Fibroscan Reliably Rules Out Advanced Liver Fibrosis and Significant Portal Hypertension in Alcoholic Patients

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Background/Goals: To date, there is no consensus on optimal cut-off values and timing of transient elastography (TE, Fibroscan) for fibrosis staging and prediction of portal hypertension in alcoholic liver disease. We evaluated the accuracy of Fibroscan for the diagnosis of fibrosis and clinically significant portal hypertension in alcoholic patients.

Study: Heavy drinkers admitted to our standardized alcohol withdrawal program were evaluated by Fibroscan, by transjugular hepatic venous pressure gradient (HVPG) measurement and liver biopsy if significant fibrosis was suspected and by upper gastrointestinal endoscopy. All investigations were performed within 3 days of admission. Patients who had remained abstinent for 2 weeks underwent a second Fibroscan.

Results: A total of 118 patients were included. Fibroscan correlated well with histology and HVPG. Negative predictive value of 92% and 93% for ruling out severe fibrosis ($\geq$F3) and cirrhosis, and optimal cut-offs at $\geq$11.7, $\geq$15.2, and $\geq$21.2 kPa for F2, F3, and F4, respectively, were found. In abstinent patients, a mean decrease of 2.7 kPa improved concordance between Fibroscan and histology. A TE value of 30.6 kPa predicted a HVPG > 10 mm Hg with 94% specificity and showed a good negative predictive value of 84% for ruling out the presence of varices at endoscopy. Steatosis, alcoholic hepatitis, sinusoidal fibrosis, cholestasis, and high transaminases did not influence TE values.

Conclusions: Fibroscan is an accurate non-invasive method for the diagnosis of fibrosis in alcoholic patients. TE values below 11 and 30 kPa likely rule out significant fibrosis and varices, respectively.

Key Words: transient elastography, hepatic venous pressure gradient, liver stiffness, liver biopsy

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Alcohol abuse causes about 5.9% of deaths worldwide mainly due to alcoholic liver diseases (ALD), especially cirrhosis.[1] ALD comprises a spectrum of manifestations ranging from steatosis (fatty liver), alcoholic (steato-) hepatitis, alcoholic fibrosis, and cirrhosis.

Liver biopsy is considered the gold standard for liver fibrosis assessment but carries a risk of serious adverse events including pain, severe hypotension, bleeding, and mortality in 10,000 to 12,000 cases.[2] Moreover, it is prone to sampling error as well as to intrapathologist and interpathologist discordant interpretations.[3]

Among the noninvasive methods that have been developed, Fibroscan (transient elastography, TE) is the most widely used device. It measures liver stiffness in kilopascals, which is correlated with the severity of liver fibrosis on histology. Obesity and ascites limit the use of Fibroscan and acute hepatitis, extrahepatic cholestasis, hepatic congestion, and active alcohol intake may lead to overestimation of liver stiffness.[4–7] Fibroscan has been widely validated in patients with chronic hepatitis C[8] but a recent Cochrane review states that the optimal cut-offs for ALD are not established yet and would need further validation.[9] The few studies performed in exclusively alcoholic patients are not conclusive as they suggest the use of very different cut-off values.[5,6,10–15] The prognosis and management of cirrhosis depend on the presence of portal hypertension (PHT) which can be assessed by measuring the hepatic venous pressure gradient (HVPG). Evidence suggests that Fibroscan may identify clinically significant PHT ($\geq$10 mm Hg). However, the few available studies reporting on cohorts not exclusively composed of alcoholic patients suggest the use of different cut-off values[7,13,16] without a clear consensus on a cut-off value that should be applied to ALD.

We aimed to: (1) assess the diagnostic accuracy of Fibroscan compared with histology, first by using the cut-offs for alcoholic patients proposed by Nguyen-Khac et al,[10] for F2, F3, and F4, and second to optimize cut-off values in heavy drinkers if appropriate; (2) investigate the impact of 2 weeks of abstinence on Fibroscan results; (3) evaluate the accuracy of Fibroscan for predicting clinically significant PHT in alcoholic patients; (4) evaluate potential confounding factors that may impact Fibroscan results.

PATIENTS AND METHODS

Design and Patient Population

Alcohol dependent patients were electively admitted between January 2006 and February 2008 and between October 2010 and July 2015 to our alcohol withdrawal program consisting of 2 weeks of hospitalization separated by 1 week of outpatient care (Supplementary Fig. S1, Supplemental Digital Content 1, http://links.lww.com/JCG/A441). They undergo a highly standardized routine clinical evaluation where data are prospectively collected and recorded in the

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patients' medical files in order to allow further utilization for research purposes. All patients drank actively until the day of their admission. Self-reported minimal daily intake consisted of at least 70 g/day of alcohol. Basic demographic data (age, sex, height, weight), a routine blood sample as well as a first Fibroscan were obtained on the day of admission. A liver biopsy is routinely proposed to patients with suspicion of significant fibrosis at TE ($\geq$F2) but not to those with low TE values for evident clinical and ethical reasons. Patients also underwent upper gastrointestinal endoscopy within 3 days of admission. Additional investigations are depicted in Supplementary Figure S1 (Supplemental Digital Content 1, http://links.lww.com/JCG/A441). Starting from 2010 onwards, a second Fibroscan has been proposed during the second week of hospitalization to those who had remained abstinent during the week at home. The following laboratory parameters were routinely ordered: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase, alcalin phosphatase, bilirubin, albumin, international normalized ratio, gamma-globulins, urea, creatinine, uric acid, total cholesterol, triglycerides, platelet count, white blood cells, hemoglobin, mean corpuscular volume, iron, ferritin, saturation.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved (November 17, 2014) by the institution's human research and ethics committee (2014/14AOU/438 N°23617050). Written informed consent was obtained from all patients.

Study reporting was based on the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines for observational studies using routinely collected data.[17]

TE

TE measurements were performed after a minimum of 2 hours fasting using the Fibroscan device (Echosens, Paris, France) by an experienced examiner blinded to the patient's data. Fibroscan was considered as valid if at least 10 validated measurements were obtained with an interquartile range of <30%. The final result expressed in kilopascals was the median of all valid measurements obtained. From 2010 onward, we used the Nguyen-Khac et al[10] cut-offs for fibrosis assessment with suspicion of significant fibrosis at TE starting at $\geq$7.8 kPa. The data from the first cohort of patients hospitalized between 2006 and 2008 were reanalyzed using these cut-offs instead of the HCV cut-offs initially used in this cohort.[13]

Hemodynamic Measurements and Liver Biopsy

HVPG is defined as the difference between the occluded hepatic venous pressure and the free hepatic venous pressure. HVPG measurements and liver biopsies were performed through the right jugular vein approach by an experienced hepatologist according to standard procedures. Liver samples were fixed in formalin, paraffin embedded, and stained with hematoxylin and eosin as well as Masson trichrome blue. Biopsy samples of $\geq$15 mm of length including a minimum of 6 portal tracts were considered suitable or when the pathologist could establish the degree of fibrosis with certainty on a smaller sample. Fibrosis was evaluated according to the METAVIR scoring system by an experienced hepatopathologist blinded to the other results.[18] Perisinusoidal fibrosis, steatosis, and signs of alcoholic hepatitis were scored separately (details in Supplementary Data, Supplemental Digital Content 1, http://links.lww.com/JCG/A441).

Statistics

Data were analyzed using SPSS (23.0) software. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated using the cut-offs proposed by Nguyen-Khac et al.[10] Cut-off values that optimize specificity with a minimal sensitivity of 75% for our study population were derived from receiver-operated characteristics (ROC) curves. The Kolmogorov-Smirnov test revealed nonnormal distribution of the data and thus all statistical tests used were nonparametric. Spearman correlation test was used for correlations between data sets, the Wilcoxon test and the χ^2 or Fisher test (small sample sizes) to compare numerical and categorical variables. Analysis of variance with post hoc Bonferroni correction was applied for multiple comparisons. Odds ratios (ORs) were calculated with a 95% confidence interval. Values are presented as mean ± SD and/or median unless otherwise indicated. A P-value <0.05 was considered as statistically significant.

RESULTS

Study Population

A total of 389 patients admitted to the alcohol withdrawal program between January 2006 and February 2008 and between October 2010 and July 2015 were eligible for the study. Figure 1 details the patients' selection procedure leading to a final population of 118 patients. Baseline characteristics and biochemical data show a typical predominantly male, middle-aged alcohol-dependent population (Table 1).

Comparison of TE and Histology

Fibroscan and histology classification correlated well ($\rho = 0.680$, $P < 0.01$). Although an overlap of liver stiffness measurement (LSM) values was observed between the different histologic fibrosis groups, a significant difference was found for stage F4 compared with all other stages and for stage F3 compared with stage F0/1 (Fig. 2A). More detailed analysis comparing Nguyen-Khac and colleagues' cut-offs and histology as a gold standard revealed that 40% were correctly classified by the Fibroscan, 45% were misclassified by one stage (45 over-staged, 8 under-staged) while the remaining 15% differed by 2 or more stages (all over-staged) (Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/JCG/A441). PPVs for TE were low for all stages (Table 2A) while Fibroscan showed a very good NPV of 92% for ruling out severe fibrosis ($\geq$F3) and 93% for cirrhosis (F4). The sensitivity of TE was found to be high whereas specificity was modest.

The predictive value of LSM was further evaluated using ROC curves (Fig. 2B). The area under the ROC curves were high with 0.867 for predicting significant fibrosis ($\geq$F2), 0.886 for severe fibrosis ($\geq$F3) and 0.907 for cirrhosis. On the basis of the ROC curves, we determined cut-off values that would maximize the Youden index (YI). Using the YI formula, we calculated optimized cut-offs of 11.7 kPa (YI = 0.687) and 15.2 kPa (YI = 0.607) for F2 and F3, respectively. For F4, a cut-off of 18.8 kPa with 88% sensitivity and 79% specificity showed the maximum index of 0.666. To improve specificity with a sensibility of at least 75% as a constraint, we found similar cut-offs for optimized specificity at 11.7 and 15.2 kPa for significant fibrosis ($\geq$F2) and advanced fibrosis ($\geq$F3) but a higher value of 21.2 kPa for cirrhosis, respectively (Table 2B).

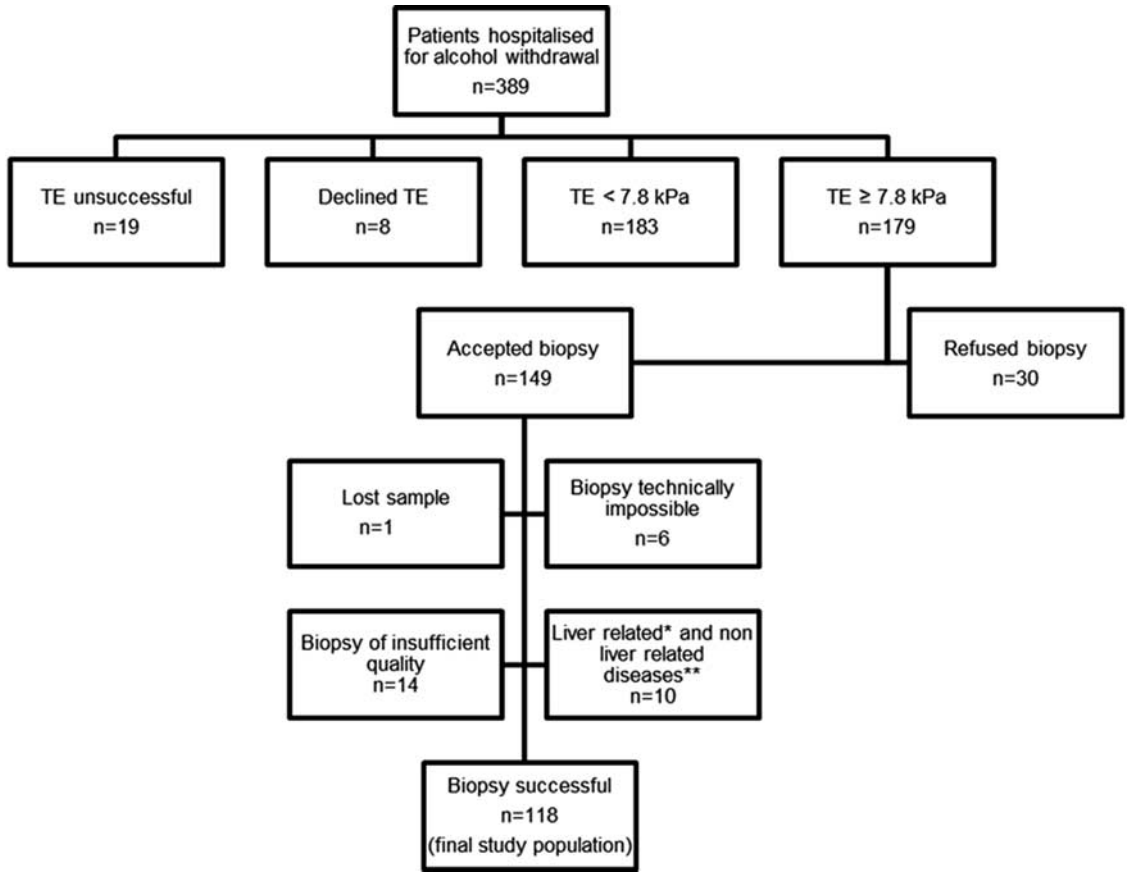

FIGURE 1. Flow chart: selection of patients. TE indicates transient elastography. *Hepatitis B, hepatitis C, and primary biliary cirrhosis. **Pancreatic head tumor, non-Hodgkin liver lymphoma, multiple clinical reasons.

Correlation Between Histology and TE After Abstinence

During the study period 2010-2015, a second Fibroscan was asked for in abstinent patients (min., 14 d). Among 70 included patients, 57 remained abstinent and accepted a second TE. A fairly good correlation of 0.625 ($P < 0.01$) between the 2 measures was observed. There was a mean decrease of 2.7 kPa (+/−0.9) between the first and the second Fibroscan (Fig. 2C), the difference being significant for patients classified F2 ($P < 0.01$) and F3 ($P = 0.01$) by the first Fibroscan but not for those classified F4 ($P = 0.756$).

We next wanted to know whether the second Fibroscan was more accurate for prediction of fibrosis. Among 57 patients who underwent a second Fibroscan, the proportion of correct classification significantly rose from 23/57 (40%) to 35/57 (61%) ($P = 0.024$) (Supplementary Table S2, Supplemental Digital Content 1, http://links.lww.com/JCG/A441). In particular, 10 patients initially misclassified as F3 or F2 by the first Fibroscan while histology showed no fibrosis (F0), were subsequently correctly staged. The ROC curves analysis in this subgroup of 57 patients showed that the second Fibroscan only performed better for assessing significant fibrosis ($\geq$F2). The other stages remained similar (area under the curve (AUC) = 0.966 vs. 0.940 for $\geq$F3; AUC = 0.997 vs. 0.995 for F4).

TABLE 1. Baseline Demographic and Biochemical Data of Included Patients

Data	Mean ± SD	Median (Range)	Normal Values
Gender (male/female)	78/40		
Age (y)	52 ± 10	51 (29-74)	
BMI	25 ± 5	25 (15-38)	20-25
AST (IU/L)	114 ± 95	87 (17-523)	6-33
ALT (IU/L)	69 ± 50	59 (12-288)	14-63
γ-GT (IU/L)	578 ± 620	355 (11-2743)	7-50
Total bilirubin (mg/dL)	1.6 ± 2.3	0.95 (0.2-18)	0.3-1.2
Serum albumin (g/dL)	3.9 ± 1	4.1 (1.7-5.6)	3.5-5.2
INR	1.02 ± 0.25	1 (0.6-1.83)	0.8-1.3
Platelet count (×1000/mm^3)	195 ± 92	190 (38-506)	150-300

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; INR, international normalized ratio; γ-GT, gamma-glutamyltransferase.

Correlation Between TE, HVPG, and Clinical Manifestation of PHT

HVPG is considered the gold standard for the evaluation of PHT. A HVPG $\geq$ 10 mm Hg determines significant PHT and the formation of varices, whereas a HVPG $\geq$ 12 mm Hg predicts the risk of variceal bleeding, although there is still doubt about HVPG's ability to distinguish bleeding and nonbleeding varices.[19]

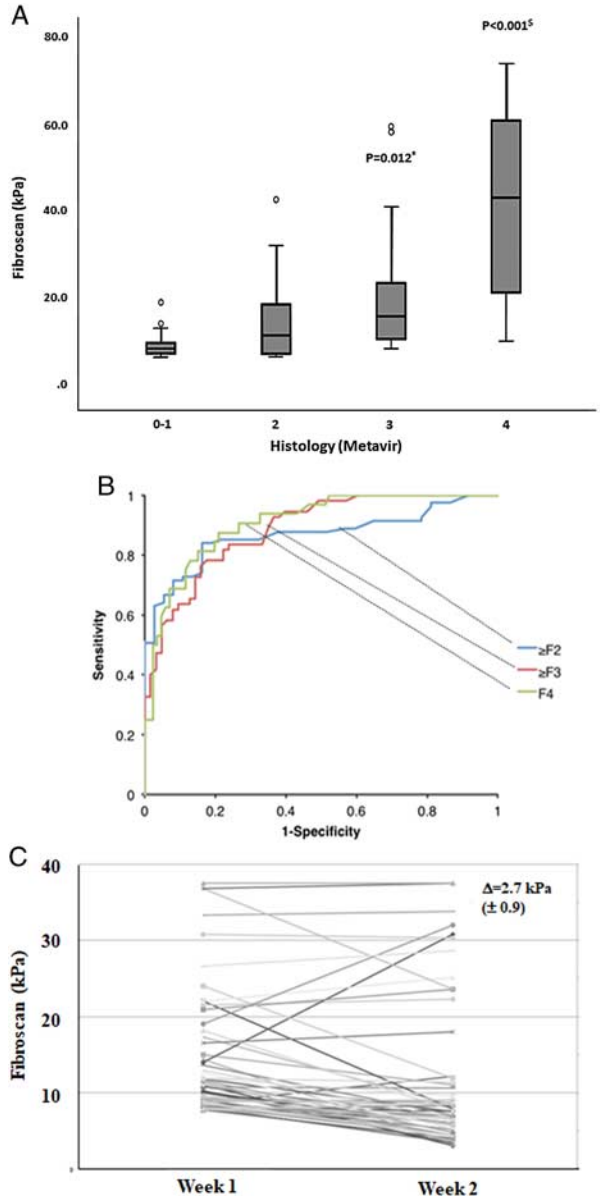

FIGURE 2. Comparison of TE (Fibroscan) with liver biopsy. A, Box plots of TE values obtained for the different fibrosis stages (METAVIR) on liver biopsy. The median is represented as a horizontal line within the box, and its lower and upper edges represent the first and the third quartiles, respectively. The bracket below and above the bow enclose 95% of the entire set of stiffness values. The dotted line indicates the cut-off of TE (7.8 kPa) for performing a liver biopsy ($compared with all other stages, *compared with F0/1), B, Predictive value of TE for different stages of fibrosis. ROC curves for significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4) on histology with TE (kPa) as a test variable. C, Comparison of Fibroscan values between week 1 (W1) and week 2 (W2) showing a decline of Fibroscan values (kPa) in the majority of patients. ROC indicates receiver-operated characteristics; TE, transient elastography. full color online

Considering the total study population, a significant linear correlation was found between HVPG and TE expressed as a continuous value (kPa) ($\rho = 0.753$, $P < 0.01$) (Fig. 3). Given this excellent correlation as well as the high area under the ROC curve for predicting an HVPG ≥ 10 mm Hg (AUC = 0.925) and an HVPG ≥ 12 mm Hg (AUC = 0.930), we determined TE cut-offs with the highest sensitivity and specificity for predicting clinically significant PHT.

TABLE 2. Sensitivity, Specificity, PPV and NPV Calculations for Fibroscan

TE (kPa)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
A. Sensitivity, Specificity, PPV and NPV for the Chosen Literature Cut-offs				
≥11 (≥F3)	95	57	66	92
≥19.5 (F4)	84	79	60	93
TE (kPa)	**Sensitivity (%)**	**Specificity (%)**		
B. Potential optimized cut-off levels to improve performance of TE for fibrosis staging (METAVIR score)				
Significant fibrosis (≥F2)				
11.1	85	76		
11.7	84	84		
12	75	84		
Severe fibrosis (≥F3)				
13.4	84	76		
15.2	78	83		
16.3	75	84		
Cirrhosis (F4)				
17	88	76		
21.2	81	85		
22.6	75	88		

NPV indicates negative predictive value; PPV, positive predictive value; TE, transient elastography.

Requiring at least 75% sensitivity and specificity, we found that TE values of 30.6 and 32.9 kPa predicted best an HVPG ≥ 10 and ≥ 12 mm Hg, respectively (Table 3), identical to those derived using the YI formula. The OR was 60 (17-216; $P < 0.001$) for patients having significant PHT (HVPG ≥ 10 mm Hg) and TE values ≥ 30.6 kPa. These cut-offs were confirmed in the 55 patients with advanced fibrosis/cirrhosis (F3+F4) on histology with 80% to 90% sensitivity and 83% to 86% specificity for HVPG ≥ 10 and ≥ 12 mm Hg, respectively.

An HVPG ≥ 16 mm Hg has been suggested as a marker of poor prognosis in decompensated cirrhosis.[20] We found a high AUC of 0.964 for predicting an HVPG ≥ 16 mm Hg in our study population. A cut-off ranging from 48.8 to 50 kPa revealed a 100% and 89% sensitivity as well as a 94.5% and 95.4% specificity, respectively.

In patients with advanced fibrosis on histology (≥F3), we further analyzed whether TE could predict the presence of esophageal varices at endoscopy. As expected, a HPVG ≥ 10mm Hg was significantly associated with the presence of varices [OR = 4.3 (1.2-16.3); $P = 0.032$). Using the previous optimized cut-off of 30.6 kPa a good NPV of 84% was found for ruling out the presence of varices at endoscopy.

Influence of Potential Confounding Factors on LSMs

Histologic Factors

Steatosis. Among the 71 patients misclassified for fibrosis by the first Fibroscan, 31 (44%) had moderate to severe steatosis while in the 41 patients correctly classified 24 (51%) presented with moderate to severe steatosis a nonsignificant difference.

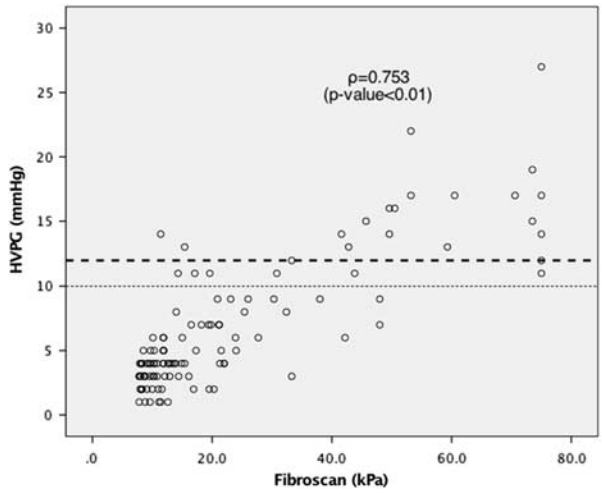

FIGURE 3. Correlation of Fibroscan values and HVPG. The HVPG (mm Hg) measured immediately before performance of a liver biopsy shows a significant linear correlation with transient elastography values (kPa). The dotted lines indicate the thresholds for clinically significant portal hypertension (10 mm Hg) and for the likelihood of variceal rupture (12 mm Hg). HVPG indicates hepatic venous pressure gradient.

Similar results were found when considering only the 18 patients misclassified by 2 stages or more with 7 patients (39%) having moderate to severe steatosis (Fig. 4, Supplementary Table S3, Supplemental Digital Content 1, http://links.lww.com/JCG/A441). Thus, it seems that moderate to severe steatosis does not have a dominant influence on Fibroscan results.

Perisinusoidal fibrosis. As the METAVIR scoring system is mainly based on septal fibrosis, we attempted to evaluate the impact of perisinusoidal fibrosis, a frequent type of fibrosis seen in ALD, on Fibroscan results. The pathologist reported histologic signs of moderate to severe perisinusoidal fibrosis in 45 of 118 patients (38%). Among those, 20 patients (44%) were misclassified compared with 30% in the subgroup with no/minimal perisinusoidal fibrosis. Considering only patients who differed by 2 or more stages, similar proportions were misclassified in the 2 subgroups (Fig. 4, Supplementary Table S3, Supplemental Digital Content 1, http://links.lww.com/JCG/A441).

To more precisely evaluate sinusoidal fibrosis, 40 biopsies were randomly selected and reexamined by the pathologist to establish a liver allograft fibrosis (LAF) score,[19] which scores fibrosis separately in portal, sinusoidal, and centrolobular areas. Overall, the total LAF scores correlated well with TE values ($\rho = 0.641$, $P < 0.01$). However, no correlation was found between being misclassified and having a high total LAF score (≥ 6) or a nonportal (sinusoidal+centrolobular) component of the score ≥ 3.

Alcoholic hepatitis (AH). Forty-two percent (8/19 patients) with histologic signs of alcoholic hepatitis were misclassified by 1 stage and none by 2 stages. No association of having AH and being misclassified was observed suggesting that mild to moderate AH does not contribute to misclassification by Fibroscan (Fig. 4, Supplementary Table S3, Supplemental Digital Content 1, http://links.lww.com/JCG/A441).

TABLE 3. Potential Cut-off Levels to Improve Performance of TE (Fibroscan) for Determining HVPG

TE (kPa)	Sensitivity (%)	Specificity (%)
HVPG ≥ 10 mm Hg		
19.5	85	75
30.6	81	94
32.9	77	95
HVPG ≥ 12 mm Hg		
20.6	90	76
32.9	90	92
42.5	79	95

HVPG indicates hepatic venous pressure gradient; TE, transient elastography.

Biochemical Factors

Transaminases. ALT values did not correlate with Fibroscan, whereas a weak but significant correlation was found for AST ($\rho = 0.275$, $P < 0.01$). Strikingly, mean AST values tended to be higher in correctly classified patients compared with misclassified ones (138 ± 104 vs. 98 ± 85 IU/L, respectively). Being clinically more pertinent, we next calculated if elevated AST and ALT values, 3 or 5 times above the upper normal limit (ULN), were associated to misclassification by Fibroscan. This was the case neither for a 1 stage difference nor for a 2 stages difference in fibrosis misclassification (Supplementary Table S4, Supplemental Digital Content 1, http://links.lww.com/JCG/A441).

Cholestasis. Cholestasis was defined as patients having a total bilirubin > 1.2 mg/dL and alkaline phosphatases > 94 IU/L. Taken separately, bilirubin and alkaline phosphatases values correlated significantly with TE values ($\rho = 0.477$, $P < 0.01$ and $\rho = 0.393$, $P < 0.01$, respectively). Surprisingly, the calculated OR did not show a negative association between being misclassified by one or more stages and having cholestasis [OR = 0.391 (0.161-0.951); $P = 0.035$].

Combined Histologic and Biochemical Factors

Given the low number of patients in several subgroups, we were only able to evaluate reliably the combination of high AST (≥ 3×ULN) with moderate/severe perisinusoidal fibrosis or moderate/severe steatosis. Among the 71 patients misclassified by 1 fibrosis stage, only 8 subjects (11%) presented high AST values and at least moderate perisinusoidal fibrosis. The calculated OR further confirmed that this combination of factors was not negatively associated with misclassification [OR = 0.332 (0.125-0.880); $P = 0.031$].

Sixteen misclassified patients (22.5%) had high AST and moderate to severe steatosis on histology. Again the calculated OR did not reveal a significant association of this combination with being misclassified by Fibroscan [OR = 0.469 (0.209-1.053); P = NS].

DISCUSSION

For clinical use, Fibroscan cut-offs need to be validated separately for each underlying etiology but currently there is no consensus for these in alcoholic patients. Therefore, we aimed at evaluating the diagnostic accuracy of Fibroscan compared with histology based on the cut-offs determined by Nguyen-Khac et al[10] for alcoholic patients (7.8 kPa for ≥ F2, 11 kPa for ≥ F3, and 19.5 kPa for F4). TE values correlated well with the METAVIR and the LAF[21] histologic scoring systems. Although the latter particularly emphasizes perisinusoidal and centrolobular fibrosis, it did not improve the accuracy of Fibroscan staging compared

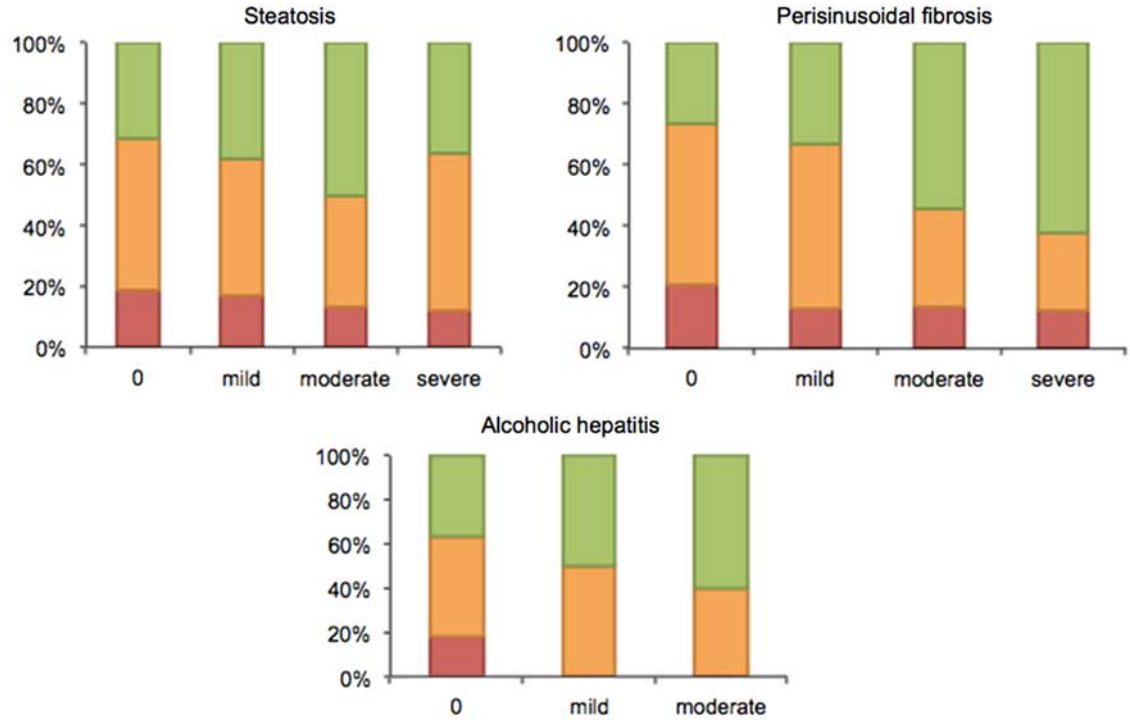

FIGURE 4. Proportion of patients correctly classified (in green, upper bar), misclassified by 1 stage (in orange, middle bar) or misclassified by 2 stages (in red, lower dark bar) in the subgroups of patients with no, mild, moderate or severe steatosis, perisinusoidal fibrosis, alcoholic hepatitis. There were no patients with severe alcoholic hepatitis in our study group. full color online

with the METAVIR score thus arguing against perisinusoidal and centrolobular fibrosis as an important confounder in alcoholic patients.

The applied cut-offs yielded good NPVs beyond 90% for the 11 kPa ($\geq$F3) and 19.5 kPa (F4) cut-offs but performed suboptimal for PPVs. As a reasonable compromise between sensitivity and specificity, we found that cut-offs of $\geq$11.7 kPa for F2, $\geq$15.2 for F3, and $\geq$21.2 for F4 performed best in our study population which are close to those proposed by other studies.[11,13] In a recent study performed in a primary and secondary care setting authors confirmed that TE values >15 kPA predicted advanced fibrosis in heavy drinkers. They also found that combining a serum marker of fibrosis and TE did not have a higher diagnostic accuracy than TE alone.[22] Taken together, our results and a recent meta-analysis[9] that included studies with alcoholic patients only suggest that TE values <11 kPa in actively drinking patients rule out severe fibrosis or cirrhosis which is the main goal in the management of ALD and that liver biopsy should be avoided in these patients. We also assessed if abstinence could resolve TE's tendency to overestimation. As reported by others,[5,23,24] we also observed a decrease of TE values after abstinence which was associated with a significantly better concordance between Fibroscan and histology. However, the clinical significance of this finding is questionable as a decrease was not seen in all patients, a minority of patients even had increased TE values while some patients who were correctly classified by the first Fibroscan were not anymore by the second one. Fibroscan is an immediately available and easily applicable screening tool that is mainly used in routine out-patient practice. It is often difficult to obtain long periods of abstinence in heavy drinkers during their initial assessment in the out-patient setting. Therefore, we do not recommend deferring Fibroscan until the patient has been abstinent for several weeks but rather to repeat/confirm initially high Fibroscan values if a significant period of abstinence has been observed by the patient.

Several studies have looked into the impact of cholestasis, steatosis, alcoholic hepatitis, and transaminases on Fibroscan measurements with contradictory results.[5,6,10,11,24,25] Our study focused on the potential influence of steatosis and histologic signs of alcoholic hepatitis but we could not find any significant impact. AST showed an overall weak correlation with TE which, however, completely disappeared when we looked for a correlation between high AST values and misclassification. Cholestasis, defined as a combination of increased bilirubin and alkaline phosphatases values, was also not significantly associated with misclassification. To date, it remains controversial whether biochemical values (eg, high transaminases, cholestasis) should be taken into consideration when interpreting TE values in asymptomatic alcohol dependent patients.

Finally, we evaluated if Fibroscan could predict the presence of PHT. As suggested by literature,[7,13,16] we found a good correlation between TE and HVPG measurements to predict the presence of clinically significant PHT (HVPG $\geq$10 mm Hg). Given the good specificity and a reasonable sensitivity, it seems justified not to perform endoscopy if TE is below 30 kPa as the probability to find endoscopic manifestations of PHT is low. Our cut-off is higher than the 20 kPA proposed by Baveno VI.[26] Conceivably, an universal cut-off may not exist and cut-offs likely require validation for different etiologies as it is the case for fibrosis staging.

The principal strength of our study is that it was prospectively conducted in strictly alcoholic patients in a standardized, rigorously controlled setting of an elective

withdrawal program. This allowed us to add further evidence that cut-offs for advanced fibrosis in alcoholic patients need to be higher than for most other diseases. We propose an adaptation of the Nguyen-Khac and colleagues cut-offs and for the first time suggest a cut-off for varices screening in a purely alcoholic population. A limitation might be the absence of a true histologic gold standard as the METAVIR system has not been developed and validated in alcoholic patients. Patients with F0-1 at TE were excluded from biopsies thereby creating a potential selection bias leading to overrepresentation of more severe ALD. However, this decision was based on the medical risks associated with biopsy and is close to the real life situation. Finally, our study might suffer from the limited number of patients in some subgroup analyses.

In conclusion, Fibroscan can reliably predict advanced fibrosis and clinically significant PHT in alcoholic patients. Abstinence improved the performance of Fibroscan but further studies are required to determine confounding factors in actively drinking patients that could influence TE values.

REFERENCES

1. Sassi F. *Tackling Harmful Alcohol Use: Economics and Public Health Policy*. Paris: OECD Publishing; 2015:82–83.
2. Stevenson M, Lloyd-Jones M, Morgan MY, et al. Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease: a systematic review and economic evaluation. *Health Technol Assess*. 2012;16:1–174.
3. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol*. 2002;97:2614–2618.
4. Berzigotti A, Castera L. Update on ultrasound imaging of liver fibrosis. *J Hepatol*. 2013;58:180–182.
5. Mueller S, Millonig G, Sarovska L, et al. Increased liver stiffness in alcoholic liver disease: Differentiating fibrosis from steatohepatitis. *World J Gastroenterol*. 2010;16:966–972.
6. Fernandez M, Trepo E, Degre D, et al. Transient elastography using Fibroscan® is the most reliable non-invasive method for the diagnosis of advanced fibrosis and cirrhosis in alcoholic liver disease. *Eur J Gastroenterol Hepatol*. 2015;27:1074–1079.
7. Bureau C, Metivier S, Peron JM, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. *Aliment Pharmacol Ther*. 2008;27:1261–1268.
8. Castéra L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*. 2005;128:343–350.
9. Pavlov CS, Casazza G, Nikolova D, et al. Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease. *Cochrane Database Syst Rev*. 2015;1:CD010542. Doi:10.1002/14651858.CD010542.pub2.
10. Nguyen-Khac E, Chatelain D, Tramier B, 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.
11. Nahon P, Kettaneh A, Tengher-Barna I, et al. Assessment of liver fibrosis using transient elastography in patients with alcoholic disease. *J Hepatol*. 2008;49:1062–1068.
12. Kim SG, Kim YS, Jung SW, et al. The usefulness of transient elastography to diagnose cirrhosis in patients with alcoholic liver disease. *Korean J Hepatol*. 2009;15:42–51.
13. Janssens F, de Suray N, Piessevaux H, et al. 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.
14. Thiele M, Detlefsen S, Sevelsted MØller L, et al. Transient and 2-dimensional shear-wave elastography provide comparable assessment of alcoholic liver fibrosis and cirrhosis. *Gastroenterology*. 2016;150:123–133.
15. Nguyen-Khac E. Non-invasive diagnosis of liver fibrosis by Fibroscan® in patients with alcoholic liver disease: a meta-analysis with individual data. *J Hepatol*. 2014;60:S34.
16. Lemoine M, Katsahian S, Ziol M, et al. Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus and alcohol-related cirrhosis. *Aliment Pharmacol Ther*. 2008;28:1102–1110.
17. Benchimol EI, Smeeth L, Guttmann A, et al. RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med*. 2015;12:e1001885.
18. Bedossa P. and The French METAVIR Cooperative Study Group. Intra-observer and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology*. 1994;20:15–20.
19. Zardi EM, Di Matteo FM, Pacella CM, et al. Invasive and non-invasive techniques for detecting portal hypertension and predicting variceal bleeding in cirrhosis: a review. *Ann Med*. 2014;46:8–17.
20. Albillos A, Garcia-Tsao G. Classification of cirrhosis: the clinical use of HVPG measurements. *Disease Markers*. 2011;31:121–128.
21. Venturi C, Sempoux C, Bueno J, et al. Novel histologic scoring system for long-term allograft fibrosis after liver transplantation in children. *Am J Transplant*. 2012;12:2986–2996.
22. Thiele M, Madsen BS, Hansen JF, et al. Accuracy of the enhanced liver fibrosis test vs fibrotest, elastography, and indirect markers in detection of advanced fibrosis in patients with alcoholic liver disease. *Gastroenterology*. 2018;154:1369–1379.
23. Trabut JB, Thépot V, Nalpas B, et al. Rapid decline of liver stiffness with alcohol withdrawal in heavy drinkers. *Alcohol Clin Exp Res*. 2012;8:1407–1411.
24. Bardou Jacquet E, Legros L, Soro D, et al. Effect of alcohol consumption on liver stiffness measured by transient elastography. *World J Gastroenterol*. 2013;19:516–522.
25. Castera L, Bedossa P. How to assess liver fibrosis in chronic hepatitis C: serum markers or transient elastography vs. liver biopsy? *Liver Int*. 2011;31(suppl 1):13–17.
26. de Franchis R. Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015;63:743–752.