Transient elastography using Fibroscan is the most reliable noninvasive method for the diagnosis of advanced fibrosis and cirrhosis in alcoholic liver disease

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Objective Fibroscan (FS) is a reliable noninvasive method for the diagnosis of advanced fibrosis and cirrhosis in chronic liver disease. However, there is no clear consensus with respect to the best FS cut-off values for use in alcoholic liver disease (ALD). The aims of this study were as follows: (a) to compare the performance of FS and different biochemical markers in ALD patients; (b) to assess the best FS cut-off values for the prediction of fibrosis stage in our ALD population; and (c) to assess the influence of aspartate aminotransferase (AST) values on FS.

Patients and methods This retrospective study included 135 consecutive and compensated ALD patients who underwent liver biopsy between November 2006 and March 2012 at Erasme Hospital. FS, Fibrotest, FIB-4, aspartate aminotransferase to platelet ratio index (APRI), and Forns' scores were tested in all patients.

Results The diagnostic accuracy of FS was 0.89 (95% confidence interval: 0.83–0.95) for the diagnosis of advanced fibrosis and 0.93 (95% confidence interval 0.90–0.97) for the diagnosis of cirrhosis. FS performed better than Fibrotest (0.81 and 0.88), APRI (0.65 and 0.75), Forns' (0.64 and 0.78), and FIB-4 (0.70 and 0.73). The optimal cut-off values of liver stiffness (LS) for predicting METAVIR fibrosis stage $F \geq 3$ and F4 disease were 10.3 and 18.0 kPa, respectively. AST showed a significant positive correlation with LS ($r = 0.24$, $P = 0.001$). However, exclusion of patients with AST more than 50 IU/l only lowered the LS cut-off for the diagnosis of F4 (14 vs. 18.0 kPa).

Conclusion FS is currently the most reliable noninvasive method for the diagnosis of advanced liver fibrosis and cirrhosis in ALD.
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Introduction

Chronic alcohol abuse is a major public health problem. Alcohol is the third leading cause of premature death in the world, representing 4% of global mortality [1]. Alcohol-induced liver injury is the most prevalent cause of liver disease worldwide. It affects 10–20% of the population [2]. Alcoholic liver disease (ALD) is a complex disease with a wide spectrum of presentations ranging from simple steatosis, alcoholic steatohepatitis (ASH) that can lead to progressive fibrosis, cirrhosis, and finally hepatocellular carcinoma [3]. Among individuals consuming 50 g or more of ethanol per day, the vast majority will develop steatosis, whereas only a minority (15–40%) will develop liver fibrosis and cirrhosis [4,5]. In addition to the amount and the pattern of alcohol consumption, clinical factors such as sex, obesity, and, more recently, genetic factors, have been identified to explain, at least partly, the discrepancies in susceptibility to the development of fibrosis [6,7]. Early diagnosis of advanced fibrosis and cirrhosis before the onset of end-stage liver disease is of major interest to motivate patients to decrease or, ideally, interrupt alcohol consumption, and to implement specific screening procedures for the complications of cirrhosis. Liver biopsy remains the gold standard for the assessment of liver fibrosis in ALD patients. However, it is an invasive procedure with rare, but potentially life-threatening complications [8]. In addition, it is poorly accepted by patients, expensive, and the accuracy of liver biopsy in assessing fibrosis is limited owing to sampling error and inter-observer variability [9–12]. For all these reasons, development of a noninvasive diagnostic approach is of great interest in ALD patients.

Several noninvasive laboratory tests have been developed to assess liver fibrosis combining different biomarkers, such as the aspartate aminotransferase to platelet ratio index (APRI) [13,14], Forns' index [15], FIB-4 [16],

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and Fibrotest (FT) [17,18]. Although initially designed for patients with chronic hepatitis C, some of these tests also seem promising in patients with ALD [5,19]. More recently, Fibroscan (FS), a noninvasive technique involving ultrasound-based transient elastography, has enabled evaluation of liver fibrosis by measuring liver stiffness (LS) [20]. This technique has been validated widely in hepatitis C virus patients [21–23], but has not yet been studied extensively in ALD [24–28]. In particular, no clear consensus with respect to the best LS cut-offs for the degree of liver fibrosis exists in ALD. Moreover, the best noninvasive tool to diagnose advanced fibrosis and cirrhosis in ALD patients is currently unknown.

The aims of this study were as follows: (a) to evaluate and compare the performance of LS and different biochemical markers for the diagnosis of advanced fibrosis and cirrhosis in ALD patients; (b) to assess the best LS cut-off values for the prediction of extensive fibrosis and cirrhosis in this population; and (c) to study the possible influence of aspartate aminotransferase (AST) values on LS.

Patients and methods

Patients

This was a retrospective study carried out on patients who underwent liver biopsy at Erasme Hospital, Brussels, Belgium, between November 2006 and March 2012. Patients treated during this period who had compensated ALD, were 18 years of age or older, had alcohol intake more than 50 g/day for more than 5 years, were candidates for a liver biopsy (by the transcutaneous or the transjugular technique) for assessment of ALD, and had biochemical scores from APRI, FIB-4, Forns' index, and FT testing, and LS measurement included in their record were included and recruited consecutively. Exclusion criteria included the presence of concomitant liver disease, presence of ascites and/or encephalopathy, and HIV positivity. The study was approved by the institutional review board at Erasme Hospital.

Study methodology

The following data were recorded: age, sex, BMI and waist circumference, daily alcohol intake, and the presence or absence of clinical or imaging (ultrasound, tomodensitometry, or MRI) signs of chronic liver disease. Patients with unequivocal clinical and/or imaging signs of cirrhosis were defined as cirrhotic patients, irrespective of the result of the liver biopsy. The following laboratory parameters were measured: prothrombin time, platelet counts, total bilirubin, AST, alanine aminotransferase (ALT), γ-glutamyltranspeptidase (GGT), alkaline phosphatase, α-2 macroglobulin, apolipoprotein A1, haptoglobin, albumin, cholesterol, triglycerides, C-reactive protein, serum iron, transferrin saturation, ferritin, hepatitis virus B, hepatitis virus C, HIV status, and autoantibodies.

Histological analysis

Liver biopsies were performed either by the percutaneous or by the transjugular technique, enabling measurement of the portosystemic gradient. Specimens were fixed, embedded in paraffin, sliced, and stained with hematoxylin–eosin and picrosirius coloration and examined by one experienced pathologist blinded to the other results. Liver fibrosis was staged using the METAVIR classification: F0: absence of fibrosis, F1: minimal portal fibrosis without septa, F2: portal fibrosis, F3: septal fibrosis, and F4: cirrhosis [29–31].

Hepatic steatosis was evaluated according to the percentage of hepatocytes containing fatty vacuoles. ASH was defined by the association of hepatocyte ballooning, Mallory's hyaline, and neutrophil infiltration [3,32].

Serum fibrosis markers

FT [17,18,22], APRI, Forns' index, and FIB-4 scores were calculated according to published procedures. The APRI score was calculated as follows [13,14,33]: AST/(upper limit of normal) × 100/platelet count (10^9/l). Forns' score was calculated using this algorithm [15]: 7.811–3.131 × ln [platelet count (10^9/l)] + 0.781 × ln[GGT (IU/l)] + 3.467 × ln [age (years)]–0.014 × [cholesterol (mg/dl)]. The FIB-4 score was calculated as follows [16]: [age (years) × AST (IU/l)]/[number of platelets (10^9 l) × ALT (IU/l)$^{(1/2)}$].

Liver stiffness measurements

LS measurement was performed using FS (Echosens, Paris, France) by an experienced operator. Details of the technical description and examination procedure have been described previously [20]. Ten successful acquisitions were performed for each patient. The success rate was calculated as the ratio of the number of successful acquisitions over the total number of acquisitions. The final result was the median of all valid measurements performed. Only results obtained with 10 successful acquisitions and a success rate of at least 60% were considered reliable. Results were expressed in kilopascal.

Statistical analysis

Statistical analyses were carried out using Statistix9 software (Statistix 9.0: analytical software, Tallahassee, Florida, USA) for descriptive, correlation, and nonparametric analyses. Variables with a normal distribution are represented as mean ± SE. Skewed variables are presented as the median (interquartile range). Spearman's correlation coefficient was used. Box plots were drawn to show the distribution of the observed LS values, FT, FIB-4, Forns', and APRI scores as a function of the METAVIR fibrosis stage. To compare skewed variables, we used the Mann–Whitney *U*-test. The diagnostic performance of FS and the different biochemical scores were evaluated using receiver-operating characteristic (ROC) curves and by calculating the area under the receiver-operating characteristic curve (AUROC). The optimal LS cut-offs for the detection of advanced fibrosis (F ≥ 3) and cirrhosis (F4) were determined from ROC curves according to a sensitivity of at least 90% and then choosing the best specificity. ROC curves were determined using the SPSS software (SPSS 22.0, IBM Corp., Armonk, New York, USA).

Results

Patient characteristics and liver histology

One hundred and thirty-five consecutive ALD patients were included in this study. Patient characteristics are summarized in Table 1. The majority of patients were men

(70%), mean age 56 ± 0.9 years. The median daily alcohol intake was 70 g/day (IQR: 50–150).

A total of 83 patients (61%) underwent a transjugular liver biopsy, enabling portosystemic gradient measurement [median 7 mmHg (4–13.5)]. The mean liver biopsy length was 19.9 ± 0.8 mm. Fifty-seven patients (42%) had cirrhosis (41 patients with histological features and 16 patients with unequivocal clinical and/or imaging signs). Histological features of ASH were observed in 40 patients (29.6%) (Table 2).

Liver stiffness measurements, biochemical fibrosis markers, and comparison with liver histology

LS values measured using FS ranged from 3.4 to 75 kPa, with a median of 14.4 kPa. The mean success rate was 86.2 ± 17.9% (Table 1). Of 135 patients, 12 FS failures were reported. The results of the four biochemical scores of liver fibrosis are presented in Table 1.

Portal hypertension, assessed by the portosystemic gradient, was correlated positively with LS measures ($r = 0.67$, $P < 0.0001$). LS did not correlate significantly with steatosis ($r = -0.0116$, $P = 0.205$). For the 40 patients with histological signs of ASH, LS values were significantly higher compared with those without ASH histological features [median 28 kPa (12–55.6) vs. 12.5 kPa (7.6–28.9), $P = 0.0005$].

Transient elastography using the FS was correlated significantly with METAVIR fibrosis stage ($r = 0.68$, $P < 0.00001$) as were FT, FIB-4, APRI, and Forns' index ($r = 0.5$, $P < 0.00001$; $r = 0.357$, $P = 0.001$; $r = 0.355$, $P = 0.001$; $r = 0.26$, $P = 0.004$, respectively). Box plots show the distribution of observed LS (Fig. 1), FT, FIB-4, Forns' index, and APRI values (Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A27*) as a function of METAVIR fibrosis stage.

Table 1. Characteristics of the patients included

Characteristics	Included patients ($n = 135$)
Clinical	
Male sex [*n* (%)]	94 (70%)
Age (years)	56 ± 0.9
BMI (kg/m^2)	26.1 ± 0.5
Daily alcohol intake (g)	70 (50–150)
Biological	
Prothrombin time (%)	83.5 ± 1.8
Platelets (/mm^3)	201 (147–255)
Alanine aminotransferase (ALT) (IU/l)	43 (29–70)
Aspartate aminotransferase (AST) (IU/l)	53 (33–91)
γ-Glutamyltranspeptidase (GGT) (IU/l)	168 (96–528)
Total bilirubin (mg/dl)	0.7 (0.4–1.3)
Haptoglobin (mg/dl)	145 ± 8.4
α2-macroglobulin (mg/dl)	202.6 ± 6.4
Apolipoprotein A1 (mg/dl)	132 (103–168)
Serum ferritin (ng/ml)	426 (221–936)
Albumin (g/dl)	4.2 (3.7–4.6)
Biochemical scores	
FT	0.46 (0.21–0.79)
Forns' index	6.5 ± 0.2
APRI	0.75 (0.56–1.6)
FIB-4	2.2 (1.2–3.5)
Liver stiffness	Included patients ($n = 123$)
LSM (kPa)	14.4 (8.1–40)
IQR	2.0 (0.9–5.0)
Success rate (%)	86.2 ± 17.9

Variables with a normal distribution are represented as mean ± SE. Skewed variables presented as median (interquartile range).
APRI, aspartate aminotransferase to platelet ratio index; FT, Fibrotest; IQR, interquartile range; LSM, liver stiffness measure.

Table 2. Characteristics of liver biopsies

Liver biopsies	Included patients ($n = 135$)
Transjugular/percutaneous [*n* (%)]	83 (61.5%)/52 (38.5%)
Length (mm)	19.9 ± 0.8
Portosystemic gradient (mmHg)	7.0 (4–13.5)
Fibrosis stage (METAVIR) [*n* (%)]	
F0	27 (20)
F1	10 (7.4)
F2	33 (24.4)
F3	24 (17.8)
F4	41 (30.4)
ASH histological signs [*n* (%)]	40 (29.6)
Steatosis	15% (5–40%)

Variables with normal distributions are represented as mean ± SE. Skewed variables are presented as medians (interquartile range).
ASH, alcoholic steatohepatitis.

The median value (first–third quartiles) of LS measure was significantly different between patients according to METAVIR fibrosis stage [F1: 8.8 (7.5–10.7), F2: 9.3 (8.0–13.0), F3: 13.4 (7.7–20.8), F4: 44.0 (26.9–75.0), $P < 0.0001$].

Determination of liver stiffness cut-offs using Fibroscan for the diagnosis of advanced fibrosis and cirrhosis according to the METAVIR classification

The diagnostic value of LS using FS for advanced fibrosis (METAVIR classification of F ≥ 3) and cirrhosis (METAVIR classification of F4) was determined using ROC curves. The AUROCs were 0.89 (95% confidence interval: 0.83–0.95) for F ≥ 3 and 0.93 (95% confidence

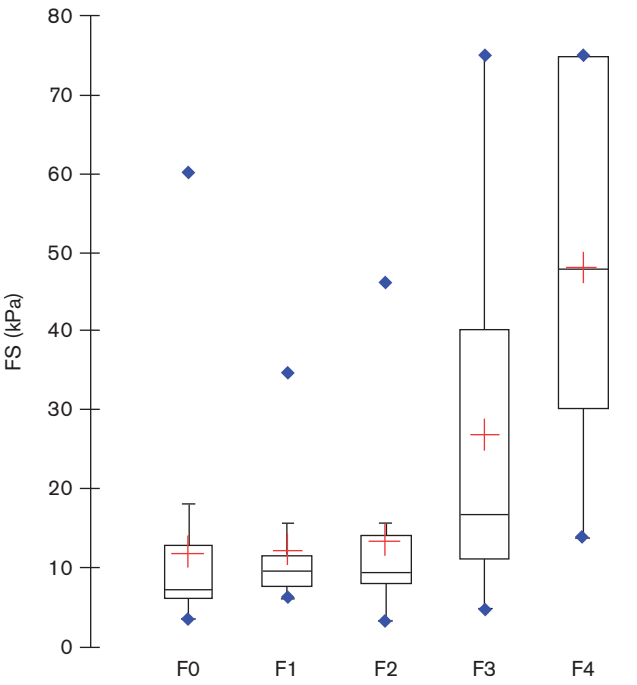

Fig. 1. Box plot of liver stiffness (kPa) as a function of METAVIR fibrosis stage. The top and the bottom of the boxes are the first and third quartiles. The lines through the boxes represent the median values. The length of the box represents interquartile ranges, within which are located 50% of the values. The brackets below and above the box enclose 95% of the entire set of stiffness values. The red cross represents the mean; the blue point at the top is the maximum value and the bottom blue point is the minimum value.

interval: 0.90–0.97) for F4 (Fig. 2). Using AUROC curve values, we determined the best LS cut-offs: 10.3 kPa for F ≥ 3 and 18.0 kPa for F4, and the corresponding sensitivities, specificities, negative predictive values, and positive predictive values, which are shown in Table 3.

Comparison between Fibroscan and serum markers for the diagnosis of advanced fibrosis and cirrhosis

We compared AUROCs for FT, APRI, FIB-4, and Forns' index fibrosis scores with LS scores using FS for the diagnosis of F ≥ 3 and F4 fibrosis. AUROCs are presented in Fig. 2 and Supplementary Table 1 (Supplemental digital content 1, *http://links.lww.com/EJGH/A27*). For advanced fibrosis and cirrhosis, LS AUROCs were higher than the other biochemically derived scores. Among the four biochemically derived scores, FT appears to be the most efficient, with AUROCs of 0.81 and 0.88 for advanced fibrosis and cirrhosis, respectively. Combining FS and the best biochemical score, that is FT, did not improve AUROC compared with using FS only (0.89 and 0.93 for F ≥ 3 and F4, respectively).

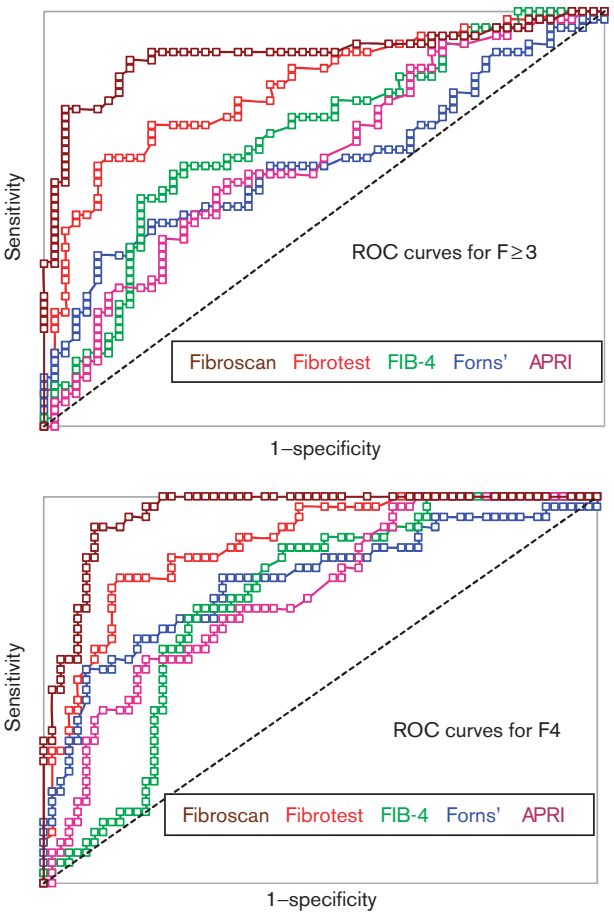

Fig. 2. Receiver-operating characteristic curves (ROC) for Fibroscan, Fibrotest, FIB-4, Forns' index, and aspartate aminotransferase to platelet ratio index (APRI) score in patients with advanced fibrosis (F ≥ 3) and cirrhosis (F4). The areas under the receiver-operating characteristic curve are shown in Supplementary Table 1, Supplemental digital content 1 (*http://links.lww.com/EJGH/A27*).

Table 3. Liver stiffness cut-offs for the diagnosis of advanced fibrosis and cirrhosis

	Best LS cut-off (kPa)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
F ≥ 3	10.3	91	67	76	87
F4	18.0	90	86	82	93

LS, liver stiffness; NPV, negative predictive value; PPV, positive predictive value.

Determination of the influence of aspartate aminotransferase values on liver stiffness cut-offs

AST values correlate positively with LS ($r = 0.24$ $P = 0.007$). LS was significantly higher in patients with AST more than 100 IU/l [31.6 (9.6–54.6) kPa vs. 13.7 (8.1–32.4) kPa, $P = 0.036$]. Similarly, LS in patients with AST more than 50 IU/l was significantly higher than those with AST less than or equal to 50 IU/l [18.4 (9.1–48.0) vs. 11.6 (7.6–28.4), $P = 0.015$]. Table 4 summarizes LS AUROCs for the diagnosis of advanced fibrosis and cirrhosis after the exclusion of patients with AST more than 100 IU/l and AST more than 50 IU/l. AUROC values did not increase after the exclusion of patients with AST more than 100 IU/l or AST more than 50 IU/l. The optimal LS cut-offs selected for the diagnosis of F ≥ 3 did not change after the exclusion of patients with AST more than 100 IU/l or AST more than 50 IU/l. However, the optimal LS cut-off selected for the diagnosis of F4 was lower after the exclusion of patients with AST more than 50 IU/l, 14 kPa instead of 18.0 kPa.

Discussion

This study confirms that transient elastography using FS is a reliable diagnostic tool for the diagnosis of advanced fibrosis and cirrhosis in ALD patients. Moreover, this study shows that FS performs better compared with biochemical scores such as FT, APRI, FIB-4, and Forns' index.

The use of FS for the noninvasive diagnosis of liver fibrosis has been validated widely in patients with chronic viral hepatitis C [21–23], and has become, in clinical practice, one of the tools most often used to guide the initiation of antiviral therapy decisions. Assessment of liver fibrosis in patients with ALD has less practical consequences as the diagnosis of mild fibrosis does not lead to a specific therapy. However, ignoring a diagnosis of advanced fibrosis or cirrhosis in such patients could lead to missed screening for hepatocellular carcinoma and portal hypertension [34]. As the aim of this study was to validate the efficacy of transient elastography for the diagnosis of advanced fibrosis in asymptomatic, heavy-drinking patients, patients with decompensated cirrhosis and severe alcoholic hepatitis were excluded. Overall, our ALD study population is comparable to those reported in other series in terms of age, sex, laboratory tests, and distribution of hepatic lesions on biopsy – 18% had grade F3 and 30% had F4 lesions [19,25–27].

AUROCs of 0.89 and 0.93 for the detection of advanced fibrosis and cirrhosis reported in our study are similar to those reported in other series [24–27] and confirm the effectiveness of this noninvasive technique. The cut-offs for F ≥ 3 and F4 were selected favoring a sensitivity of at least 90% for the best specificity. Thus,

Table 4. Influence of aspartate aminotransferase values on liver stiffness cut-offs and area under receiver-operating characteristic curves

	LS cut-off (kPa)	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
F ≥ 3	10.3	0.89	91	67	76	87
F ≥ 3 removing AST > 50 IU/l	11.3	0.83	87	69	67	88
F ≥ 3 removing AST > 100 IU/l	11.3	0.86	90	66	72	87
F4	18.0	0.93	90	86	82	93
F4 removing AST > 50 IU/l	14.0	0.90	94	77	63	97
F4 removing AST > 100 IU/l	18.8	0.94	91	88	80	95

AST, aspartate aminotransferase; AUROC, area under receiver-operating characteristic curve; LS, liver stiffness; NPV, negative predictive value; PPV, positive predictive value.

Table 5. Area under receiver-operating characteristic curve and liver stiffness cut-offs for the diagnosis of advanced fibrosis and cirrhosis in alcoholic liver disease in published studies

		F ≥ 3				F4			
References	*N*	AUROC	Best LS cut-off (kPa)	Sensitivity (%)	Specificity (%)	AUROC	Best LS cut-off (kPa)	Sensitivity (%)	Specificity (%)
Nguyen *et al.* [26]	103	0.9	11	86.7	80.5	0.92	19.5	85.7	84.2
Nahon *et al.* [25]	147	0.94	12.9	81	89	0.87	22.6	84	80
Janssens *et al.* [27]	49	0.77	17	72	76.5	0.86	21.1	75	80
Mueller *et al.* [24]	101	0.91	8	91	75	0.92	11.5	100	77
Kim *et al.* [28]	45	ND	ND	ND	ND	0.97	25.8	90	87

AUROC, area under ROC curve; LS, Liver stiffness; ND, not done; Se, sensitivity; Sp, specificity.

using cut-offs of 10.3 kPa for F ≥ 3 and 18 kPa for F4, 98/123 (80%) and 108/123 (88%) patients of F ≥ 3 and F4, respectively, were correctly identified, and 15% of F ≥ 3 and 8% of F4 were false positives, and would not benefit from screening for potential complications of cirrhosis. Only 5% of F ≥ 3 and 4% of F4 patients were false negatives.

Even if liver biopsy remains the gold standard for assessing liver fibrosis in ALD patients, its accuracy in diagnosing cirrhosis is limited, with an underestimation of cirrhosis in up to 20% of cases in the different series [9–12] and 12% in our study.

Our cut-offs for diagnosing F ≥ 3 and F4 in our ALD cohort are higher than those reported for chronic hepatitis C [21–23] and are close to those reported previously in ALD, as summarized in Table 5 [24–28].

In this study, we have also compared the diagnostic accuracy of FS to four biochemical scores frequently used to assess liver fibrosis in chronic liver diseases including FT, APRI, Forns' index, and FIB-4. The performance of FS for diagnosing advanced fibrosis and cirrhosis was slightly better than the performance of the noninvasive laboratory scores tested, as reported in other studies [26]. Diagnostic values of APRI, Forns', and FIB-4 scores are worse, for the diagnosis of both advanced fibrosis and cirrhosis compared with FT, which appeared to be the best biochemical marker in our series, as already reported in the literature [19]. In addition to its diagnostic performance in the screening of fibrosis [35], FT might be useful in predicting liver-related mortality in alcoholic patients [19].

The combination of FS with FT (which appeared to be the best biochemical marker in our series) did not improve diagnostic performance relative to FS alone, with no improvement in the AUROCs for fibrosis stages F ≥ 3 and F4.

We finally examined whether aspartate transaminase levels impacted the performance of FS, as reported previously [24]. Although we found a positive correlation between FS and AST levels, exclusion of patients with AST more than 100 IU/l or AST more than 50 IU/l did not significantly impact the diagnostic accuracy of FS, except for the optimal cut-off for diagnosing cirrhosis, which decreased to 14.4 kPa from 18 kPa when patients with AST more than 50 IU/l were excluded. The other factors that correlated with FS were portal hypertension assessed by HVPG measurement and the presence of histologic signs of alcoholic hepatitis, as underlined in previous studies [25–27].

A limitation of our study is its retrospective design. Another limitation is that specific histological vascular lesions encountered in ALD [30,36] were not described by the pathologist. It would have been interesting to examine the correlation between those histological features and FS values. A final limitation is the absence of evaluation of FS accuracy in ALD patients following alcohol withdrawal as previous studies suggest that LS values (over a week) decrease rapidly after alcohol withdrawal [24,37]. Nevertheless, most of the patients included in our study were heavy drinkers, and alcohol withdrawal, even for a short period of time, is difficult to achieve in this population.

In conclusion, this study confirms that FS is a powerful noninvasive method for the diagnosis of advanced fibrosis and cirrhosis in ALD patients. These results will help clinicians to better identify ALD patients who need screening for cirrhosis complications and could reinforce the management of alcohol abuse.

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Conflicts of interest

There are no conflicts of interest.

References

1 Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; 373:2223–2233.
2 World Health Organization (WHO) (2014). *Global status report on alcohol and health 2011*. Switzerland: World Health Organization (WHO).
3 MacSween RN, Burt AD. Histological spectrum of alcoholic liver disease. *Semin Liver Dis* 1986; 6:221–232.
4 Ho AM, Contardi LH, Ho AM, Contardi LH, Teli MR, Day CP, *et al*. Pure alcoholic fatty liver and progression to cirrhosis or fibrosis. *Lancet* 1995; 346:1562–1563.
5 Naveau S, Raynard B, Ratziu V, Abella A, Imbert-Bismut F, Messous D, *et al*. Biomarkers for the prediction of liver fibrosis in patients with chronic alcoholic liver disease. *Clin Gastroenterol Hepatol* 2005; 3:167–174.
6 Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology* 2011; 141:1572–1585.
7 Becker U, Deis A, Sørensen TI, Grønbaek M, Borch-Johnsen K, Müller CF, *et al*. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology* 1996; 23:1025–1029.
8 Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). *Hepatology* 2000; 32:477–481.
9 Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003; 38:1449–1457.
10 Bedossa P, Poynard T, Naveau S, Martin ED, Agostini H, Chaput JC. Observer variation in assessment of liver biopsies of alcoholic liver disease in drinkers. *Gastroenterology* 1991; 100:1397–1402.
11 Poynard T, Ratziu V, Bedossa P. Appropriateness of liver biopsies. *Can J Gastroenterol* 2000; 14:543–548.
12 Gordon H. Detection of alcoholic liver disease. *World J Gastroenterol* 2001; 7:297–302.
13 Tran A, Hastier P, Barjoan EM, Demuth N, Pradier C, Saint-Paul MC, *et al*. Non invasive prediction of severe fibrosis in patients with alcoholic liver disease. *Gastroenterol Clin Biol* 2000; 24:626–630.
14 Lieber CS, Weiss DG, Morgan TR, Paronetto F. Aspartate aminotransferase to platelet ratio index in patients with alcoholic liver fibrosis. *Am J Gastroenterol* 2006; 101:1500–1508.
15 Forns X, Ampurdanès S, Llovet JM, Aponte J, Quintó L, Martínez-Bauer E, *et al*. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology* 2002; 36 (4 Pt 1):986–992.
16 Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, *et al*. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology* 2007; 46:32–36.
17 Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. MULTIVIRC Group. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001; 357:1069–1075.
18 Halfon P, Imbert-Bismut F, Messous D, Antoniotti G, Benchetrit D, Cart-Lamy P, *et al*. A prospective assessment of the inter-laboratory variability of biochemical markers of fibrosis (FibroTest) and activity (ActiTest) in patients with chronic liver disease. *Comp Hepatol* 2002; 1:3.
19 Naveau S, Gaudé G, Asnacios A, Agostini H, Abella A, Barri-Ova N, *et al*. Diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with alcoholic liver disease. *Hepatology* 2009; 49:97–105.
20 Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, *et al*. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003; 29:1705–1713.
21 Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, *et al*. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology* 2005; 41:48–54.
22 Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, *et al*. Prospective comparison of transient elastography, Fibrotest, APRI and liver biopsy for the assessment of fibrosis in chronic hepatits C. *Gastroenterology* 2005; 128:343–350.
23 Ganne-Carrié N, Ziol M, de Ledinghen V, Douvin C, Marcellin P, Castera L, *et al*. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. *Hepatology* 2006; 44:1511–1517.
24 Mueller S, Millonig G, Sarovska L, Friedrich S, Reimann FM, Pritsch M, *et al*. Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis. *World J Gastroenterol* 2010; 16:966–972.
25 Nahon P, Kettaneh A, Tengher-Barna I, Ziol M, de Lédinghen V, Douvin C, *et al*. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. *J Hepatol* 2008; 49:1062–1068.
26 Nguyen-Khac E, Chatelain D, Tramier B, Decrombecque C, Robert B, Joly JP, *et al*. Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: prospective comparison with seven non-invasive laboratory tests. *Aliment Pharmacol Ther* 2008; 28:1188–1198.
27 Janssens F, de Suray N, Piessevaux H, Horsmans Y, de Timary P, Stärkel P. Can transient elastography replace liver histology for determination of advanced fibrosis in alcoholic patients: a real-life study. *J Clin Gastroenterol* 2010; 44:575–582.
28 Kim SG, Kim YS, Jung SW, Kim HK, Jang JY, Moon JH, *et al*. The usefulness of transient elastography to diagnose cirrhosis in patients with alcoholic liver disease. *Korean J Hepatol* 2009; 15:42–51.
29 Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatits C. The Metavir Cooperative Study Group. *Hepatology* 1996; 24:289–293.
30 Michalak S, Rousselet MC, Bedossa P, Pilette C, Chappard D, Oberti F, *et al*. Respective role of porto-septal fibrosis and centrilobular fibrosis in alcoholic liver disease. *J Pathol* 2003; 201:55–62.
31 Poynard T, Mathurin P, Lai CL, Guyader D, Poupon R, Tainturier MH, *et al*. A comparison of fibrosis progression in chronic liver diseases. *J Hepatol* 2003; 38:257–265.
32 Maddrey WC, Boitnott JK, Bedine MS, Weber FL Jr, Mezey E, White RI Jr. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; 75:193–199.
33 Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; 38:518–526.
34 European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer (EASL–EORTC). Clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; 56:908–943.
35 Poynard T, Morra R, Halfon P, Castera L, Ratziu V, Imbert-Bismut F, *et al*. Meta-analyses of FibroTest diagnostic value in chronic liver disease. *BMC Gastroenterol* 2007; 7:40.
36 Burt AD, MacSween RN. Hepatic vein lesions in alcoholic liver disease: retrospective biopsy and necropsy study. *J Clin Pathol* 1986; 39:63–67.
37 Trabut JB, Thépot V, Nalpas B, Lavielle B, Cosconea S, Corouge M, *et al*. Rapid decline of liver stiffness following alcohol withdrawal in heavy drinkers. *Alcohol Clin Exp Res* 2012; 36:1407–1411.