

ORIGINAL ARTICLE

# Liver elastography can predict degree of advanced fibrosis for autoimmune hepatitis in biochemical remission

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## Key words

acoustic radiation force imaging, autoimmune hepatitis, liver biopsy, liver fibrosis, METAVIR score, transient elastography.

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## Introduction

Autoimmune hepatitis (AIH) is a chronic and progressive immune-mediated liver disease that can progress to cirrhosis, liver transplantation, and, more unusually, to hepatocellular carcinoma and death.<sup>1</sup> The diagnosis of AIH is established using clinical, laboratory, and histological features.<sup>1</sup> Although liver biopsy is not essential for diagnosis, it allows differential diagnosis from other liver diseases, stages the severity of liver inflammation and the degree of fibrosis, and defines the need for treatment.<sup>1,2</sup> The goal of treatment for AIH is normalization of aminotransferases

## Abstract

**Background and Aim:** The aim was to analyze the concordance of liver stiffness measurement (LSM) either by transient elastography (TE) or ARFI with liver biopsy in autoimmune hepatitis (AIH) patients with biochemical remission and to identify those with histological remission. Liver biopsy is still the golden standard for AIH diagnosis. However, it is an invasive procedure and these patients, most of the time, require many biopsies, so it would be valuable to search for noninvasive method that could select all these patients and keep under observation.

**Methods:** Thirty-three patients with AIH were submitted for liver biopsy to evaluate histological remission after at least 18 months of normal aminotransferases. The efficiency of LSM and fibrosis stages was tested by a receiver operating characteristic curve analysis (AUROC).

**Results:** One patient (3%) was F0, 6 (18.2%) were F1, 8 (24.2%) were F2, 10 (30.3%) were F3, and 8 (24.2%) were F4, according to METAVIR. Thirteen of thirty-three (39.4%) patients did not achieve histological remission. AUROC for F4 stage was 0.83 (IC: 0.76–0.99) for TE and 0.78 (IC: 0.65–0.95) for ARFI. Optimal LSM cutoff values were 12.3 kPa (Se = 87.5%, Sp = 88%) for TE and 1.65 m/s (Se = 87.5%, Sp = 76%) for ARFI. The tests were unable to differentiate patients with histological activity from those in histological remission ( $P < 0.05$ ).

**Conclusion:** TE and ARFI accurately identify liver fibrosis by METAVIR score in AIH patients with biochemical remission. No cutoff value was detected to indicate whether the patient achieved histological remission.

as well as immunoglobulin G (IgG) levels, with absent or minimal histological activity. Despite biochemical remission, liver biopsy is recommended to evaluate histological activity prior to the decision to withdraw immunosuppression, due to the high risk of relapse in patients with histological disease activity (hepatitis activity index  $>3$ ).<sup>1,3</sup> Liver biopsy, however, is an expensive and invasive procedure with associated risks, such as bleeding, pain, infection, and very occasionally death.<sup>4,5</sup> It requires good sampling and experienced pathologists.<sup>6,7</sup> Therefore, noninvasive liver assessment is a desirable option. The two best-established

forms to assess liver stiffness measurement (LSM) are transient elastography (TE) performed using a FibroScan<sup>®</sup> device and point shear wave elastography (pSWE), also known as acoustic radiation force impulse imaging (ARFI) technology using Siemens equipment. However, routine use of noninvasive methods of assessment of liver fibrosis is still controversial in AIH, because stiffness measurements are often overestimated in cases of significantly elevated aminotransferase, which is a common characteristic of this disease at onset.<sup>8</sup>

The primary aim of this study was to analyze the concordance of the LSMs by two shear wave techniques: TE and ARFI technology comparing LSM findings with staging of liver fibrosis according to the METAVIR score in AIH patients with at least 18 months of biochemical remission who underwent liver biopsy for evaluation of histological remission. The secondary aim was to define a cutoff value for liver stiffness able to identify patients in histological remission.

## Methods

**Patients.** All patients had a definite diagnosis of AIH according to the scoring system proposed by International Autoimmune Hepatitis Group Criteria (IAIHG) and underwent liver biopsy to evaluate histological remission after at least 18 months of biochemical remission and 2 years of immunosuppressive treatment in the period from 2012 to 2015. Biochemical remission was defined as aminotransferase levels within the normal reference value (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] <31 U/l for woman and AST <37 U/l and ALT <41 U/l for men) and normalization of IgG and/or gamma globulin (IgG <1538 g/dl and gamma globulin <1.5 g/dl). Histological remission was defined as minimal or no inflammatory activity.

Exclusion criteria were chronic infection with hepatic virus B or C, overlapping with primary biliary cholangitis and primary sclerosing cholangitis, drug-induced liver disease, alcoholic or non-alcoholic fatty liver disease, metabolic liver disease, hepatobiliary parasitic infection and decompensated liver disease (characterized by ascites, hepatic encephalopathy, gastrointestinal bleeding, and/or hepatocellular carcinoma).

Patients were submitted to laboratory tests, Doppler ultrasound, TE, ARFI and liver biopsy preferably on the same day, and upper gastrointestinal endoscopy within 6 months before or after inclusion. In some patients, it was not possible to perform all the exams on a single day because of scheduling difficulties. There were excluded patients in whom the time interval between laboratory test and biopsy/TE/ARFI was greater than 3 months and patients who did not reach the targets for good quality examination of both biopsy and LSMs.

The study was approved by the Ethics Committee of Hospital das Clínicas of Sao Paulo University School of Medicine, and written informed consent was obtained from each participant.

**Histological examination.** All liver biopsies were performed by different operators percutaneously using a 14G needle. Fibrosis and necroinflammatory activity staging was performed according to the METAVIR score. The histological specimens were analyzed by an experienced liver pathologist who had no knowledge of the elastography findings or biochemical results.

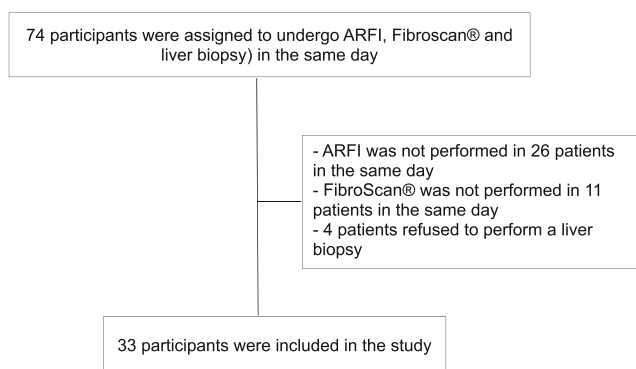
**Clinical measurements.** Medical records of all patients diagnosed with AIH were reviewed. Clinical data recorded included age, sex, ethnicity, BMI, serological markers, date of AIH diagnosis and treatment commencement, type of treatment, and associated co-morbidities (arterial hypertension, diabetes, and dyslipidemia). Laboratory evaluation included ALT, AST, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, gamma globulin, albumin, serum IgG, blood routine (white blood cell count and platelet count) and prothrombin activity/INR, blood glucose, and HDL and LDL cholesterol. AIH was classified into types 1 and 2 according to autoantibodies reactivity. Antinuclear, anti-smooth muscle, anti-liver kidney microsome type 1 (anti-LKM1), anti-liver cytosol type 1, and antimitochondrial antibodies were detected by indirect immunofluorescence according to the techniques defined by the IAIHG.<sup>9</sup>

**LSM by TE and by ARFI.** LSMs assessment was performed using TE with FibroScan<sup>®</sup> with a 3.5-MHz ultrasound transducer (M probe) from Echosens<sup>®</sup>, Paris, France.<sup>10</sup> ARFI technology, an elastography point shear wave quantification (pSWE), an US-based system technology of Siemens Company known as Virtual Touch Tissue Quantification, (VT<sup>®</sup>). pSWE/ARFI was also performed with an abdominal 3.5-MHz curved-array transducer.<sup>11</sup> An experienced blind operator (>500 examinations) carried out the procedures following the standardized protocol.<sup>12</sup> Results were expressed in kilopascals (kPa) or meters/s (m/s), and the median value was taken as representative of LSM.<sup>13</sup>

**Statistical analysis.** SPSS 19 was used to determine the mean, median, standard deviation, and range. The diagnostic accuracy of fibrosis staging was estimated using the area under the receiver operating characteristic curve (AUROC). The optimal LSM cutoff values for F2-4 fibrosis were determined based on the highest combined sensitivity and specificity (Youden index). The area under ROC curves (AUROC) were used to compare the diagnostic ability of each noninvasive test to predict the presence of advanced fibrosis. The performance characteristics of each cutoff value in terms of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, and diagnostic accuracy were calculated. Positive predictive values and negative predictive values were also calculated to evaluate clinical utility according to the ROC curves, considering the prevalence of each fibrosis stage in our center.<sup>14</sup> The comparison between two or more groups was tested by Kruskal–Wallis and paired comparison groups were verified by Mann–Whitney test. A *P*-value <0.05 was considered statistically significant.

## Results

**Patient characteristics.** A total of 74 patients were assigned to undergo ARFI, FibroScan<sup>®</sup> and liver biopsy on the same day. Of these, 33 patients were included in the study as shown in Figure 1. The mean age at AIH diagnosis was 35.6 ± 19.9 years. The two main forms of disease presentation were acute on chronic AIH (mimicking acute viral hepatitis) in 16 (48.5%) patients, and liver biochemistry abnormalities detected during follow-up of extra-hepatic diseases in 8 (24.2%). The mean age at study inclusion was 37.9 ± 20.2 years. Twenty-eight (84.8%) were female and had type 1 AIH. At inclusion,



**Figure 1** Flowchart of patients assigned to the study.

**Table 1** Clinical and autoantibodies profile at AIH diagnosis with histological data

Characteristic	<i>n</i> = 33
Age (years, mean ± SD)	37.9 ± 20.2
Female gender, <i>n</i> (%)	28 (84.8)
Autoantibodies profile at AIH diagnosis	
Anti-SLA/LP <i>n</i> (%)	10 (34.5)
Anti-LKM 1 <i>n</i> (%)	2 (6.1)
Antinuclear antibody and/or anti-smooth muscle	28 (84.9)
Gamma-globulin levels at inclusion (Mean ± SD)	1.37 ± 0.46
Liver biopsy*	
Fibrosis stage <i>n</i> (%)	
0	1 (3)
1	6 (18.2)
2	8 (24.2)
3	10 (30.3)
4	8 (24.2)
Liver inflammatory activity	
0	13 (39)
1	13 (39)
2	7 (22)
3	0

\*Biopsy specimen size measured between 0.8 and 2.5 mm length. Classification according to METAVIR score.

immunosuppression was a combination of azathioprine and prednisone in 87.9% (*n* = 29) of patients. Clinical, laboratory, and histological data of the patients are shown in Table 1; all patients had normal AST and ALT levels. The mean body mass index (BMI) was 28.6 kg/m<sup>2</sup> (range, 21.5–41.7). Esophageal varices were present in 12 (37.5%) patients; eight (24.2%) patients were using beta-blockers for variceal bleeding prophylaxis (according to BAVENO VI). Six patients (18.2%) had steatosis in ultrasound, although none of them showed evidence of non-alcoholic steatohepatitis at liver biopsy. Table 2 shows the LSM parameters by both methods.

**Diagnostic accuracy of LSM.** Histological fibrosis stage according to the METAVIR classification were distributed as follows: F0: *n* = 1 (3%), F1: *n* = 6 (18.2%), F2: *n* = 8

**Table 2** Laboratory data and elastography parameters values in 33 AIH patients

	MEAN ± SD	MEDIAN (min–max)
Treatment duration at inclusion (months)	35.6 ± 19.8	36.1 (2.6–64.3)
Glucose (mg/dl)	90.1 ± 21.6	86.5 (65–188)
HDL (mg/dl)	61.4 ± 18.1	60 (32–110)
Triglycerides (mg/dl)	127 ± 80	108 (40–454)
Hemoglobin (g/dl)	13.1 ± 1.6	13.4 (8.7–16.1)
Leukocytes (10 <sup>3</sup> /mm <sup>3</sup> )	6921 ± 2780	6530 (2780–14 860)
Neutrophils (10 <sup>3</sup> /mm <sup>3</sup> )	4552 ± 2521	3700 (1564–12 880)
Lymphocytes (10 <sup>3</sup> /mm <sup>3</sup> )	1636 ± 899	1400 (240–3770)
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	203 000 ± 103 486	200 000 (48000–534 000)
Prednisone dose (mg/day)	9.3 ± 2.3	10 (5–15)
Azathioprine dose (mg/day)	82.8 ± 36.7	87.5 (50–150)
IMC (kg/m <sup>2</sup> )	28.6 ± 4.93	27.60 (21.5–41.7)
Skin-liver distance (cm)	1.89 ± 0.49	1.70 (1.2–2.9)
Success rate (%)	84 ± 14	83 (60–100)
LSM (kPa)	12.5 ± 10.7	8.6 (3–41.6)
IQR / med (%)	14.1 ± 6.2	14 (3–29)
IQR	3.6 ± 10.9	1 (0.3–62)
CAP (dB/m)	202 ± 46	218 (100–256)
ARFI (m/s)	1.62 ± 0.69	1.37 (0.71–3.47)
IQR	0.30 ± 0.18	0.27 (0.06–0.86)

(24.2%), F3: *n* = 10 (30.3%) and F4: *n* = 8 (24.2%). LSM was successfully performed in all patients.

For fibrosis stage F ≥ 2, AUROC curves were 0.907 (0.806–1.000) for TE and 0.882 (0.767–0.997) for ARFI. Optimal stiffness cutoff values were 6.3 kPa (Se = 76.9%, Sp = 100%) for TE and 1.27 m/s (Se = 76.9%, Sp = 100%) for ARFI. For fibrosis stage F ≥ 3, AUROC curves were 0.833 (0.685–0.982) for TE and 0.787 (0.628–0.946) for ARFI. Optimal stiffness cutoff values were 8.7 kPa (Se = 72.2%, Sp = 80%) for TE and 1.5 m/s (Se = 66.7%, Sp = 80%) for ARFI. For fibrosis stage F = 4, AUROC curves were 0.880 (IC: 0.76–0.99) for TE and 0.803 (IC: 0.65–0.95) for ARFI. Optimal stiffness cutoff values were 12.3 kPa (Se = 87.5%, Sp = 88%) for TE and 1.65 m/s (Se = 87.5%, Sp = 76%) for ARFI (Table 3).

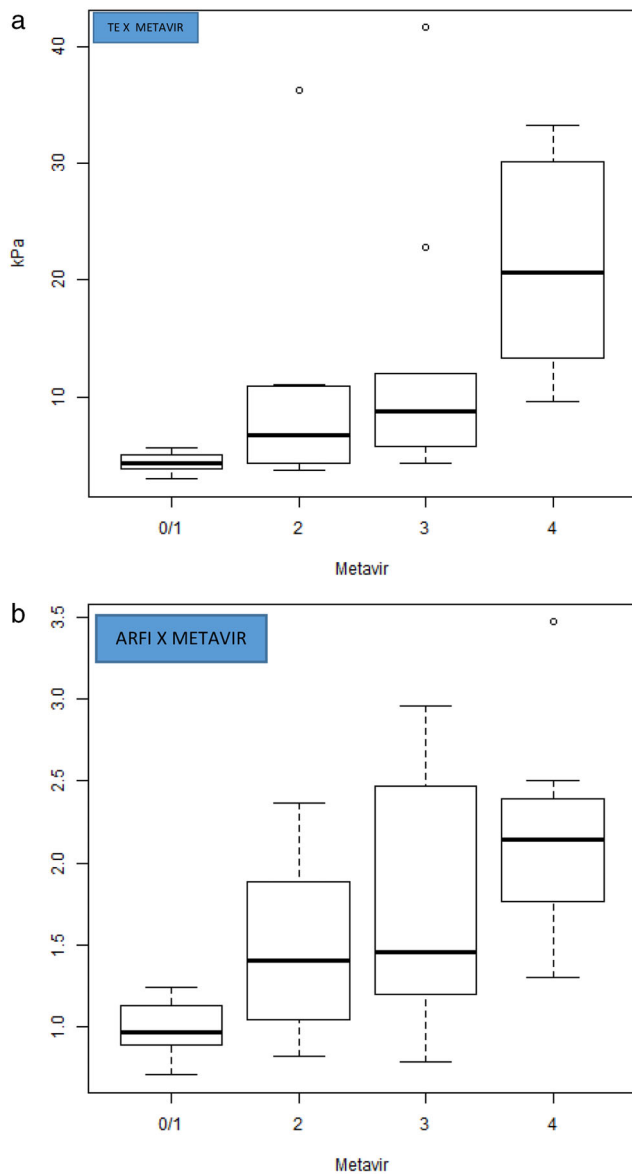
The successful performance of LSM in all patients according to the histological fibrosis stages by TE can also be verified in Figure 2. There was a significant difference between liver stiffness TE values of patients with fibrosis stages F0, 1, and F3 (*P* < 0.006), and stages F0, 1, and F4 (*P* < 0.0001).

The median values of LSM by TE were 4.3 kPa for fibrosis 0/1, grade 2 = 6.8 kPa, grade 3 = 8.7 kPa, and grade 4 = 20.6 kPa. The median values of LSM by ARFI were 0.97 m/s for fibrosis 0/1, grade 2 = 1.41 m/s, grade 3 = 1.46 m/s, and grade 4 = 2.15 m/s.

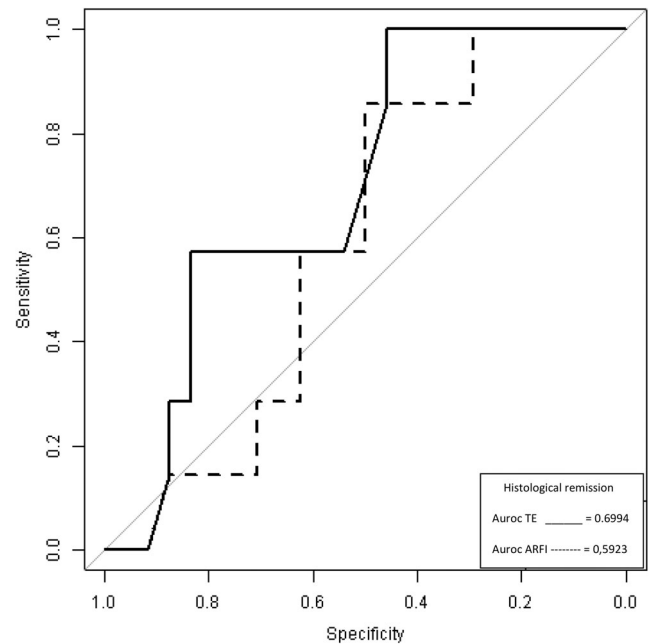
Despite normal liver enzymes and IgG levels, 13 of 33 (39.4%) patients did not achieve histological remission (Activity Histological Index >3). All 20 patients with histological remission could be classified according to fibrosis stage as

**Table 3** Comparison of ROC curves for TE and ARFI in detection of fibrosis stages F2-4

MARKER	Prevalence	AUROC (95%)	cutoff	Sensitivity (Se)	Specificity (Sp)	PPV	NPV	LR+	LR-
LSM (kPa)			kPa						
≥F2	81.9%	0.907 (0.806–1)	6.3	76.9%	100.0%	100.0%	48.9%		0.23
≥F3	71.8%	0.833 (0.685–0.982)	8.7	72.2%	80.0%	90.2%	53.1%	3.61	0.35
F4	56.0%	0.880 (0.760–1)	12.3	87.5%	88.0%	90.3%	84.7%	7.29	0.14
ARFI (m/s)			m/s						
≥F2	81.9%	0.882 (0.767–0.997)	1.27	76.9%	100.0%	100.0%	48.9%		0.23
≥F3	71.8%	0.787 (0.628–0.946)	1.5	66.7%	80.0%	89.5%	48.5%	3.33	0.42
F4	56.0%	0.803 (0.65–0.955)	1.65	87.5%	76.0%	82.3%	82.7%	3.65	0.16



**Figure 2** (a) Correlation between liver stiffness measurement by TE and each histological fibrosis stage. (b) Correlation between liver stiffness measurement by ARFI and each histological fibrosis stage.



**Figure 3** Diagnostic performances of both methods by ROC curves to discriminate histological remission.

described below, seven patients were F0/1, seven patients were F2, three patients were F3, and three were F4. When we analyzed the proportion of patients who achieved histological remission according to the degree of liver fibrosis, we found that 7 of 7 (100%) were F0/1, 7 of 8 (87.5%) were F2, 3 of 10 (30%) were F3, and 3 of 8 (37.5%) were F4. Almost 100% of patients without advanced fibrosis (F0-2) could achieve histological remission, on the other hand, only 37.5% of the patients with advanced liver fibrosis reached this end point.

Although mean elastography values were higher in the group without histological remission, when compared with those with disease remission, the difference was not statistically significant ( $10.4 \pm 9.6 \times 15.7 \pm 12$  kPa,  $P = 0.17$ ). The ROC curves were unable to differentiate between patients with active disease and those in histological remission (TE = 0.10 and ARFI = 0.40), (Fig. 3).

## Discussion

We found strong correlation between the TE and ARFI stiffness values in comparison with histological fibrosis from the METAVIR score. These findings are consistent with other studies, with different liver chronic disease etiologies that showed good correlation between LSM values and liver fibrosis grade.<sup>15–18</sup> FibroScan<sup>®</sup> showed slightly better diagnostic accuracy than VT<sup>®</sup> in detecting F4. Our cutoff stiffness values for F4 (12.3 kPa and 1.65 m/s) were similar to those found by Qinyu Xu *et al* in an AIH population, which proposed a cutoff of 12.5 kPa for F4, reporting an accuracy curve of 0.914.<sup>15</sup> Hartl *et al* proposed that the best cutoff for F4 in AIH was 16 kPa with AUROC 0.95.<sup>18</sup> In this study, however, the patients did not achieve biochemical remission, which may explain why their stiffness cutoff was higher than ours. In a large-scale multicenter retrospective study for hepatitis B and hepatitis C, values for F4 were 11.6 and 14.5 kPa respectively.<sup>19</sup> Comparing these values with the ones we found for AIH, we can consider that liver disease etiology does not significantly interfere with LSM when evaluating cirrhosis in the presence of chronic hepatitis where patients present normal liver enzyme blood levels. However, the confounding factors such as higher elevated transaminase ( $5 \times$  LV), the presence of cholestasis (extra bile obstruction), and liver congestion (right cardiac insufficiency) may indeed interfere with LSM values, as has already been demonstrated in other papers.<sup>20</sup> We should highlight that we could measure and compare two elastography machines with good performance between them and even in three different fibrosis stages. But the best concordance was observed in the extreme fibrosis groups: mild fibrosis or advanced than intermediate fibrosis. In addition, TE had small advantage over ARFI since TE included all F3 and almost all F4 patients. ARFI included only few F3 and all F4. For mild fibrosis, F2/F1/F0, the performance of both methods was quite similar.

We all know how important is to stratify patients with advanced liver fibrosis, since they must be followed by ultrasound every 6 months and or upper digestive endoscopy. In addition, in this scenario, ARFI had the advantage to study the liver anatomy and to include patients where the right hepatic lobe is reduced because of portal hypertension component and could be a limitation to the TE.

Our results could demonstrate that the use of both methods in routine clinical follow-up for AIH is reliable and values above 1.65 m/s from ARFI present sensibility and specificity of 87.5% and 70.6% to determine F4 (Table 3).

Unfortunately, we were not able to establish liver stiffness cutoff values for each of the low fibrosis stages because of the small sample size (F0 = 1, F1 = 6). This is because our center is a tertiary referral center for AIH treatment, and 45% of patients have liver cirrhosis at initial liver biopsy, before starting immunosuppression therapy. So we decided to associate patients with fibrosis F0 and F1 for statistical analysis.<sup>14</sup>

Liver biopsy is still the gold standard for AIH staging and assessment of fibrosis, and may be essential for diagnosis in some cases, particularly in AIH without serological markers. Furthermore, the aim of immunosuppression treatment includes not only biochemical normalization (transaminase and IgG levels) and also histological remission, defined as minimal or absent

inflammatory activity in the post-treatment control biopsy and effective treatment may result in reversal of fibrosis. Therefore, liver biopsy is important in several determinants of the follow-up of AIH. However, it is an invasive procedure associated with risk of serious adverse events in up to 1.1% of cases, with bleeding in 0.6%, which makes it difficult to dynamically monitor the histological improvement of fibrosis after starting treatment.<sup>21</sup> Therefore, it is important to search for noninvasive methods for assessing liver fibrosis. LSM evaluated by TE is already a widely recognized and used method for assessing liver fibrosis in patients with viral hepatitis.<sup>16,17</sup> However, there are still not enough large studies related to its usefulness in AIH to provide conclusive evidence for change in clinical practice management.

A recent systematic review of the diagnostic accuracy of noninvasive tests for staging liver fibrosis in AIH observed that TE has good diagnostic performance for detecting significant fibrosis, advanced fibrosis, and cirrhosis, but it may be affected by liver inflammation and high transaminase levels, which is common at AIH diagnosis. To minimize this effect, the authors conducted a subgroup analysis by treatment status (treatment naïve or post-treatment patients) and TE maintained good performance in both cases, but the data were limited by sample size.<sup>22</sup> Other studies have also shown the impact of significant transaminase elevation, especially of ALT in overestimating LSM and affecting the accuracy of this procedure.<sup>13,23,24</sup> In our study, to avoid this bias, we selected a population that had already achieved biochemical remission to improve the accuracy of the methods to evaluate liver fibrosis.

In some studies, almost 50% of patients presented histological inflammatory activity despite complete biochemical remission; in our center, 40% of patients with biochemical remission still have histological activity at control liver biopsy.<sup>14,25</sup> This finding is important because such patients are at high risk of disease progression, clinical worsening, and relapse of AIH in cases of treatment withdrawal. It would be useful if TE could define which patients in biochemical remission also present histological remission. We compared the groups with and without histological remission but, unfortunately, the FibroScan<sup>®</sup> and VT<sup>®</sup> results were not able to demonstrate the resolution of the liver inflammatory activity, which was in accordance with other studies in the literature,<sup>15,18</sup> which found that LSM reflects changes in liver fibrosis and not variations in hepatic inflammation. Similar data were verified in a cohort where 25% of patients in complete biochemical remission also showed residual liver inflammation at biopsy.<sup>25</sup> It appears that after complete biochemical remission with at least 6 months of treatment, residual hepatic inflammation may indeed not interfere with the accurate performance of the LSM by TE and ARFI for the detection of severe fibrosis and cirrhosis, as it was also verified in our study.

This study has some limitations, such as the sample size; which could be justified by the fact that it is single center, and that AIH is a disease with low population prevalence. That FibroScan<sup>®</sup> and VT<sup>®</sup> were performed by a single experienced specialist in a single device and patients had follow-up of AIH in a single center with pre-established and great experience for the management of the disease can be considered a strength. A larger sample size would allow ranking of the patients into subgroups



according to the time of immunosuppression treatment (naïve and post-treatment groups). This would be a useful future study. Interestingly, our results showed that patients with less fibrosis have greater chance of achieving complete response, with histological remission. It would be very interesting if we could perform an analysis of the drop in liver stiffness over the disease course, after immunosuppressive treatment, to correlate the delta of the drop with treatment response and clinical outcomes. We could not perform this analysis in our study because all patients were in biochemical remission at study inclusion.

In conclusion, noninvasive liver fibrosis evaluation by mechanical methods such as FibroScan® and VT® can accurately identify liver fibrosis by METAVIR score in patients with AIH in clinical remission. TE ≥ 12.3 kPa and ARFI ≥ 1.65 m/s were the best cutoff values to predict cirrhosis. No cutoff value was detected that could indicate whether the patient achieved histological remission. New studies including more patients are necessary to confirm this finding.

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## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

**Table S1.** Supplementary data of liver biopsy of the patients at autoimmune hepatitis diagnosis.