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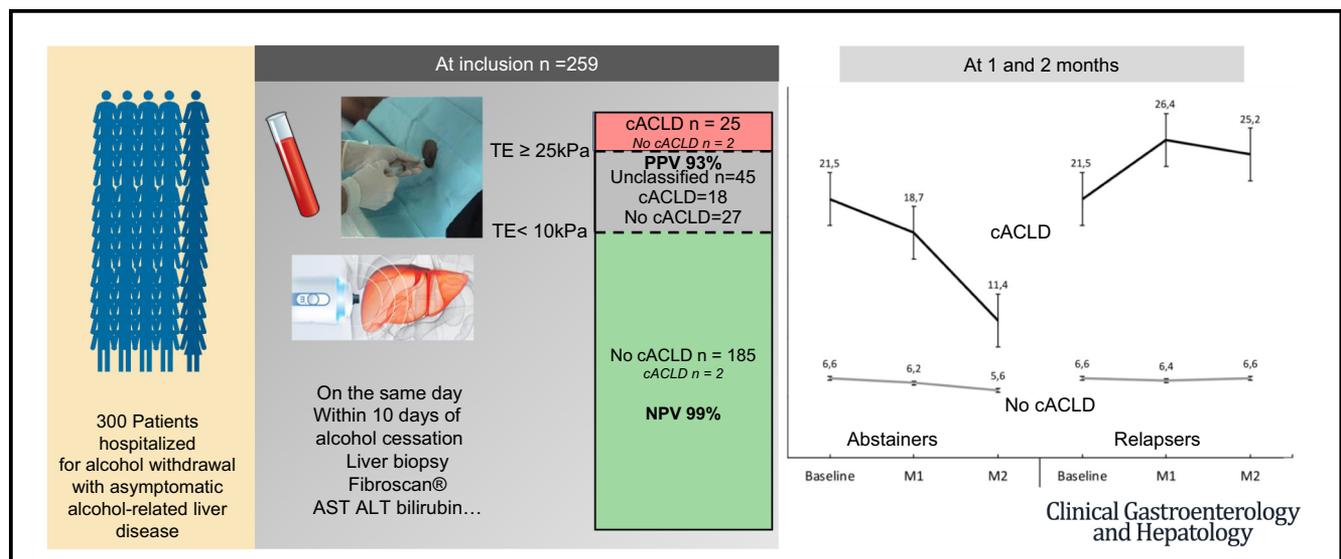


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Transient Elastography Accurately Screens for Compensated Advanced Chronic Liver Disease in Patients With Ongoing or Recent Alcohol Withdrawal

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BACKGROUND & AIMS:

Liver stiffness measurement by transient elastography (TE) is a promising method for staging fibrosis in alcohol-related liver disease, but uncertainties remain regarding the influence of alcohol consumption and thus the ideal timing for TE performance. We evaluated the performance of TE compared with liver biopsy to exclude compensated advanced chronic liver disease (cACLD) in patients hospitalized for alcohol detoxification.

METHODS:

Patients were recruited prospectively at 6 in-patient addiction centers in France. Eligible patients had increased aspartate aminotransferase levels, and no history or signs of overt cirrhosis. TE, histology, and biochemistry measurements were obtained within a median of 6 days after alcohol withdrawal. TE and biochemistry were repeated 1 and 2 months later.

Abbreviations used in this paper: ALD, alcohol-related liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristics curve; cACLD, compensated advanced chronic liver disease; γ GT, gamma-glutamyltransferase; IQR, interquartile range; LS, liver stiffness; M1, 1 month after inclusion; M2, 2 months after inclusion; NPV, negative predictive value; PF, perisinusoidal fibrosis; PPV, positive predictive value; TE, transient elastography.

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RESULTS:

The study included 259 patients for per-protocol analysis, of whom 45 (17%) had cACLD. TE identified patients with high accuracy at inclusion and at the 1- and 2-month follow-up evaluation, with area under the curve values of 0.96 (95% CIs, 0.94–0.99), 0.96 (95% CIs, 0.92–0.99), and 0.93 (95% CIs, 0.85–1.00), respectively. In 84% of patients, cACLD was ruled out when liver stiffness was less than 10 kPa (negative predictive value, 99% (95% CIs, 98%–100%)) or ruled in when greater than 25 kPa (positive predictive value, 93% (95% CI, 83%–102%)). Algorithms based on aminotransferase levels and/or bilirubin did not add to the diagnostic performance of TE in this period. Among patients with initial liver stiffness of 10 to 25 kPa, more than half of those with no cACLD showed liver stiffness of less than 10 at 1- and 2-month follow-up testing.

CONCLUSIONS:

TE performed during the first 2 months after alcohol cessation is an excellent method for excluding alcohol-related cACLD. Clinical trial number: NCT01789008.

Keywords: Alcoholic Liver Disease; Liver Cirrhosis; Liver Fibrosis; Elasticity Imaging Techniques; Alcohol Withdrawal.

Alcohol-related liver disease (ALD) is responsible for an estimated 607,000 deaths resulting from liver cirrhosis.¹ ALD may be asymptomatic for years, before the occurrence of severe complications.² The term *compensated advanced chronic liver disease* (cACLD) has been introduced to describe asymptomatic patients with either severe fibrosis or compensated cirrhosis who are at high risk of complications.³ Advanced fibrosis predicts long-term mortality,⁴ and the detection of alcohol-related cACLD potentially could improve survival. Identified patients can enter screening programs for hepatocellular carcinoma and portal hypertension and may be motivated to reduce alcohol consumption. Persistent alcohol intake is an independent predictive factor for death in alcoholic cirrhosis,⁵ and ALD screening via noninvasive tests in primary care practices in the United Kingdom have a significant positive impact on alcohol consumption.⁶

Liver biopsy is the reference method for cACLD diagnosis, but its cost and morbidity make it unacceptable for screening large at-risk populations.⁷ Liver stiffness (LS) measured by transient elastography (TE) is widely used to assess liver fibrosis from any underlying cause.⁸ TE is simple, noninvasive, and reproducible, making it appealing for ALD screening. Some prospective biopsy-controlled studies have specifically evaluated TE performance in patients with ALD and confirmed its efficiency for assessing liver fibrosis.⁹ However, the thresholds determined for severe fibrosis or cirrhosis have varied and are substantially higher than for other etiologies. LS decreases rapidly in patients with alcohol withdrawal,^{10–15} but histology and TE follow-up evaluation have not been correlated. Thus, current excessive alcohol consumption seems to influence TE in ALD, and whether it is preferable to perform TE during active intoxication or to wait for abstinence is unclear.

To obtain more precise information regarding the influence of alcohol consumption on LS, and to better characterize the optimal conditions for using TE to assess fibrosis in ALD, we conducted a prospective biopsy-controlled study with standardized monitoring of TE and alcohol consumption. In the present study, we aimed to precisely evaluate the performance of TE for

excluding alcohol-related cACLD in a homogeneous population of heavy drinkers during hospitalization for alcohol detoxification, and then 1 and 2 months later.

Patients and Methods

We performed a prospective, multicenter study in 6 hospitals in France. The study protocol was approved by the comité consultatif de protection des personnes pour la recherche biomédicale (CCPPRB) in accordance with French laws.

All authors had access to the study data and reviewed and approved the final manuscript. For further details, see the [Supplementary Methods](#).

Patients

We screened consecutive patients hospitalized for alcohol detoxification. Inclusion criteria were age older than 18 years, excessive alcohol consumption (>30 g/d for men or >20 g/d for women) for at least 5 years, ALD defined by aspartate aminotransferase (AST) level greater than 1.5 times the upper limit of normal, and increased γ -glutamyl-transferase (γ GT). Exclusion criteria included known or overt cirrhosis, refusal or contraindication of liver biopsy, pregnancy, lack of medical insurance, and evidence of other causes of liver disease, although metabolic co-factors were acceptable if alcohol was the main cause of liver disease on the basis of biological results. TE and biochemistry were performed on the same day as the liver biopsy, within 10 days after the cessation of alcohol consumption.

Baseline Demographic and Biological Data

Age, sex, body mass index, and metabolic risk factors were recorded at inclusion. Accurate data regarding the consumption of alcohol, tobacco, cannabis, and coffee were recorded using a self-questionnaire. To verify the inclusion criteria, blood samples were taken on the day of hospitalization or the day after. On the same day as TE

and liver biopsy, we measured AST, alanine aminotransferase (ALT), γ GT, platelets, hyaluronic acid, and α_2 -macroglobulin levels. Bilirubin was not measured routinely during alcohol detoxification, and we measured bilirubin retrospectively in frozen (-80°C) sera taken the day of the biopsy, when available.

Transient Elastography

After overnight fasting, patients underwent TE with Fibroscan® (Echosens; Paris, France). TE was considered valid if at least 10 measurements were performed and if the interquartile range (IQR) was less than 30% of the median or if the median was less than 7.1 kPa

Liver Biopsy

Biopsy specimens smaller than 10 mm in length were excluded from analysis unless cirrhosis was obvious. Each liver biopsy was read by 2 blinded and experienced liver pathologists from 2 different centers (B.T. and S.M.). In the case of a discrepancy regarding fibrosis stage, both pathologists met to reach a consensus. Liver fibrosis was staged according to METAVIR score: F0, no fibrosis; F1, portal fibrosis; F2, mild extensive portal fibrosis (less than half of portal tracks have septa); F3, severe extensive portal fibrosis; and F4, cirrhosis. Patients with F3 and F4 fibrosis were considered to have cACLD. Other recorded data included biopsy length, percentage of steatosis, presence or absence of steatohepatitis, and hepatocyte ballooning or Mallory bodies. Perisinusoidal fibrosis (PF) was assessed using the Brunt classification¹⁶: PF 0, no; PF 1, mild (less than one third of zone III); PF 2, moderate (between one third and two thirds of zone III); and PF 3, severe (more than two thirds of zone III).

Follow-Up Evaluation

Patients underwent a follow-up examination at 1 and 2 months after the initial TE, with an evaluation of their alcohol consumption. We measured LS and prothrombin time, platelets, AST, ALT, γ GT, desialylated transferrin, hyaluronic acid, and α_2 -macroglobulin. Bilirubin was measured on frozen sera taken at 1 month when available. Based on self-declaration and laboratory test results, patients were divided into 2 groups: low-risk consumers (abstainers or drinking <30 g/d for men or <20 g/d for women) or relapsers.

Statistical Analysis

All analyses were performed for the per-protocol population, which comprised all patients with no major protocol deviations, valid TE, and biopsy. We summarized patient characteristics as medians and IQRs or numbers and percentages when appropriate. All analyses were

What You Need to Know

Background

Liver stiffness measurement is valuable for evaluating the presence of severe fibrosis/cirrhosis in alcohol-related liver disease, but there are limited data about the validity of these measurements after alcohol cessation. Thus, it is unclear when to assess liver stiffness measurement relative to alcohol cessation

Findings

Transient elastography performed during the first 2 months of alcohol cessation was able to identify patients with or without advanced fibrosis/cirrhosis. Algorithms based on aminotransferases and/or bilirubin do not add to diagnostic performance in this period

Implications for patient care

In heavy drinkers, transient elastography provides valid results and can be performed within 2 months of alcohol cessation.

performed using SAS version 9.4 statistical software (SAS, Cary, NC), and $P < .05$ was considered significant.

We evaluated the accuracy of TE for the diagnosis of cACLD and cirrhosis by analyzing the area under the receiver operating characteristics curve (AUROC). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the 95% CIs were calculated for 3 cut-off values: one to rule in the diagnosis (sensitivity, $\geq 95\%$), one to rule out the diagnosis (specificity, $\geq 95\%$), and the optimal cut-off value based on the highest Youden index. These analyses were repeated for 3 time points: inclusion, 1 month after inclusion (M1), and 2 months after inclusion (M2).

We performed analysis of variance with repeated measures to analyze variations in liver enzyme levels and stiffness during the follow-up period. To investigate potential associations between various factors and TE values, we applied a mixed-effects model for linear regression with backward lasso selection including all variables selected from the univariate analysis (1-way analysis of variance for categorical variables, Pearson correlation for quantitative variables, $P < .20$). To confirm the results, we rebuilt the model excluding histologic variables. The time point for these analyses was inclusion.

We then assessed the influence of time and alcohol withdrawal by introducing the values collected at M1 and M2 in a mixed-effects model for linear regression, accounting for repeated measures. The model only included patients with valid values for TE at inclusion, M1, and M2 and known alcohol consumption; thus, the results should be interpreted cautiously.

As a sensitivity analysis, we performed an intention-to-diagnose analysis for the primary outcome. Invalid

LS measurements were included without transformation, and missing values were replaced using the hot-deck imputation method.

Results

Patients

The inclusion period lasted from February 2013 to April 2017. A detailed flow chart of patient inclusion was obtained only for the largest center where patients were screened, where 1791 patients were hospitalized for detoxification (Supplementary Figure 1). Of these patients, 1573 were excluded, most commonly because of an AST value less than 1.5 N or known or overt cirrhosis. Overall, 300 patients were enrolled in the study, 285 of whom were included in an intention-to-diagnose analysis (Supplementary Figure 2) and 259 in the per-protocol analysis. Tables 1 and 2 provide these patients' baseline and follow-up characteristics. Of these patients, 189 were analyzed at the 1-month follow-up evaluation and 160 were analyzed at the 2-month follow-up evaluation.

Liver Histology

The median biopsy length was 30 mm (IQR, 25–37 mm). Liver fibrosis results were discordant between the 2 pathologists for 60 patients and required consensus reviewing: discordant for cACLD yes/no in 10 (3.9%) and between F3 and F4 for 19 (7.3%). A total of 45 patients (17%) had cACLD. Table 1 provides details regarding perisinusoidal fibrosis, steatosis, and steatohepatitis.

Transient Elastography Diagnosis Accuracy at Inclusion

The median delay between inclusion TE and last alcohol consumption was 6 days [5–8]. LS increased with fibrosis stage (Supplementary Figure 3). Variables associated with LS are listed in Supplementary Table 1.

The accuracy of TE for cACLD diagnosis was excellent in both the per-protocol (AUROC, 0.96) and intention-to-diagnose (AUROC, 0.95) analyses (Table 3, Figure 1). The best cut-off value was 10 kPa to rule out cACLD (NPV, 99%). To rule in cACLD, the cut-off value based on 95% specificity had an insufficient PPV and 25 kPa was the best to rule in cACLD (PPV, 93%). Using the Youden index, the optimal cut-off value was 12 kPa, which had a good NPV of 98%, but the PPV decreased to 72%.

Overall, our results showed that TE led to an accurate diagnosis when less than 10 kPa or more than 25 kPa in 214 (84%) patients, or 229 patients (88%) with 12 kPa as the inferior cut-off value. Between these 2 values, TE could not rule out or rule in cACLD. Within this grey area, 27 patients (60%) had F0 to F2 fibrosis, and 18 patients (40%) had cACLD (Figure 1). We compared the clinical,

Table 1. Patient Characteristics at Inclusion in the Per-Protocol Population

	n = 259
Age, y	45 [38–52]
Sex, male/female	207/52
BMI, kg/m ²	23 [20–26]
Arterial hypertension	44 (18)
Diabetes	7 (2.8)
Dyslipidemia	20 (8.5)
Active tobacco users	194 (75)
Active cannabis users	93 (37)
Duration of excessive drinking, y	20 [13–27]
Alcohol drinking/wk in the month before hospitalization, standard drinks (10 g of pure alcohol)	108 [70–175]
Still drinking on the day of entry	168 (69)
Delay between last alcohol consumption and transient elastography, d	6 [5–8]
Liver fibrosis	F0: 26 (10.0) F1: 142 (55) F2: 46 (18) F3: 22 (8.5) F4: 23 (8.9)
PF	PF0: 121 (47) PF1: 83 (32) PF2: 44 (17) PF3: 9 (3.5)
Steatosis	
S1 5%–33%	151 (60)
S2 33%–66%	60 (24)
S3 >67%	39 (16)
Presence of steatohepatitis	80 (31)
Presence of ballooning hepatocytes	89 (34)
Presence of Mallory bodies	75 (29)

NOTE. Data are presented as median [IQR] or as n (%). BMI, body mass index; PF, perisinusoidal fibrosis.

biological, and histologic characteristics of patients with or without cACLD within this unclassifiable subgroup and found that the only difference was that stages 2 and 3 perisinusoidal fibrosis were much more frequent in patients without cACLD (17 of 27; 63%) than in patients with cACLD (3 of 18, 17%; $P = .0016$, χ^2 test). We attempted to increase the diagnostic performance of TE using biochemistry. Bilirubin increased significantly with fibrosis stage but AST did not, both decreased with time, less so in relapsers (Supplementary Table 2). The use of AST-adapted cut-off values¹⁷ or cut-off values adapted according to bilirubin and AST¹⁸ did not increase diagnostic performance (Supplementary Table 3). TE AUROCs were similar when calculated in the whole population or in patients with an AST value less than

Table 2. Patient Characteristics on the Day After Admission, Day of Liver Biopsy and Transient Elastography (Inclusion), and 1- and 2-Month Follow-Up Evaluations

	Admission	Inclusion	M1	M2
N	259	259	189 ^a	160 ^b
Abstainers	^c	^c	72 (41)	73 (45)
Low-risk drinkers	^c	^c	8 (4.5)	6 (3.7)
Relapsers	^c	^c	96 (54)	82 (51)
AST, U/L ^d	113 [76–173]	70 [49–102]	33 [24–47] ^{d,e}	30 [21–49] ^{d,e}
Abstainers/low-risk relapsers should be on the line below			24 [20–30] 45.5 [31–70]	21 [18–28] 49.5 [36–96]
ALT, U/L ^d	73 [52–112]	70 [45–111]	28 [21–46] ^{d,e}	26 [17–47] ^{d,e}
Abstainers/low-risk same as above			24 [18–29] 36 [25–56]	19 [13–25] 42 [26–69]
γGT, U/L ^{d,e}	387 [180–825]	285 [143–558]	104 [53–181] ^{d,e}	59 [32–176] ^{d,e,f}
Abstainers/low-risk same			61 [35–155] 135 [75–328]	34 [22–55] 181 [65–436]
Prothrombin time ^g		100 [91–107]	100 [93–106]	100 [92–107]
Abstainers/low-risk same			100 [94–105] 100 [92–107]	100 [93–109] 100 [90–106]
Platelets count, Gi/L ^d	158 [115–205]	190 [148–244]	239 [189–303] ^{d,f}	239 [190–287] ^{d,e}
Abstainers/low-risk same			269 [218–324] 214 [167–278]	252 [201–299] 200 [164–264]
Total bilirubin, μmol/L ^g	–	7.1 [4.9–10.2] ^h	6.5 [5.3–9.1] ⁱ	–
Abstainers/low-risk same			5.9 [4.9–7.6] 7.6 [5.8–11.5]	
Liver Stiffness kPa ^g	–	6.1 [4.5–10.6]	6.3 [4.9–10.1] ^f	6.3 [4.5–9.2] ^{e,f}
Abstainers/low-risk same			6.3 [5.1–9.2] 6.8 [5.1–14.1]	5.3 [4.3–7.8] 7.8 [5.6–17.1]

NOTE. Data are presented as median [IQR] or as n (%).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, γ-glutamyltransferase; M1, 1 month after inclusion; M2, 2 months after inclusion.

^aFifty-eight were lost to follow-up evaluation, 3 unfeasible and 9 unreliable TE.

^bEighty-five were lost to follow-up evaluation, 3 unfeasible and 11 unreliable TE.

^cA total of 168 patients were actively drinking on the day of admission, and the median delay between admission and biopsy was 5 days [IQR, 3–6 d].

^dSignificant variation with time ($P < .0001$), multivariate analysis of variance with repeated measures.

^eSignificant interactions between time and alcohol consumption ($P < .05$), multivariate analysis of variance with repeated measures.

^fSignificant effect of alcohol consumption ($P < .05$), multivariate analysis of variance with repeated measures.

^gNonsignificant variation with time, multivariate analysis of variance with repeated measures.

^hBilirubin level was available for 179 patients.

ⁱBilirubin level was available for 128 patients.

normal, 50 U/L, or 100 U/L (17%, 26%, and 73% of the population, respectively). The diagnostic performance for cirrhosis is shown in [Supplementary Table 4](#).

Influence of Time and Alcohol Withdrawal

At M1 and M2, 96 (54%) and 82 patients (51%) were relapsers, respectively. Liver enzyme levels decreased markedly between the onset of hospitalization and biopsy (median, 5 d), and between hospitalization and M1 or M2 ([Table 2](#) and [Supplementary Table 2](#)). We also found a significant interaction between time and alcohol consumption because liver enzyme levels continued to decrease with time in all patients, but less in relapsers. The median TE for the whole population did not differ

between inclusion, M1, and M2, but varied with time according to alcohol consumption. Indeed, multivariate analysis showed that TE evolution was associated strongly with alcohol consumption, strongly interacting with fibrosis stage ([Table 4](#)). Among patients without cACLD, TE tended to decrease between inclusion, M1, and M2 in low-risk consumers, and was stable in relapsers ([Figure 2](#)). However, among patients with cACLD, median TE varied markedly, decreasing from 22 kPa at inclusion to 11 kPa at M2 in low-risk consumers, and increasing from 22 kPa at inclusion to 25 kPa at M2 in relapsers. Perisinusoidal fibrosis and steatohepatitis also were associated with TE time variation.

TE at M1 and M2 still showed excellent accuracy for cACLD diagnosis (AUROC, 0.96 and 0.93, respectively) ([Table 3](#)). The 10-kPa cut-off value remained very

Table 3. Diagnostic Accuracy of Transient Elastography for cACLD at M0, M1, and M2, With PP and ITD Analyses

	Cut-off	FN	FP	TN	TP	Sensitivity	Specificity	NPV	PPV	AUROC
M0-PP	10 kPa ^a	2	29	185	43	96 [89–102]	87 [82–91]	99 [97–100]	60 [48–71]	
M0-PP	12 kPa ^b	4	16	198	41	91 [83–99]	92 [89–96]	98 [96–100]	72 [60–84]	0.96 [0.94–0.99]
M0-PP	25 kPa ^c	20	2	212	25	56 [41–70]	99 [98–100]	91 [88–95]	93 [83–102]	
M0-ITD	10 kPa ^a	2	41	195	47	96 [90–101]	83 [78–87]	100 [98–100]	53 [43–64]	
M0-ITD	12 kPa ^b	4	24	212	45	92 [84–100]	90 [86–94]	98 [96–100]	65 [54–76]	0.95 [0.93–0.98]
M0-ITD	25 kPa ^c	22	6	230	27	55 [41–69]	97 [95–99]	91 [88–95]	82 [69–95]	
M1-PP	10 kPa ^a	2	23	136	28	93 [84–102]	86 [80–91]	99 [97–101]	55 [41–69]	
M1-PP	12 kPa ^b	6	12	147	24	80 [66–94]	92 [88–97]	96 [93–99]	67 [51–82]	0.96 [0.92–0.99]
M1-PP	25 kPa ^c	15	1	158	15	50 [32–68]	99 [98–101]	91 [87–96]	94 [82–106]	
M2-PP	10 kPa ^a	3	14	122	21	87 [74–101]	90 [85–95]	98 [95–100]	60 [44–76]	
M2-PP	12 kPa ^b	4	6	130	20	83 [68–98]	96 [92–99]	97 [94–100]	77 [61–93]	0.93 [0.85–1.00]
M2-PP	25 kPa ^c	15	2	134	9	37 [18–57]	99 [97–101]	90 [85–95]	82 [59–105]	

NOTE. Data are presented as results with their 95% CIs.

AUROC, area under the receiver operating characteristics curve; cACLD, compensated advanced chronic liver disease (F3/F4 fibrosis in the METAVIR System); FN, false negative; FP, false positive; ITD, intention-to-diagnose; M0, inclusion; M1, 1-month follow-up evaluation; M2, 2-month follow-up evaluation; NPV, negative predictive value; PP, per-protocol; PPV, positive predictive value; TN, true negative; TP, true positive.

^aOptimal cut-off value to rule out cACLD based on inclusion.

^bOptimal cut-off value selected using the Youden index based on inclusion.

^cOptimal cut-off value to rule in cACLD based on inclusion.

efficient for cACLD exclusion (NPV of 99% at 1 month and 98% at 2 months) regardless of alcohol consumption. Notably, among the initially unclassifiable patients (initial TE, 10–25 kPa), the M1 LS value was less than 10 in 11 of 25 patients (44%) without cACLD vs 1 of 16 patients (6%) with cACLD ($P = .0052$), and the M2 LS value was less than 10 in 13 of 19 patients (68%) without cACLD vs 2 of 11 patients (18%) with cACLD ($P = .006$). Thus, in more than half of the initially unclassifiable patients without cACLD, LS less than 10 kPa at M1 or M2 could exclude cACLD with very good accuracy. The 25-kPa cut-off value was able to rule in cACLD with a good, but decreasing, PPV (94% and 82% at 1 and 2 months, respectively). TE decreased with time in nonrelapsers with cACLD; at M2, a 20-kPa cut-off value showed better performance for ruling in (Supplementary Table 3).

Discussion

The results of this large, prospective, biopsy-proven study showed that a suitable period for assessing cases of ALD for cACLD using TE is the time of alcohol detoxification and the 2 months thereafter. In these patients, LS less than 10 kPa ruled out cACLD, regardless of alcohol consumption, and LS more than 25 kPa ruled in cACLD. Eighty percent of our patients could be classified initially, and follow-up TE further excluded cACLD in some patients over 2 months.

TE is a simple and reproducible tool for assessing liver fibrosis in chronic liver diseases. Prior studies have indicated that TE is a valuable method in ALD,⁹ but the optimal timing for TE, either in patients still consuming alcohol or after a phase of abstinence, remained questionable. Thresholds for diagnosing severe fibrosis or cirrhosis in ALD have been heterogeneous and often greater than in other etiologies, likely owing to the inflammation related to alcoholic hepatitis.⁹ However, in prior biopsy-based studies, the interval between last alcohol consumption and performance of TE and biopsy was largely unknown or variable. Mueller et al¹³ found an AUROC of 0.946 in the absence of inflammation, probably some time from alcohol consumption, but in real life patients often are evaluated while currently drinking. Prior studies have shown decreasing LS during the first week of alcohol detoxification.^{11,13–15} Mueller et al¹⁴ showed a parallel decrease in LS, aminotransferase levels, and total cyto-keratin.¹⁸ Such decreases are more marked in patients remaining abstinent after initial detoxification.^{10–12} Our study combined a prospective follow-up evaluation of LS with clinical and biological data and liver histology. TE was performed after a median of 6 days of abstinence, making it plausible that LS already had decreased in some patients. All patients had at least 1 week of total alcohol withdrawal, which permitted prompt improvement in liver enzyme levels. Even in relapsers, liver enzyme levels continued to decrease during follow-up evaluation, although to a lesser extent

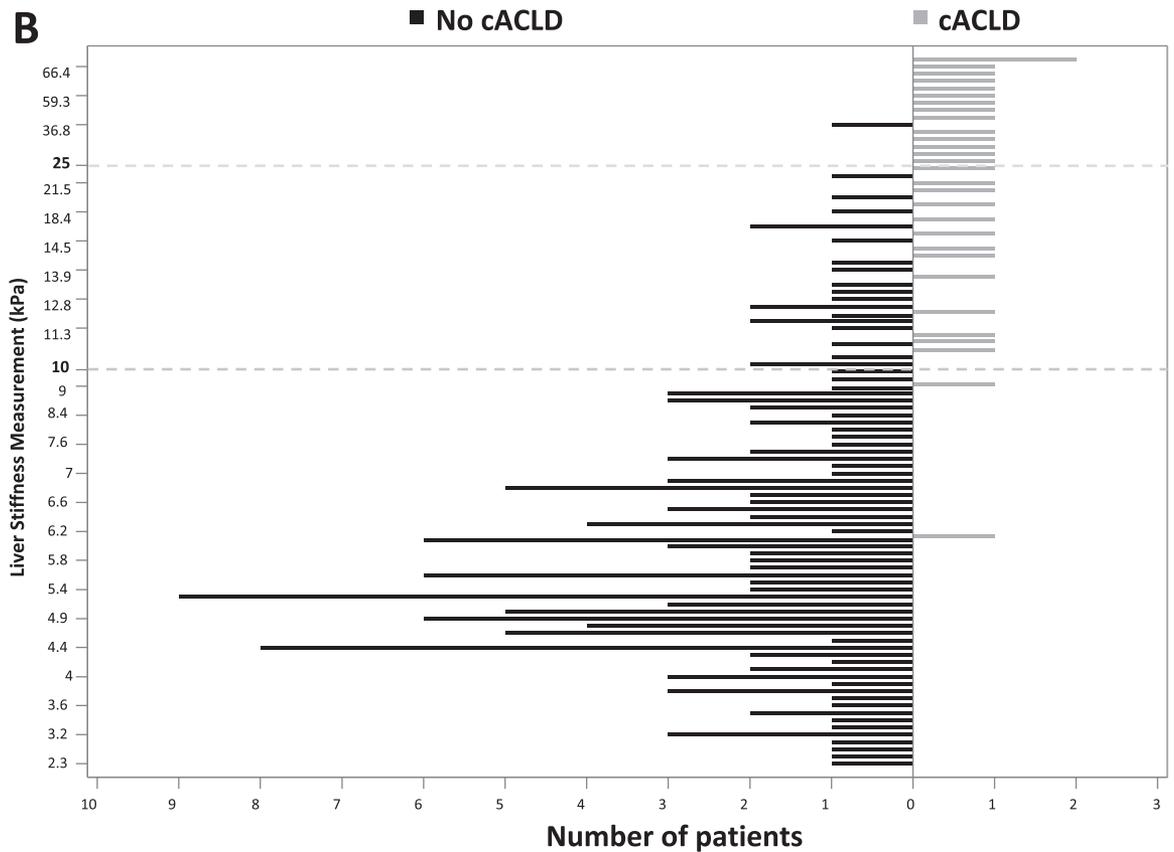
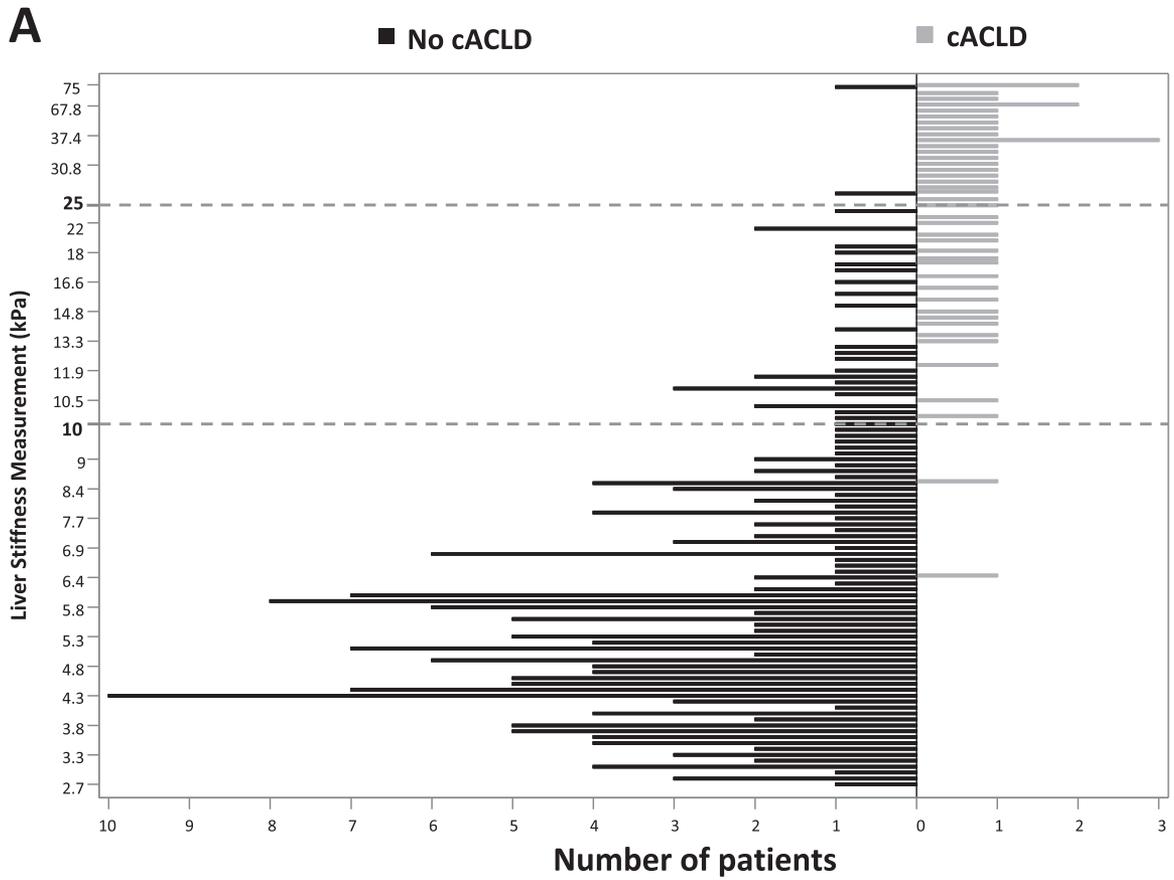


Figure 1. Liver stiffness according to liver fibrosis. At (A) inclusion, (B) 1 month, and (C) 2 months. The *dotted lines* represent the chosen thresholds for ruling out (10 kPa) or ruling in (25 kPa) compensated advanced chronic liver disease (cACLD).

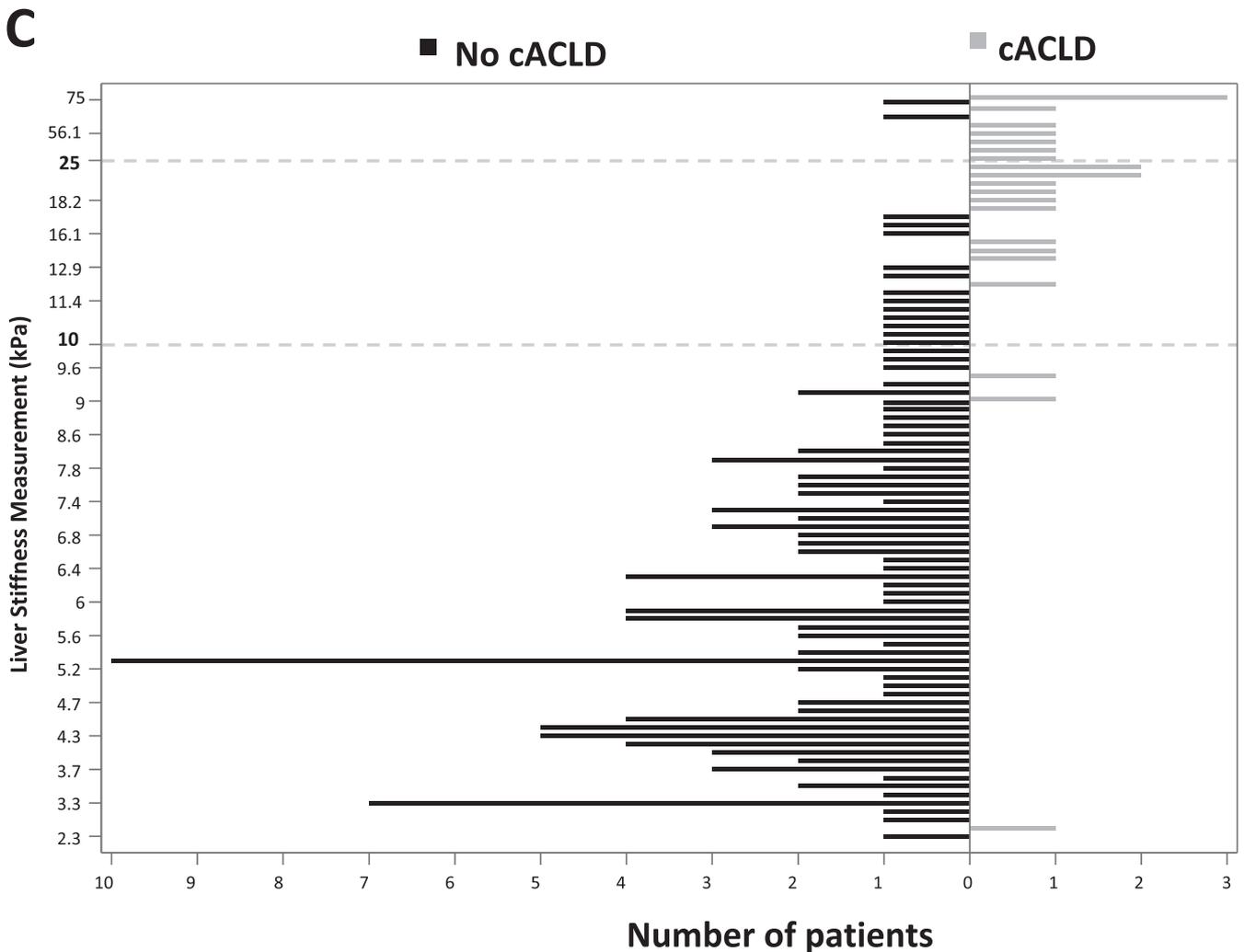


Figure 1. Continued.

than in nonrelapsers. Our study showed that the decrease in LS during alcohol withdrawal was driven mainly by patients with cACLD. Most patients without cACLD showed low LS throughout the study, regardless of alcohol consumption. Only a minority of patients without cACLD showed increased LS at inclusion, which often decreased during follow-up evaluation. In contrast, patients with cACLD had high LS at inclusion, which decreased markedly, although it remained high, among nonrelapsers, and increased further in relapsers. Importantly, the diagnostic performance of TE remained high at M1 and M2, especially in ruling out cACLD.

The study was designed initially to look for 2 cut-off values, one with a very high NPV to rule out cACLD (for which the number of patients needed was calculated) and the other with a very high PPV to rule in cACLD. This approach has been tested in some previous studies,¹⁹ but most other studies typically have proposed 1 cut-off value. Thiele et al¹⁹ selected a cut-off value of 19.9 kPa for cirrhosis, which had a good NPV of 99%, but a PPV of only 68%. Our 10-kPa cut-off value had a very high NPV

of 99% and is easy to remember. However, using the Youden index to select the best unique threshold resulted in a very similar NPV, confirming that TE performs best in excluding cACLD. This is concordant with previous results,¹⁹ and the Baveno VI consensus recently recommended a 10-kPa cut-off value to exclude cACLD with underlying liver disease of any etiology.³ However, we also found that TE performed well for ruling in cACLD with a cut-off value greater than 25 kPa. This is higher than usual. Baveno VI³ recommends 15 kPa, but is based mainly on studies of viral hepatitis, and our study found that the 15-kPa cut-off value had a poor PPV. The rule-in cut-off value could decrease during follow-up evaluation; in this study, 20 kPa at M2 had better accuracy, but this could be difficult to interpret for a given patient. Using these 2 thresholds, we correctly classified 83% of our patients. We did not confirm that correcting LS values with AST and bilirubin, as previously proposed,^{13,17,18} allowed better classification of patients in our population in the 2-month follow-up period. However, we did show that for patients in the grey area, LS

Table 4. Mixed Models on Repeated Variables, Accounting for Time

Effect	Model 1 <i>P</i> value	Model 2 <i>P</i> value
BMI	.0175	.1760
Visit M0, M1, or M2	.0562	.0739
Low-risk drinking, yes/no	.0165	–
cACLD, yes/no	.8278	.3345
Steatohepatitis, yes/no	.1279	.3251
% Steatosis in four classes <15%, 15%–30%, 30%–60%, ≥60%	.0003	.0128
Perisinusoidal fibrosis, 0 vs 1 vs 2–3	.0003	.0005
γGT, log	–	<.0001
AST, log	–	.0294
ALT, log	–	<.0001
cACLD × steatohepatitis	.6908	.7574
cACLD × % steatosis	.0316	.1895
cACLD × perisinusoidal fibrosis	<.0001	<.0001
cACLD × BMI	.1857	.8317
cACLD × γGT	–	.0001
cACLD × AST	–	.9110
cACLD × ALT	–	.0059
Low-risk drinking × cACLD	.0032	–
Low-risk drinking × steatohepatitis	.5731	–
Low-risk drinking × % steatosis	.0727	–
Low-risk drinking × perisinusoidal fibrosis	.9241	–
Low-risk drinking × BMI	.3408	–
Visit × steatohepatitis	.0434	.0663
Visit × % steatosis	.2852	.9969
Visit × perisinusoidal fibrosis	.0178	.0431
Visit × BMI	.3185	.3679
Visit × cACLD	.0067	.0118
Visit × low-risk drinking × cACLD	.0064	–

NOTE. The dependent variable is liver stiffness (log) measured by transient elastography at the initial hospitalization, at M1, and at M2. The low-risk drinking and liver enzyme variables were so highly correlated that they could not be introduced in the same model. Therefore, low-risk drinking is included in model 1, and liver enzymes in model 2. Only patients with valid liver stiffness values at M0, M1, and M2 and with known alcohol consumption were kept in the models ($n = 113$). The results illustrate the complex relationships between liver stiffness and alcohol withdrawal (as reflected by the patient's declaration or by liver enzymes) and liver histology. Both models showed a significant

interaction between cACLD and visit, and very significant interactions between low-risk drinking, visit, and cACLD. These findings indicate that cACLD modifies liver stiffness evolution over time. The interaction between cACLD and perisinusoidal fibrosis also was very significant in both models, but not with steatohepatitis or steatosis, indicating that perisinusoidal fibrosis plays a role in increasing LS. Boldface indicates statistical significance.

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; cACLD, compensated advanced liver disease; γGT, γ-glutamyltransferase; M0, inclusion; M1, 1-month follow-up evaluation; M2, 2-month follow-up evaluation.

less than 10 kPa in the 2 months after alcohol withdrawal allows further ruling out of cACLD.

Our study had some weaknesses. First, TE was not performed at admission, and bilirubin was available for only 69% of the population. Advanced fibrosis cases were fewer than expected and could have contributed to the lack of utility of the adapted cut-off values. For ethical reasons, we did not propose a biopsy to patients with known or overt cirrhosis as we did in patients with normal enzyme levels while currently drinking considering their low cACLD prevalence (as illustrated by Thiele et al¹⁹). The possibility of an invalid or unfeasible LS measurement is a general limitation of TE, but diagnostic performance was similar in the intent-to-diagnose analysis, which included invalid measurements. However, our study should be interpreted with consideration of its strengths. First, the population was homogenous—heavy drinkers during alcohol cessation with abnormal liver enzyme levels but no overt cirrhosis. Most other cohorts studied patients from liver units, which include a high proportion of patients with (often severe) cirrhosis, occasionally mixed¹⁹ with patients in addiction centers and with current drinkers and abstainers. Our patients represented a real-life group as found in primary care practices, hepatology clinics, or beginning specialized addiction care, for whom TE could enable the diagnosis of completely asymptomatic severe liver disease. Second, our histologic data were accurate, with a substantial median biopsy size and blinded interpretation by 2 experienced pathologists. This allowed us to verify that the distinction between F3 and F4 was somewhat difficult, and justified the choice of cACLD rather than cirrhosis as the primary objective of the study. Finally, histology, TE, and biochemistry were performed on the same day.

Conclusions

In conclusion, this study showed that 2 months from the beginning of care is a suitable period to assess fibrosis by TE in heavy drinkers identified from primary care, hepatology clinics, or addiction units. TE rules out cACLD if LS is less than 10 kPa and rules in cACLD if LS is greater than 25 kPa. TE can be repeated if patients are in the grey area and resume drinking, to improve

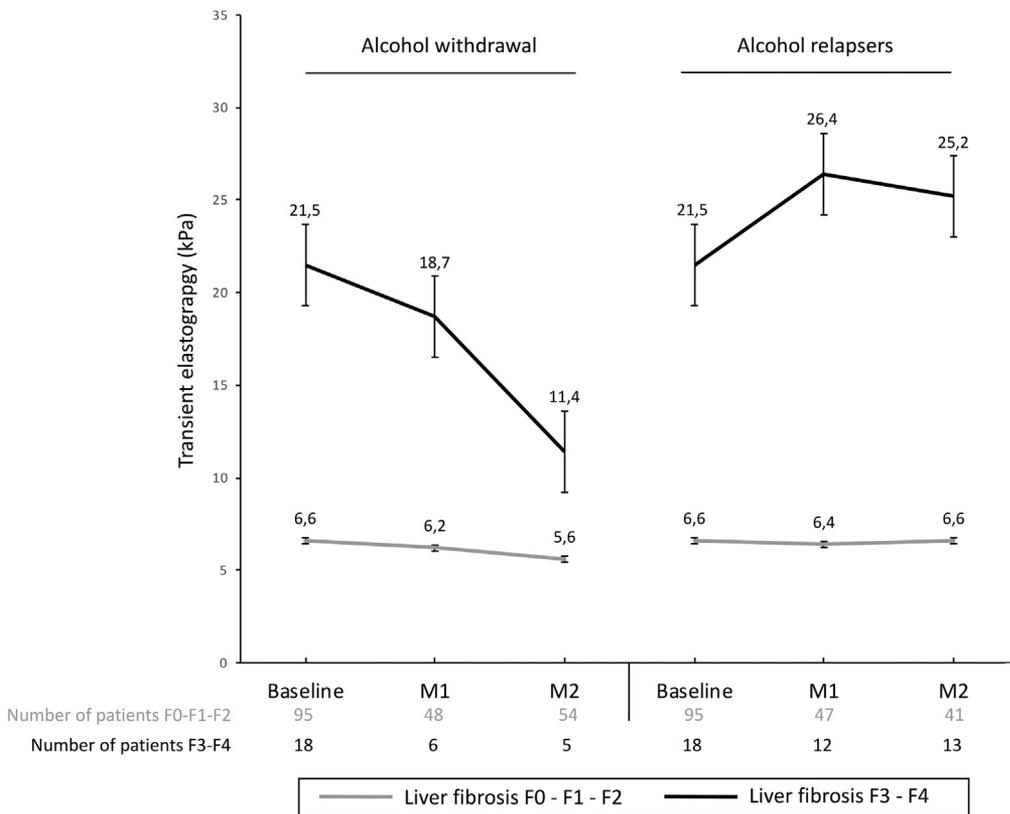


Figure 2. Evolution of transient elastography over time according to liver fibrosis and alcohol consumption. Liver stiffness did not vary significantly among patients without compensated advanced chronic liver disease (cACLD), but tended to decrease in low-risk consumers without cACLD. Among patients with cACLD, liver stiffness sharply decreased in low-risk consumers and tended to increase in relapsers. M1, month 1 after inclusion; M2, month 2 after inclusion.

diagnosis performance. Further studies are needed to determine the optimal intervals for further evaluation if patients continue excessive alcohol consumption and the possibility of a 2-step strategy incorporating liver enzymes.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2021.02.021>.

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Reprint requests

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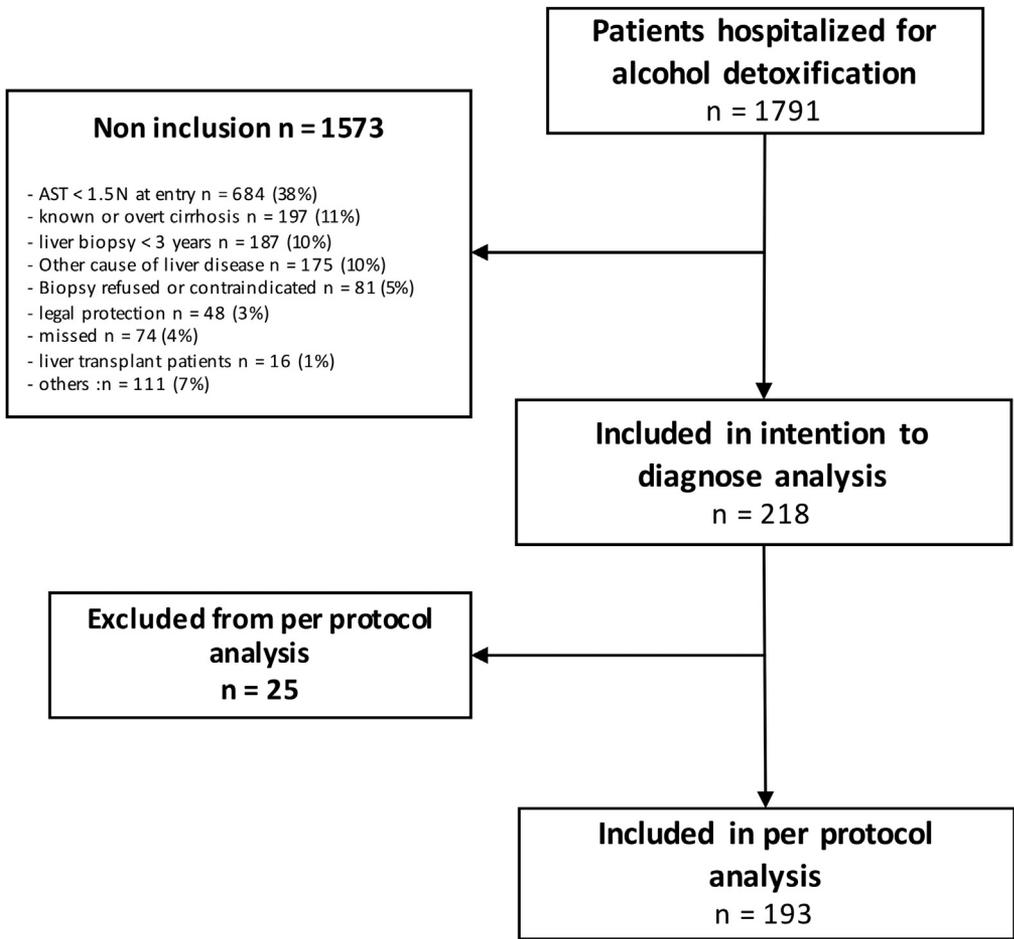
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Conflicts of interest

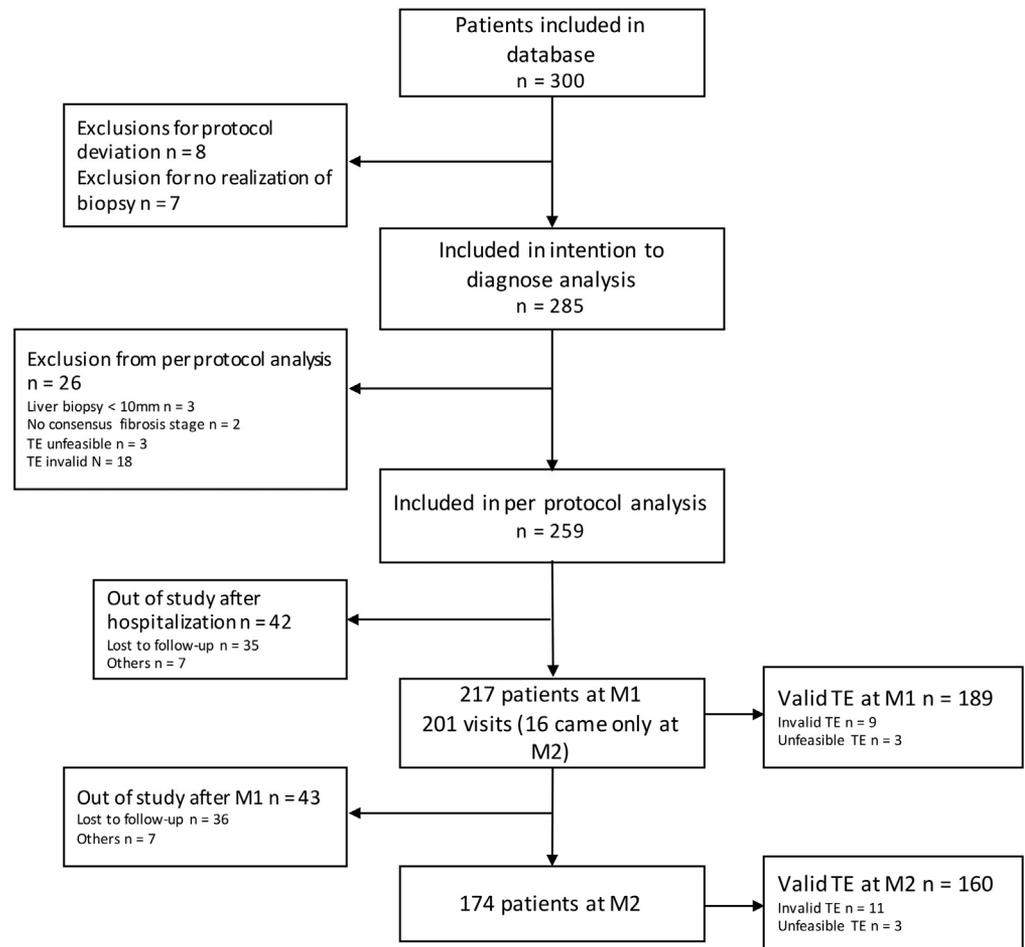
The authors disclose no conflicts.

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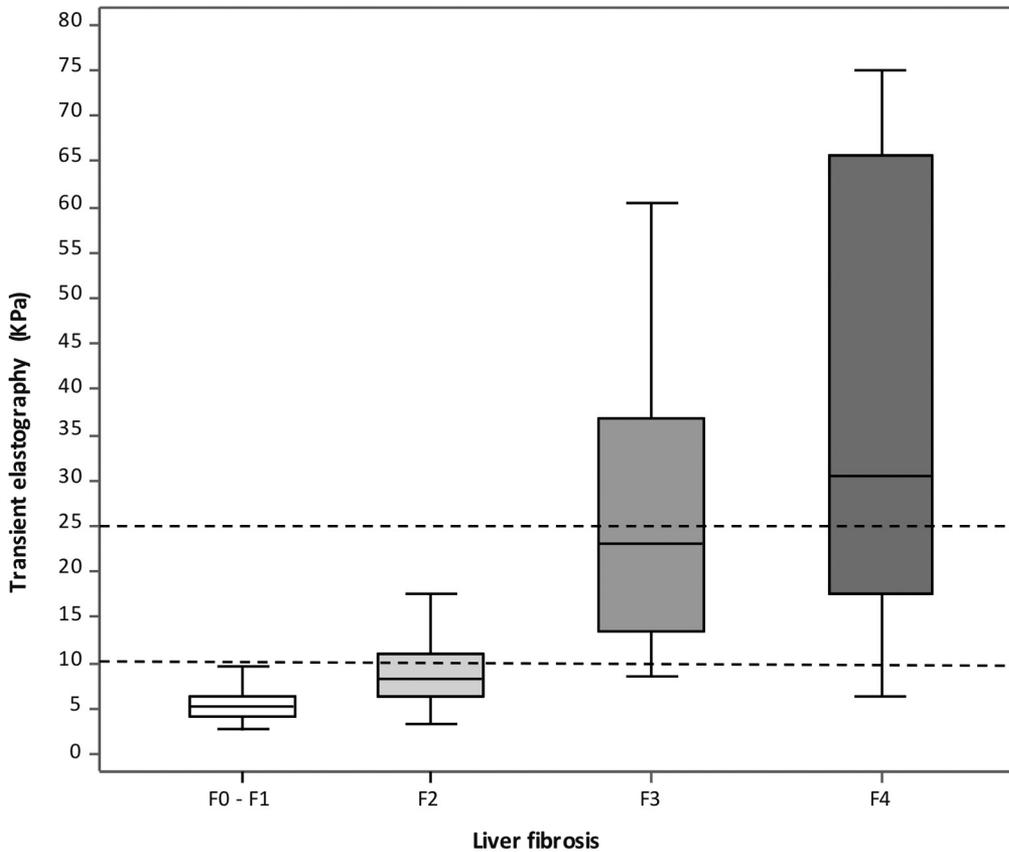
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Supplementary Figure 1. Flow chart of patients included from the largest center (University Hospital, Rennes, France). AST, aspartate aminotransferase.



Supplementary Figure 2. Flow chart of patients studied at all centers. M1, 1-month follow-up evaluation; M2, 2-month follow-up evaluation; TE, transient elastography.



Supplementary Figure 3. Distribution of transient elastography at baseline according to histology.

Supplementary Table 1. Statistical Associations with TE Results According to Mixed-Effect Models for Linear Regression

	<i>P</i> value in univariate analyses	Model 1 including histologic variables (n = 242)	Model 2 excluding histologic variables (n = 251)
Age, y	.0175	NS	0.0110
BMI, kg/m ²	.0003	0.0017	<0.0001
cACLD, yes/no	<.0001	<0.0001	–
Perisinusoidal fibrosis, 0 vs 1 vs 2–3	<.0001	0.0020	–
% Steatosis in four classes <15%, 15%–30%, 30%–60%, ≥60%	.0025	0.0495	–
Steatohepatitis, yes/no	<.0001	0.0291	–
Coffee consumption, cups/wk	.0200	NS	0.0339
Tobacco consumption, cigarettes/d	.0438	NS	0.0532
Cannabis consumption, in a year	.0046	NS	NS
γGT, log	<.0001	<0.0001	<0.0001
AST, log	.0006	0.0043	<0.0001
ALT, log	.0166	<0.0001	<0.0001
Bilirubin	<.0001		

NOTE. In the first model, liver stiffness was associated very significantly with BMI, cACLD, perisinusoidal fibrosis, γGT, AST, and ALT. In the second model, histologic variables were excluded as a sensitivity analysis, and the results confirmed highly significant associations of liver stiffness with BMI, γGT, AST, and ALT. Boldface indicates statistical significance.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; cACLD, compensated advanced liver disease; γGT, γ-glutamyltransferase; TE, transient elastography.

Supplementary Table 2. AST and Bilirubin According to Fibrosis Stage and Alcohol Consumption

AST	F0	F1	F2	F3	F4
Admission ^a	86 [70–141]	113 [75–169]	74 [78–183]	128 [84–247]	132 [77–195]
Inclusion ^a	71 [41–93]	61 [42–99]	70 [55–128]	88 [74–117]	76 [59–98]
M1 ^a	29 [21–43]	29 [23–42]	33 [25–48]	44 [38–82]	43 [29–68]
Abstainers/low risk ^a	21 [18–24]	23 [19–27]	27 [25–36]	38 [35–41]	25 [20–32]
Relapsers ^a	31 [29–123]	39 [25–65]	61 [45–90]	55 [42–112]	64 [42–73]
M2 ^b	22 [20–32]	28 [20–42]	33 [23–54]	57 [34–108]	50 [36–53]
Abstainers/low risk ^c	21 [18–23]	21 [18–26]	21 [18–28]	31 [26–35]	22 [11–36]
Relapsers ^a	41	43 [32–87]	51 [34–121]	97 [52–122]	52 [46–70]
Bilirubin					
Inclusion ^d	5 [4.1–7]	6.6 [4.7–8.8]	8.5 [5.4–14.7]	10.2 [6.7–16.9]	9.8 [6.9–22]
M1 ^e	5.7 [5.2–6.2]	6 [5–7.8]	7.4 [6–12]	7.8 [5.7–11]	9.8 [8–24]
Abstainers/low risk ^a	5.9 [3.3–8.5]	5.4 [4.7–6.7]	7 [6–9.5]	7.8 [5.3–10]	6.7 [2.7–8.3]
Relapsers ^f	5.5 [5.3–7.7]	6.8 [5.7–9.1]	10.5 [7.1–15]	7.3 [5.6–14]	12 [9.6–43]

NOTE. Data are presented as median [IQR].

AST, aspartate aminotransferase; M1, 1-month follow-up evaluation; M2, 2-month follow-up evaluation.

^aNonsignificant for F3–F4 vs F0–F2.

^b $P = .0216$ for F3–F4 vs F0–F2.

^c $P = .0187$ for F3–F4 vs F0–F2.

^d $P = .0073$ for F3–F4 vs F0–F2.

^e $P = .0003$ for F3–F4 vs F0–F2.

Supplementary Table 3. Comparison of Performance of LSM for cACLD Diagnosis Using Different Cut-Off Values for Patients at M0, M1, and M2

Cut-off		FP	FN	Se	Sp	PPV	NPV
M0	10 kPa						
	<i>a</i>	19	1	97	87	61	99
	<i>b</i>	29	2	96	86	60	99
	12 kPa (Youden)						
	<i>a</i>	10	3	90	93	74	98
	<i>b</i>	16	4	91	93	72	98
	15 kPa (rule-out cut-off proposed by Baveno VI)						
	<i>a</i>	8	8	74	95	74	95
	<i>b</i>	11	10	77	95	76	95
	25 kPa						
	<i>a</i>	2	14	55	99	89	91
	<i>b</i>	2	20	55	99	92	91
	AST-adapted cut-off values according to Mueller et al ¹⁰						
	<i>a</i>	15	4	87	90	64	97
<i>b</i>	20	5	89	91	66	97	
AST-/bilirubin-adapted cut-off values according to Nguyen-Khac et al ^{24 a}	8	5	84	95	76	97	
M1 ^c	10 kPa	27	2	93	82	50	98
	12 kPa (Youden)	16	6	79	90	59	96
	15 kPa (rule-out cut-off proposed by Baveno VI)	7	9	69	95	74	94
	20 kPa	3	12	59	98	85	93
	25 kPa	1	13	55	99	94	92
	AST-adapted cut-off values according to Mueller et al ¹⁰	27	2	93	83	51	98
	AST-/bilirubin-adapted cut-off values according to Nguyen-Khac et al ^{24 d}	13	1	95	87	58	99
M2 ^e	10 kPa	14	3	87	89	55	97
	12 kPa (Youden)	6	4	83	95	76	97
	15 kPa (rule-out cut-off proposed by Baveno VI)	5	7	7	96	76	95
	20 kPa	2	9	61	98	88	93
	25 kPa	2	15	35	98	80	89
	AST-adapted cut-off values according to Mueller et al ¹⁰	15	3	87	88	57	97

NOTE. The formula proposed by Mueller et al¹⁷ and the algorithm proposed by Nguyen-Khac et al¹⁸ were used to correct LSM in our population. AST, aspartate aminotransferase; cACLD, compensated advanced liver disease; FN, false negative; FP, false positive; LSM, liver stiffness measurement; M0, inclusion; M1, 1-month follow-up evaluation; M2, 2-month follow-up evaluation; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

^aPopulation restrained to patients with valid AST and bilirubin the day of Fibroscan and biopsy realization (n = 178).

^bPopulation restrained to patients with valid AST the day of Fibroscan and biopsy realization (n = 256).

^cPopulation restrained to patients with valid AST and Fibroscan at M1 (n = 183).

^dPopulation restrained to patients with valid AST, bilirubin, and Fibroscan at M1 (n = 120).

^ePopulation restrained to patients with valid AST and Fibroscan at M2 (n = 150).

Supplementary Table 4. Diagnostic Accuracy of Transient Elastography for Cirrhosis at M0, M1, and M2, With Per-Protocol Analysis

	Cut-off	Sensitivity	Specificity	NPV	PPV	AUROC
M0	14 kPa ^a	96 [87–104]	88 [84.0–92]	99 [99–100]	44 [30–58]	
M0	14.8 kPa ^b	96 [87–104]	89 [85–93]	99 [98–100]	46 [32–60]	0.94 [0.90–0.98]
M0	65 kPa ^c	26 [8–44]	99 [98–100]	93 [90–96]	75 [45–105]	
M1	14 kPa ^a	72 [52–93]	90 [85–94]	97 [94–100]	42 [25–59]	
M1	14.8 kPa ^b	67 [46–88]	92 [88–96]	93 [93–99]	46 [27–65]	0.93 [0.86–0.99]
M1	65 kPa ^c	22 [3–41]	99 [98–101]	92 [89–96]	80 [45–115]	
M2	14 kPa ^a	80 [55–105]	89 [84–94]	98 [96–101]	33 [15–52]	
M2	14.8 kPa ^b	80 [55–105]	91 [86–95]	99 [97–101]	36 [16–56]	0.86 [0.67–1.00]
M2	65 kPa ^c	30 [1.6–58]	98 [96–100]	95 [92–99]	50 [10–90]	

NOTE. Data are presented as values and 95% CIs. TE showed excellent accuracy for cirrhosis diagnosis. A cut-off value of 14 kPa ruled out cirrhosis with an NPV of 99.5. It was difficult to find a useful cut-off value to rule in cirrhosis because of the large overlap of liver stiffness between F3 and F4 cases. Using the Youden index, the optimal cut-off value for distinguishing cirrhosis was 14.8 kPa, with a very good NPV but a poor PPV.

AUROC, area under the receiver operating characteristics curve M0, inclusion; M1, 1-month follow-up evaluation; M2, 2-month follow-up evaluation; NPV, negative predictive value; PPV, positive predictive value.

^aOptimal cut-off value to rule out cirrhosis based on inclusion.

^bOptimal cut-off value selected using the Youden index based on inclusion.

^cOptimal cut-off value to rule in cirrhosis based on inclusion.