity and accuracy were 83, 71.4 and 79.7%, respectively. The PPV and NPV were 88 and 62.5%, respectively. And when increasing the cutoff value to 1.96, sensitivity, specificity and accuracy were 79, 100 and 85%. PPV and NPV were 100, 65.6%, respectively. For F0-1 versus F2-4 when the cutoff value was 2.4, the sensitivity, specificity and accuracy were 84.6, 85.4 and 85%, respectively.The NPV to exclude F2 or greater stage was 91% and the PPV was 75.9%. For F0-2 versus F3-4, when the cutoff value was 2.96, the sensitivity, specificity and accuracy were 94, 93 and 93%, respectively. The NPV to exclude advanced fibrosis was 98% and the PPV was 80% (Table 2). Table (3) lists the previously published LFI cut off values found in literature.

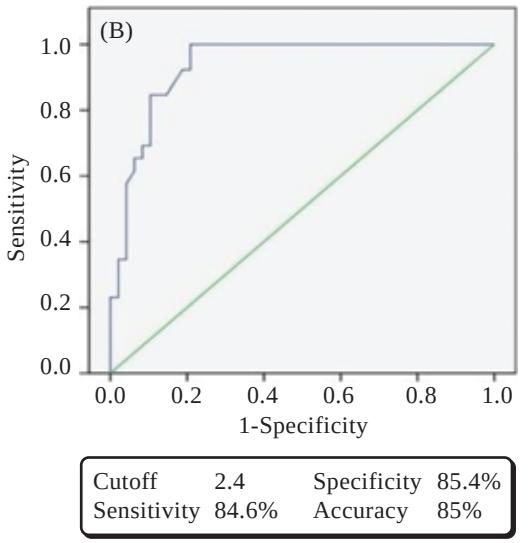
Effect of inflammation: The Spearman's correlation coefficient showed no correlation between LFI and the degree of necro-inflammation (r=0.419, p=0.002).

Effect of hepatic steatosis: Hepatic steatosis was classified into 3 groups as no steatosis (n=17), 0%-30% (n=24), and >30% (n=9). The correlation coefficient showed no correlation between LFI and steatosis (r=0.385, p=0.006). Furthermore, thecorrelation coefficient was calculated for LFI and fibrosis stage in each group of patients, and showed no influence of steatosis on LFI measurements among the different groups.

Effect of BMI: Patients were classified into two groups according to BMI: patients with no obesity (BMI <29.9kg/m^2) (n=31) and patients suffering from obesity (BMI ≥30kg/m^2) (n=23). The correlation coefficient was calculated for the LFI and fibrosis stage in each group of patients, and showed no influence of BMI on LFI measurements among the different groups.

Comparison between LFI and APRI: APRI showed a positive correlation with the degree of fibrosis (r=0.433, p=0.002) and also with the grade of inflammation (r=0.471 and p=0.001). AUROCs were 0.734 and 0.757 for F≥2 and F≥3, respectively. ROC curve analysis identified optimal cutoff value of APRI as 0.5 for F≥2 and 0.8 for F≥3. The corresponding sensitivity, specificity and accuracy were 78.3, 71.4 and 74.5%, respectively for F≥ 2, and 71.4, 78.4 and 76%, respectively for F≥3. PPV and NPV were 69, and 80% for F≥2; 55 and 90% for F≥3. Comparing AUROC of LFI to that derived from APRI, The AUROC by LFI was superior (Table 4).





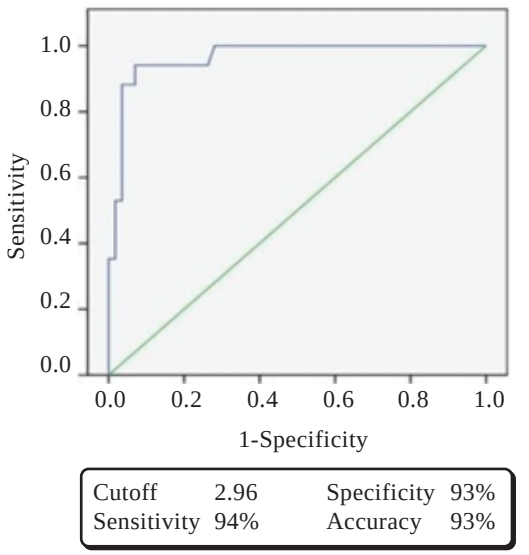


Fig. (4): ROC analysis differentiating (A) F0 from F1-4, (B) F0-1 from F2-4 and (C) F0-2 from F3-4.

Table (2): Cutoff values of LFI for the determination of fibrosis stage.

	≥F1	≥F2	≥F3
Cut-off	1.65	2.4	2.96
AUC	0.876	0.935	0.964
Sensitivity (%)	83	84.6	94
Specificity (%)	71.4	85.4	93
Accuracy (%)	79.7	85	93
PPV	88	75.9	80
NPV	62	91	98

Table (3): Published cut off values for LFI in different liver fibrosis stages.

	F≥2		F≥3		F4	
	Cut off	Sensitivity/ Specificity (%)	Cut off	Sensitivity/ Specificity (%)	Cut off	Sensitivity/ Specificity (%)
Fujimoto (2013)	1.92	78.6/78	NA	NA/NA	2.56	79.2/80.5
Tomeno (2013)	2.39	90.2/44.2	2.62	92.3/46.2	3.59	100/78
Kim (2014)	NA	NA/NA	NA	NA/NA	3.51	82.4/68.2

NA: Not Available.

Table (4): AUROC of LFI and APRI for predicting liver fibrosis stage.

	F≥2		F≥3	
	AUROC	*p*-value	AUROC	*p*-value
LFI	0.935	0.000	0.964	0.000
APRI	0.734	0.004	0.757	0.005

Discussion

In this study we used a newly developed RTE image analysis method to reflect liver elasticity in the form of Liver Fibrosis Index (LFI), which is automatically calculated by the Hitachi elastography module. LFI was evaluated in multiple previous studies Fujimoto et al. **[17]**; Tatsumi et al. **[18]**; Tomeno et al. **[19]**; Yada et al. **[20]**; Tamaki et al. **[21]** and Kim et al. **[22]**. Ferraioli et al. **[23]** used the same 9 features to calculate the LFI but in a different multiple regression analysis algorithm.

In our study LFI highly correlated with the stage of liver fibrosis (r=0.746, p<0.001). LFI showed high diagnostic accuracy for F≥3 (AUROC 0.96, sensitivity 94%, and specificity 93%), excluding advanced fibrosis with a NPV of 98%, and for F≥2 (AUROC 0.93, sensitivity 84.6%, and specificity 85.4%), meanwhile it showed a lower accuracy for F≥1 (AUROC 0.87, sensitivity 83%, and specificity 71.4%).

Partial overlapping of LFI values was observed, particularly for (F1 and F2) and for (F3 and F4) stages, indicating a lower efficiency in discriminating between the contiguous stages of hepatic fibrosis. Yada et al. **[20]** reported that no significant differencein LFI was found between F2and F3stages, while Tatsumi et al. **[18]** reported the same for F3 and F4 stages. Considering the fact that LB which is the standard reference is not perfect, it will be difficult to precisely determine the performance of RTE to discriminate between different stages of intermediate fibrosis as this could be coming from limitations of biopsy analysis for the intermediate-stage fibrosis **[24]**. This also stands for cirrhosis (F4 stage) where LB can result in understaging cirrhosis in 10-30% of cases **[3]**. Another point to consider is that pathological fibrosis staging is defined by architectural changes, with no consideration of the total amount of fibrosis **[25]**, and that it moves in big steps ignoring the fact that fibrosis progression itself is a gradient process, which means that exact concordance between RTE and LB cannot be present.

In the meta-analysis by Hong et al. **[14]**, the overall results suggested that LFI was excellent in diagnosing F≥3 (AUC 0.94,sensitivity 91%, and specificity 68%) and had moderate accuracy for F≥2 (AUC 0.79, sensitivity 78%, and specificity 63%), and for F4 (AUC 0.85, sensitivity 77%, and specificity 78%). Using Fagan plot analysis, performed to evaluate the clinical utilities of LFI, Hong et al. **[14]**. Reported that LFI could not be applied to accurately differentiate F2 versus F0-1 and F4 versus F0-3. Moreover, they compared the performance of LFI with the pooled performance of TE, and reported that LFI had no potential to substitute for TE.

"The International Liver Pathology Study Group" suggested that the term "cirrhosis" should

no longer be used and to be replaced by the diagnosis of advanced stage chronic liver disease within an integrated clinicopathologic approach to accurately stage the disease. Advanced stage should include cases previously diagnosed as cirrhosis (F4), and shortly falls backwards to include F3 cases with architectural distortion **[26]**. Also, in the context of prognosis, the worst survival curves were seen to a similar extent in patients with stage 3 (transitional) fibrosis and stage 4 (established) cirrhosis **[27]**. On the basis of these data, we considered stage 3 and 4 fibrosis as a single class in our study. This has enabled to increase the accuracy of RTE to identify cirrhosis and has decreased the false-negative rate in the present series, which allowed for identification of all patients with the worst prognosis.

Out of the 9 image features used, 5 features (%AREA, MEAN, SD, COMP and SKEW) were known to have a high correlation with the stages of hepatic fibrosis **[12]**. In Morikawa et al. and Fujimoto et al., studies, LFI and %Area were associated with the largest correlation coefficients, suggesting that %Area may directly represent liver elasticity **[11,17]**. So in this study, we also assessed the performance of % Area (area ratio of low-strain region) which showed a high correlation with the stage of liver fibrosis (r=0.739, p<0.001) and a high ability to differentiate F0 and F1-4, F0-1 and F2-4, F0-2 and F3-4 stages (AUROC were0.989, 0.930 and 0.964, respectively). Optimal cutoff values were 13.64, 23.95 and 28.73 for F≥1, F≥2, and F≥3 respectively.

RTE was successfully performed in overweight and obese patients. Our study did not show any association between BMI and LFI measurements. We found no influence of inflammation grade on LFI measurements, this was in consistency with Fujimoto et al. **[17]** who reported that none of the 9 image features nor LFI had a correlation with the grades (r=0.30), implicating that RTE image depends mainly upon liver fibrosis. Hepatic steatosis did not also seem to have influence on LFI. These findings were also in agreement with Ferraioli et al. **[23]** results, however further studies with higher grades of steatosis are needed to further validate these results. So, RTE can be performed in cases for which the results of TE (fibroscan) are considered unreliable.

RTE in our study showed a better performance than TE in assessing significant and advanced liver fibrosis, compared to the pooled performance of TE in a meta-analysis done by Friedrich-Rust et al. **[28]**. Involving 50 studies (AUROC of TE were 0.84, and 0.89 for F≥2 and F≥3, respectively. In a comparative study by Tatsumi et al. **[18]**, RTE was more successful than TE in diagnosing the degree of liver fibrosis, however further studies comparing RTE and TE in the same population are needed to assess if RTE has the ability to substitute for TE.

According to our results, APRI showed a fair performance in the assessment of liver fibrosis. Comparison of ROC curves showed that RTE performed better than APRI in the assessment of significant (≥F2) and advanced fibrosis (≥F3). Applying a high and low cutoff, APRI can be used in clinical practice for predicting advanced fibrosis/cirrhosis or low risk of significant fibrosis. Combined with LFI, this can increase RTE performance.

To conclude: RTE is easy to use, cost-effective and painless. However, RTE can have limitations related to being operator dependent. Training is needed to avoid artifacts related to obesity, to set the ROI not to include vessels or rib shadowing and to adjust the position of the probe to image the liver where compression/relaxation is homogeneous and axial to the probe. In the era of the new oral antiviral drugs for hepatitis C, once RTE is widely approved, it can be used as a screening tool before treatment and for follow-up.

Study limitations: The distribution of patients in our study was not equal through METAVIR scores, 36.5% of subjects were in the F1 stage, but since the studied population represented potential candidates to antiviral therapy, we think that the uneven distribution of patients reflects what is seen in clinical practice.

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الملخص العربى

الهدف من هذه الدراسة هو تقييم موثوقية مؤشر تليف الكبد (LFI)، كطريقة جديدة لتحليل كمى لتليف الكبدى باستخدام معامل المرونة بالموجات فوق الصوتية فى المرضى الذين يعانون من التهاب الكبد المزمن ضد، بالمقارنة مع خزعة الكبد.

\الأسالیب : اربع و خمسين من المرضى بالتهاب الكبد المزمن سى بالإضافة إلى مجموعة من عشرين من المتطوعين، كانوا مسجلين فى هذه الدراسة. تم تنفيذ معامل المرونة بالموجات فوق الصوتية لجميع المسجلين وتمت مقارنة النتائج بالعينة الكبدية. تعرض المرضى أيضا لاختبارات الدم الروتينية والموجات فوق الصوتية للبطن التقليدية.

\النتائج : معامل المرونة بالموجات فوق الصوتية يرتبط بعلاقة متبادلة مع مرحلة التليف فى الكبد ($p<0.001$, $r=0.746$). وأظهر تحليل ROC أن معامل المرونة كان دقة التشخيص عالية ل F≥3 : AUC 0.96، والحساسية ٩٤٪، وخصوصية ٩٣٪، و (F≥2 AUC 0.93، الحساسية ٨٤.٦٪، وخصوصية ٨٥.٤٪)، وفى الوقت نفسه أظهرت أقل دقة ل (F≥1 AUC 0.87، والحساسية ٨٣٪، وخصوصية ٧١.٤٪). وكانت AUROCs لمعامل المرونة للتنبؤ بتليف كبير ومتقدمة متفوقة على اسبارت مؤشر نسبة الألانين / الصفائح الدموية (APRI).

\الأستنتاج : معامل المرونة بالموجات فوق الصوتيه يمكن أن تكون أداة يمكن الاعتماد عليها لتقييم درجة تليف الكبد فى المرضى الذين يعانون من التهاب الكبد المزمن، والقدرة على التفريق بين غياب وتليف خفيف من التليف المتقدم .