

# Noninvasive diagnosis and prognosis of liver cirrhosis: a comparison of biological scores, elastometry, and metabolic liver function tests

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**Background** Recently, noninvasive methods for the diagnosis of liver cirrhosis have been extensively developed. We assessed the accuracy of liver stiffness measurement, aspartate aminotransferase-to-platelet ratio index (APRI) score, <sup>13</sup>C-aminopyrine breath test, and indocyanine green plasma clearance for the diagnosis of cirrhosis in patients with chronic liver disease and for the prediction of severe complications in cirrhotic patients.

**Methods** A total of 296 consecutive patients with chronic liver diseases of various causes were studied. Diagnostic accuracy was assessed by receiver operating characteristic curve analysis.

**Results** Areas under the receiver operating characteristic curve for the diagnosis of cirrhosis were (95% confidence interval) 0.93 (0.90–0.96) for liver stiffness measurement, 0.82 (0.77–0.87) for <sup>13</sup>C-aminopyrine breath test, and 0.81 (0.76–0.86) for APRI score. Using cutoff values of 14.1 kPa for liver stiffness, 4.15% dose/h for <sup>13</sup>C-aminopyrine breath test, and 1 for APRI score, the positive predictive value was approximately 90% for the diagnosis of cirrhosis. Using cutoff values of 65.2 kPa for liver stiffness, 1.17% dose/h for <sup>13</sup>C-aminopyrine breath test, 2.82 for APRI score, and 51.1% for indocyanine green plasma clearance, the positive

predictive value was approximately 80% for the occurrence of severe complications among cirrhotic patients.

**Conclusion** Liver stiffness measurement, <sup>13</sup>C-aminopyrine breath test, indocyanine green plasma clearance, and APRI score are reliable noninvasive methods for the diagnosis of cirrhosis in patients with chronic liver diseases of various causes, and are also prognostic indicators for the occurrence of severe complications in cirrhotic patients. *Eur J Gastroenterol Hepatol* 22:532–540 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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## Introduction

The prognosis and management of all chronic liver diseases strongly depend on the degree of liver fibrosis, and particularly on the existence of cirrhosis or not [1]. Until recently, liver biopsy (LB) was considered as the best way for this purpose, and remains the gold standard in assessing liver histology [1]. Although percutaneous LB is a safe procedure, it is costly, and does carry a small risk for complication, sometimes life-threatening [2]. In addition, LB is invasive and painful, resulting in its poor acceptability from both patients and physicians, which can lead to treatment delay [3]. Ultimately, the accuracy of LB examination has also been questioned because of sampling errors and interobserver and intraobserver variabilities that may lead to understaging or overstaging of liver fibrosis [4–6].

Hence, there is a need to develop accurate and reliable noninvasive methods to assess the severity of hepatic

fibrosis. Transient elastography [Fibroscan (FS), Echosens, Paris, France] is a rapid, noninvasive, and reproducible method for measuring liver stiffness. Many recent reports have shown that liver stiffness measurement (LSM) is a reproducible and reliable noninvasive method for the assessment of liver fibrosis and therefore cirrhosis, particularly in chronic hepatitis C patients [7–14], but few studies performed FS in patients with other chronic liver diseases [15–18]. Metabolic liver function tests, such as <sup>13</sup>C-aminopyrine breath test (ABT) and indocyanine green (ICG) plasma clearance, have been shown to highly correlate with Child–Pugh and Model for End-stage Liver Disease (MELD) scores in cirrhotic patients [19–21], but only few studies have been performed among patients with chronic liver diseases to evaluate their accuracy for the diagnosis of cirrhosis [22,23]. To our knowledge, only one study assessed the diagnostic accuracy of <sup>13</sup>C-aminopyrine using receiver operating characteristic (ROC) curves and proposed

cutoff levels [24]. The first aim of this study was to assess the diagnostic accuracy of FS, ABT, ICG, and aspartate aminotransferase-to-platelet ratio index (APRI), alone or in combination, for identifying patients with cirrhosis, in a large cohort of patients with chronic liver disease (CLD) of various causes. The second aim of the study was to assess the ability of these same tests to predict the occurrence of severe complications in the group of cirrhotic patients.

## Patients and methods

### Patients

The cohort study included 296 consecutive adult patients with CLD of various causes, who had undergone FS and metabolic liver function tests the same day in Edouard Herriot Hospital, Lyon, France, from January 2007 to June 2008. The cause of CLD was determined using standard diagnostic criteria. Hepatitis B (HBV) or C (HCV) virus infection was diagnosed by serological detection of HBV surface antigens and HCV antibodies, respectively. Alcoholic liver disease was diagnosed in patients with consumption of at least 40 g alcohol daily for 5 years or more. Other diseases were diagnosed according to the current criteria. Cirrhosis was diagnosed according to the French Haute Autorité de Santé criteria. Patients had previously undergone LB, except in case of corroborating epidemiological, clinical, biological, and radiological data, such as noncompensated chronic liver disease (existence of ascites, variceal bleeding, jaundice, hepatic encephalopathy) and/or biological (hypoalbuminemia, hyperbilirubinemia, thrombocytopenia, low prothrombin time) and radiological (liver dysmorphism, portal hypertension, splenomegaly) abnormalities in patients with well-known chronic liver disease (especially in case of alcoholic liver disease).

Metabolic liver function tests and elastometry were performed by nurses who were blinded to patients' previous LB results.

### Liver stiffness

LSM was performed using FS (Echosens, Paris, France), a medical device based on elastometry. Briefly, this system is equipped with a probe consisting of an ultrasonic transducer mounted on the axis of a vibrator. A vibration is transmitted from the vibrator to the tissue by the transducer itself, which induces an elastic shear wave that propagates through the tissue. In the meantime, pulse-echo ultrasonic acquisitions are performed to follow the propagation of the shear wave and measure its velocity, which is directly related to tissue stiffness; the stiffer the tissue, the faster the shear wave propagates. The results are expressed as kilopascal (kPa). Measurements were performed in the right lobe of the liver through intercostal spaces, on patients lying in dorsal decubitus with the right arm in maximal abduction. The measurement

depth was between 25 and 65 mm below the skin surface. Only procedures with 10 validated measurements and a success rate of at least 60% (ratio of the number of successful acquisitions over the total number of acquisitions) were considered reliable. The median value of the successful acquisitions was kept as representative of the liver stiffness and was called LSM.

### Clinical and biochemical parameters

The body mass index and the existence of ascites or hepatic encephalopathy at the date of the FS were noted down using electronic medical record and hard copy clinical charts. In cirrhotic patients, the occurrence of severe complications, including variceal bleeding, ascites, liver transplantation, and death related to end-stage liver disease was also noted down during follow-up.

Laboratory routine tests were performed in Edouard Herriot Hospital within 1 month from the date of FS, ABT, or ICG. The following biochemical markers were determined: prothrombin rate, international normalized ratio, albumin, bilirubin, aspartate aminotransferase, serum creatinine, and platelet count. Child-Turcotte-Pugh score [25] and MELD score [26] were referenced for the patients with cirrhosis. APRI score was calculated as originally described [27].

### Metabolic liver function tests

#### <sup>13</sup>C-aminopyrine breath test

ABT measures the metabolic capacity of the liver cells in terms of the microsomal enzymatic activity. The test is based on the demethylation and subsequent metabolism of radioactively labelled <sup>13</sup>C-aminopyrine by amino-*N*-demethylase, a cytochrome-P450-dependent microsomal hepatic enzyme. The methylation rate is measured indirectly by means of the exhaled <sup>13</sup>CO<sub>2</sub> as end product. Patients underwent ABT the same day as FS, as follows: a basal breath sample was collected after an overnight fast (at least 12 h); then 2 mg/kg of <sup>13</sup>C-aminopyrine (N,N-dimethyl-<sup>13</sup>C-aminopyrine, Euriso-Top Carbon Breath Tests Substrates, St. Aubin, France) were dissolved in 200 ml of water and administered orally. Breath samples were collected every 15 min for 1 h after <sup>13</sup>C-aminopyrine administration and were obtained as follows: patients were asked to exhale for 10 s through a small plastic tube directly into a vial that was sealed immediately. The ratio of <sup>13</sup>CO<sub>2</sub> to <sup>12</sup>CO<sub>2</sub> was determined for each sample with an isotope radio mass spectrometer and the excess <sup>13</sup>CO<sub>2</sub> was calculated by the increase in the isotope ratio. The production of CO<sub>2</sub> was estimated on the basis of the body surface area, assuming a CO<sub>2</sub> production of 5 mmol min/m<sup>2</sup>. Patients were at rest for 15 min before the test, and remained at rest and fasted during the whole test to minimize their total CO<sub>2</sub> production and to avoid the influence of food intake. The results were expressed as the percentage of the administered dose of <sup>13</sup>C recovered per hour (% dose/h).

### Indocyanine green plasma clearance

After intravenous injection, ICG is nearly exclusively eliminated by the liver into the bile and does not undergo enterohepatic recirculation. Physiologically, it appears unconjugated in the bile about 8 min after injection. Its removal from the blood depends on liver blood flow and biliary excretion. Patients underwent ICG the same day as FS, as follows: 0.25 mg/kg of ICG were injected intravenously through a peripheral vein. Blood samples were collected at time 0 (t0) and 15 min (t15), and concentration of ICG was measured photometrically at 806 nm using a spectrophotometer. The results were expressed as the percentage of the following ratio: t15 concentration to t0 concentration.

### Statistical analysis

Quantitative variables were described using mean, range, and standard deviation (SD). Qualitative values were tabulated and percentages were calculated. Pearson's coefficients of correlation ( $r$ ) between scores and tests were calculated and their relationships were grafted on log scales. The concordance statistic was calculated for the scores and tests, when used for the diagnosis of cirrhosis and when used for the prediction of severe complications in the group of cirrhotic patients. The concordance c-statistic is identical to the area under the ROC curve. The c-statistic varies between 0.5 and 1.0 for sensible models; the higher the better. Only the results of c-statistics above 0.5 were considered as statistically significant. Confidence intervals of the areas under ROC curves were calculated using the method of DeLong and DeLong [28], and statistical comparisons between these areas were made using the method of Zhou and Gatsonis [29]. Optimal cutoff values for scores and tests were chosen either to obtain a 95% sensitivity (Se), to maximize the Youden index (Se + Sp - 1), or to obtain a 95% specificity (Sp) according to the diagnostic question. When using a combination of two tests, the resulting test was defined positive when the two tests were simultaneously positives. Cutoff values retained in this case were those that led to the best Youden index for the combined test. Statistical tests were considered to be significant when  $P$  value was less than 0.05. All analyses were performed using SPSS 2004 software (Statistical Systems, Kayville, Utah, USA).

## Results

### Patients

A total of 296 patients were included and analyzed. Their characteristics at the time of LSM and metabolic liver function tests are summarized in Table 1. There were 192 males and 104 females. Etiologies of chronic liver disease are as follows: HCV ( $n = 87$ ) or HBV ( $n = 40$ ) infection, alcoholic liver disease ( $n = 83$ ), nonalcoholic steatohepatitis ( $n = 26$ ), cholestatic liver disease (primary biliary cirrhosis and primary sclerosing cholangitis,  $n = 21$ ),

Table 1 Main characteristics of the 296 patients of the study

	Cirrhosis ( $n = 142$ )	No cirrhosis ( $n = 154$ )	$P$ value
Male sex ( $n$ )	105	87	0.002
Age (mean $\pm$ SD, years)	57 $\pm$ 16	46 $\pm$ 14	<0.0001
Body mass index (mean $\pm$ SD)	26 $\pm$ 6	24 $\pm$ 4	0.002
Causes of liver disease ( $n$ )			
Hepatitis C virus	29	58	
Alcohol (including active drinkers)	72 (12)	11 (9)	
Hepatitis B virus	4	36	
NASH	12	14	
PBC or PSC	9	12	
Other	16	23	
Platelet count (mean $\pm$ SD, $\times 10^3/\text{mm}^3$ )	147 $\pm$ 91	234 $\pm$ 75	<0.0001
Prothrombin time (mean $\pm$ SD, %)	69 $\pm$ 19	92 $\pm$ 12	<0.0001
INR	1.33 $\pm$ 0.31	1.05 $\pm$ 0.13	<0.0001
Creatinin (mean $\pm$ SD, $\mu\text{mol/l}$ )	82 $\pm$ 83	96 $\pm$ 99	0.264
Albumin (mean $\pm$ SD, g/l)	37.3 $\pm$ 6	41.9 $\pm$ 5.4	<0.0001
Bilirubin (mean $\pm$ SD, $\mu\text{mol/l}$ )	33 $\pm$ 50	13 $\pm$ 7	<0.0001
AST (mean $\pm$ SD, IU/l)	61 $\pm$ 42	41 $\pm$ 24	<0.0001
Liver stiffness measurement (mean $\pm$ SD, kPa)	33.8 $\pm$ 23	7 $\pm$ 4	<0.0001
ABT (mean $\pm$ SD, % dose/h)	5.41 $\pm$ 4.54	11.36 $\pm$ 5.39	<0.0001
ICG (mean $\pm$ SD, % t15/t0)	27.9 $\pm$ 19.1	12.7 $\pm$ 16	0.001

ABT,  $^{13}\text{C}$ -aminopyrine breath; AST, aspartate aminotransferase; ICG, indocyanine green; INR, index normalized ratio; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

Wilson's disease ( $n = 13$ ), hemochromatosis ( $n = 4$ ), or miscellaneous ( $n = 22$ ). Among the 83 patients with chronic alcoholic liver disease, 21 patients had self-confessed or suspected active excessive alcohol consumption. From the entire cohort, 142 patients had cirrhosis at the time of LSM and metabolic liver function tests, of mean age 57  $\pm$  14-years-old. For these cirrhotic patients, Child-Pugh score was A in 89 (62.7%) cases, B in 43 (30.3%) cases, C in 10 (7.0%) cases; the median MELD score was 11 (SD=5, range, 6–26).

### Accuracy of APRI score, elastometry, and metabolic liver function tests for the diagnosis of cirrhosis

#### Aspartate aminotransferase-to-platelet ratio index score

APRI score was calculated in 120 noncirrhotic and 139 cirrhotic patients. Values ranged from 0 to 10.02. The median value of APRI score significantly differed from 1.33 (range, 0.12–10.02) in cirrhotic patients to 0.43 (range, 0–1.68) in noncirrhotic patients ( $P < 0.0001$ ). APRI score poorly correlated with ICG, LSM, and ABT ( $r = 0.495$ ; 0.407; 0.285, respectively,  $P < 0.001$ ) in the entire cohort. Similarly, APRI score poorly correlated with ICG, Child-Pugh score, MELD score, LSM, and ABT ( $r = 0.479$ ; 0.313; 0.297; 0.228; 0.170, respectively,  $P < 0.05$ ) in patients with cirrhosis. APRI score was significantly higher in patients with active alcohol consumption (mean  $\pm$  SD, 1.84  $\pm$  0.43) than in those without (mean  $\pm$  SD, 0.81  $\pm$  0.09) ( $P = 0.03$ ). Figure 1 shows the diagnostic value (ROC curve) of APRI score for the diagnosis of cirrhosis. The corresponding area under the ROC [95% confidence interval (CI)] was 0.81 (0.76–0.86). Three optimal cutoff values were

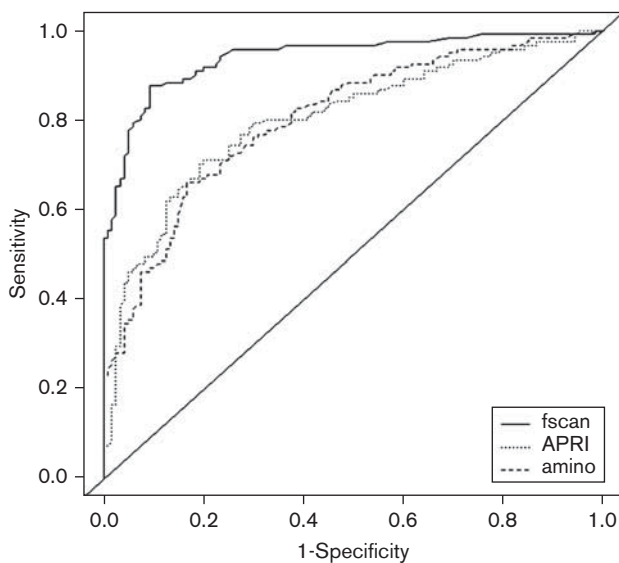
defined: cutoff value with 95% Se, cutoff value that maximized the Youden index, and cutoff value with 95% Sp. These optimal cutoffs were 0.27, 0.59, and 1, respectively (Table 2).

**Liver stiffness**

LSM was performed in all patients, and 278 were considered reliable according to our predefined criteria (see Patients and methods). The 18 patients with unreliable measurements were all cirrhotic; their median body mass index was 31 kg/m<sup>2</sup> (range, 18–40), and the existence of ascites was noticed in two patients. LSM values ranged from 2.5 to 75 kPa. The mean success rate was 95 ± 9% (range, 60–100%).

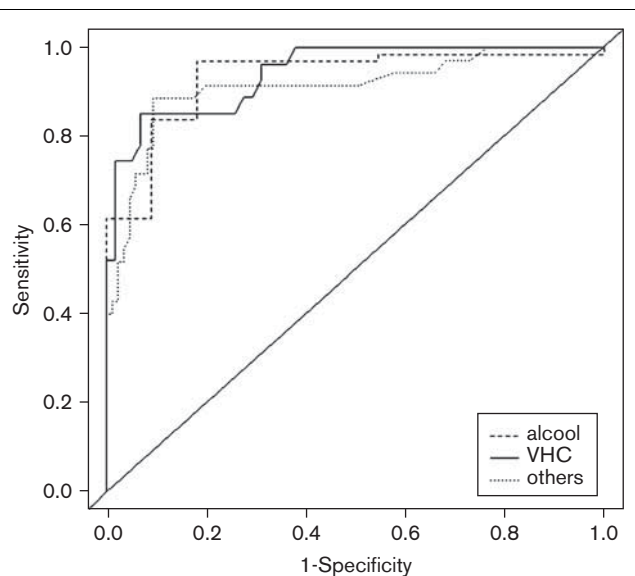
In cirrhotic patients with alcoholic liver disease, median liver stiffness was 39.8, and 27.8 kPa in others ( $P = 0.004$ ). Median liver stiffness was 33.8 kPa (range, 2.9–75) in cirrhotic patients, and 7 kPa (range, 2.5–26) in patients without cirrhosis. LSM was significantly different between cirrhotic and noncirrhotic patients ( $P < 0.0001$ ). Liver stiffness correlated with ICG, ABT, and APRI score ( $r = 0.567$ ; 0.488; 0.407, respectively,  $P < 0.001$ ) in all the 296 patients. Liver stiffness correlated with ICG, Child–Pugh score, ABT, MELD score, and APRI score ( $r = 0.529$ ; 0.458; 0.385; 0.287; 0.228, respectively,  $P < 0.05$ ) in patients with cirrhosis. Figure 1 shows the diagnostic value (ROC curve) of LSM for the diagnosis of cirrhosis. The corresponding area

**Fig. 1**



Receiver operating characteristic curves of liver stiffness measurement (LSM) (278 patients), aspartate aminotransferase-to-platelet ratio index (APRI) score (259 patients), and <sup>13</sup>C-aminopyrine breath test (ABT) (296 patients) accuracy for the diagnosis of cirrhosis. fscan: LSM; amino: ABT.

**Fig. 2**



Receiver operating characteristic curves of liver stiffness measurement accuracy for the diagnosis of cirrhosis in 85 patients with chronic hepatitis C (VHC), in 73 patients with alcoholic liver disease (alcohol), and in 120 patients with other pooled causes of chronic liver disease.

**Table 2 Diagnostic indices for diagnosis of cirrhosis according to liver stiffness (278 patients), APRI score (259 patients), and ABT cutoff value (296 patients)**

	Cutoff	Se	95% CI		Sp	95% CI		PPV	95% CI		NPV	95% CI		Youden
LSM	7.4 <sup>a</sup>	0.95	0.91	0.98	0.71	0.64	0.79	0.73	0.66	0.80	0.95	0.91	0.98	0.76
	10.5 <sup>b</sup>	0.87	0.81	0.93	0.89	0.84	0.94	0.86	0.80	0.92	0.90	0.84	0.94	
	14.1 <sup>c</sup>	0.71	0.63	0.79	0.95	0.91	0.98	0.92	0.85	0.97	0.80	0.74	0.86	
APRI	0.27 <sup>a</sup>	0.95	0.91	0.99	0.33	0.24	0.41	0.62	0.55	0.69	0.85	0.74	0.93	0.50
	0.59 <sup>b</sup>	0.67	0.59	0.75	0.83	0.77	0.90	0.82	0.75	0.89	0.68	0.61	0.76	
	1 <sup>c</sup>	0.40	0.32	0.47	0.95	0.91	0.98	0.90	0.82	0.97	0.58	0.51	0.65	
ABT	14.57 <sup>a</sup>	0.95	0.92	0.99	0.25	0.18	0.32	0.54	0.47	0.60	0.84	0.73	0.93	0.54
	7.06 <sup>b</sup>	0.73	0.65	0.80	0.81	0.74	0.86	0.78	0.70	0.84	0.77	0.70	0.83	
	4.15 <sup>c</sup>	0.49	0.40	0.57	0.95	0.91	0.98	0.90	0.82	0.96	0.67	0.60	0.73	

ABT, <sup>13</sup>C-aminopyrine breath; APRI, aspartate aminotransferase-to-platelet ratio index; CI, confidence interval; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

<sup>a</sup>Se=95%.

<sup>b</sup>Maximum Youden index.

<sup>c</sup>Sp=95%.

under the ROC (95% CI) was 0.93 (0.90–0.96). The three optimal cutoff values were 7.4, 10.5, and 14.1 kPa (Table 2).

Figure 2 illustrates the diagnostic value (ROC curves) of LSM for the diagnosis of cirrhosis according to the cause of CLD. In patients with alcoholic liver disease, the corresponding area under the ROC (95% CI) was 0.93 (0.85–1.00). The three optimal cutoff values were 7.7, 7.4, and 11.4 kPa. In patients with chronic hepatitis C, the corresponding area under the ROC (95% CI) was 0.94 (0.89–0.99). The three optimal cutoff values were 7.5, 12.6, and 14.3 kPa. In patients with other causes of CLD, the corresponding area under the ROC (95% CI) was 0.91 (0.85–0.98). The three optimal cutoff values were 5.4, 10.5, and 12.6 kPa (Table 3).

**<sup>13</sup>C-aminopyrine breath test**

ABT was performed in all the 296 patients. Values ranged from 0.1 to 35.8% dose/h. The median % dose/h was 11.36 (range, 0.86–35.8) in the noncirrhotic patients and 5.41 (range, 0.17–21.42) in the cirrhotic patients. The percentage of the administered dose of <sup>13</sup>C recovered per hour (% dose/h) was significantly different between cirrhotic and noncirrhotic patients ( $P < 0.0001$ ), and correlated with ICG, LSM, and APRI score ( $r = 0.521$ ; 0.488; 0.285, respectively,  $P < 0.001$ ) in all the 296 patients. ABT significantly correlated with ICG, Child–Pugh score, MELD score, LSM and APRI score ( $r = 0.552$ ; 0.479; 0.430; 0.385; 0.170, respectively,  $P < 0.05$ ) in patients with cirrhosis. Figure 1 shows the diagnostic value (ROC curve) of ABT for the diagnosis of cirrhosis.

The corresponding area under the ROC (95% CI) was 0.82 (0.77–0.87). The three optimal cutoff values were 14.57, 7.06, and 4.15% dose/h (Table 2).

**Indocyanine green plasma clearance**

ICG plasma clearance was measured in 124 cirrhotic and 21 noncirrhotic patients. Values ranged from 0.5 to 78.8%. The ICG plasma clearance was significantly different between cirrhotic [27.9% (range, 0.6–78.8)] and noncirrhotic [12.7% (range, 0.5–64)] patients ( $P = 0.001$ ), and significantly correlated with LSM, ABT, and APRI score ( $r = 0.567$ ; 0.521; 0.495, respectively,  $P < 0.001$ ) in all the 296 patients. ICG significantly correlated with Child–Pugh score, MELD score, ABT, LSM, and APRI score ( $r = 0.660$ ; 0.556; 0.552; 0.529; 0.479, respectively,  $P < 0.001$ ) in patients with cirrhosis.

It was impossible to build ROC curve of ICG for the diagnosis of cirrhosis because of a lack of noncirrhotic patients who had undergone this test.

**Combination of LSM, APRI score, and ABT**

The diagnostic value of LSM was significantly higher than the diagnostic value of ABT ( $P < 0.0001$ ) and APRI score ( $P < 0.0001$ ). Using a combination of LSM and ABT, Se and Sp were not higher and the optimal cutoff values remained the same. Using a combination of LSM and APRI score, the best cutoff values that maximize the Youden index were 10.5 kPa for LSM and 0.24 for APRI score. Using a combination of ABT and APRI score, these values were 8.60% dose/h for ABT and 0.29 for APRI score (Table 4).

**Table 3 Diagnostic indices for diagnosis of cirrhosis according to liver stiffness cutoff value in 73 patients with alcoholic liver disease, in 85 patients with chronic hepatitis C, and in 120 patients with other causes of chronic liver disease**

	Cutoff	Se	95% CI		Sp	95% CI		PPV	95% CI		NPV	95% CI		Youden
Alcohol	7.7 <sup>a</sup>	0.95	0.89	1.00	0.82	0.55	1.00	0.97	0.92	1.00	0.75	0.50	1.00	0.79
	7.4 <sup>b</sup>	0.97	0.92	1.00	0.82	0.55	1.00	0.97	0.92	1.00	0.82	0.55	1.00	
	11.4 <sup>c</sup>	0.84	0.74	0.92	0.91	0.73	1.00	0.98	0.94	1.00	0.50	0.30	0.70	
HCV	7.5 <sup>a</sup>	0.96	0.89	1.00	0.69	0.57	0.81	0.59	0.45	0.73	0.98	0.93	1.00	0.78
	12.6 <sup>b</sup>	0.85	0.70	0.96	0.93	0.86	0.98	0.85	0.70	0.96	0.93	0.86	0.98	
	14.3 <sup>c</sup>	0.74	0.56	0.89	0.95	0.88	1.00	0.87	0.74	1.00	0.89	0.81	0.95	
Other	5.4 <sup>a</sup>	0.94	0.86	1.00	0.42	0.32	0.53	0.40	0.29	0.51	0.95	0.87	1.00	0.79
	10.5 <sup>b</sup>	0.89	0.77	0.97	0.91	0.84	0.96	0.79	0.67	0.92	0.95	0.90	0.99	
	12.6 <sup>c</sup>	0.66	0.49	0.80	0.95	0.91	0.99	0.85	0.70	0.96	0.87	0.80	0.94	

CI, confidence interval; HCV, Hepatitis C virus; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

<sup>a</sup>Se = 95%.

<sup>b</sup>Maximum Youden index.

<sup>c</sup>Sp = 95%.

**Table 4 Diagnostic indices for diagnosis of cirrhosis according to a combination of LSM and ABT score, LSM and APRI score, and ABT and APRI score**

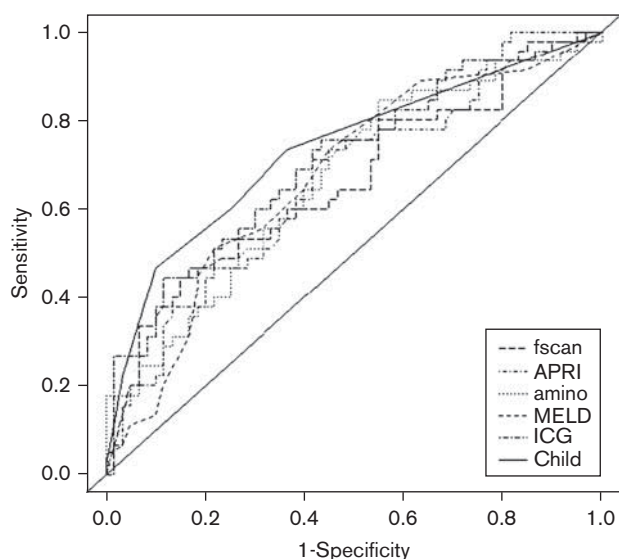
	Se	95% CI		Sp	95% CI		PPV	95% CI		NVP	95% CI		Youden
LSM cutoff 10.50	0.87	0.81	0.93	0.89	0.84	0.94	0.86	0.80	0.92	0.90	0.84	0.94	0.76
ABT cutoff 21.42													
LSM cutoff 10.50	0.86	0.79	0.92	0.93	0.88	0.97	0.92	0.87	0.96	0.87	0.80	0.92	0.78
APRI cutoff 0.24													
ABT cutoff 8.60	0.75	0.67	0.82	0.82	0.76	0.88	0.78	0.70	0.85	0.80	0.74	0.86	0.57
APRI cutoff 0.29													

ABT, <sup>13</sup>C-aminopyrine breath; APRI, aspartate aminotransferase-to-platelet ratio index; CI, confidence interval; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

**Prognostic value of elastometry, Child–Pugh and MELD scores, and metabolic liver function tests in cirrhotic patients**

From the 142 patients with cirrhosis, 56 had severe complications within the 8 months (range, 8–26) of minimum follow-up: 26 underwent liver transplantation, 16 had ascites, 11 died because of end-stage liver disease, two had severe variceal bleeding, and one had jaundice.

**Fig. 3**



Receiver operating characteristic curves of Model for End-stage Liver Disease (MELD) score, Child–Pugh score, liver stiffness measurement (LSM), indocyanine green (ICG), <sup>13</sup>C-aminopyrine breath test (ABT), and aspartate aminotransferase-to-platelet ratio index (APRI) score accuracy for the occurrence of severe complications in 138 patients with cirrhosis. fscan: LSM; amino: ABT.

Figure 3 shows the diagnostic value (ROC curves) of Child–Pugh score, ICG, MELD score, LSM, ABT, and APRI score for the occurrence of severe complications related to liver cirrhosis. The corresponding area under the ROC (95% CI) values were 0.76 (0.69–0.84), 0.73 (0.63–0.82), 0.72 (0.63–0.81), 0.69 (0.60–0.79), 0.69 (0.60–0.78), and 0.67 (0.58–0.76), respectively.

Three optimal cutoff values were defined: cutoff value with 95% Se, cutoff value that maximizes the Youden index, and cutoff value with 95% Sp. Concerning Child–Pugh score, the three optimal cutoff values were, respectively, 5, 6, and 9. About ICG, the optimal cutoff values were, respectively, 10.4, 19.6, and 51.1%. Regarding MELD score, the cutoff values were, respectively, 7, 13, and 19. About LSM, the cutoff values were, respectively, 9.3, 49.7, and 65.2 kPa. Concerning ABT, the cutoff values were, respectively, 9.71, 2.23, and 1.17% dose/h. Regarding APRI score, the optimal cutoff values were, respectively, 0.35, 0.57, and 2.82 (Table 5).

After having combined those indicators, the two best combinations that maximize the Youden index were the following: Child–Pugh score=6 associated with APRI score=0.35 and Child–Pugh score=6 associated with ABT=9.42% dose/h (Table 6).

There was no significant difference in prognosis between patients with persistent alcohol consumption and others (*P* = 0.73).

**Discussion**

Recently, noninvasive methods for the diagnosis of liver cirrhosis have been largely developed, in addition to firm liver palpation in the epigastrium or sonographic measurements of the spleen, which showed good diagnostic

**Table 5 Diagnostic indices for occurrence of severe complications according to Child–Pugh score, ICG, MELD score, liver stiffness, ABT, and APRI score in 138 patients with cirrhosis**

	Cutoff	Se	95% CI	Sp	95% CI	PPV	95% CI	NPV	95% CI	Youden
Child–Pugh	5 <sup>a</sup>	1.00	1.00	0.00	0.00	0.40	0.32	1.00	1.00	0.44
	6 <sup>b</sup>	0.77	0.66	0.88	0.67	0.57	0.77	0.81	0.71	
	9 <sup>c</sup>	0.23	0.13	0.34	0.96	0.92	1.00	0.65	0.57	
ICG	10.4 <sup>a</sup>	0.94	0.87	1.00	0.28	0.18	0.39	0.49	0.39	0.36
	19.6 <sup>b</sup>	0.79	0.67	0.88	0.57	0.46	0.68	0.57	0.46	
	51.1 <sup>c</sup>	0.27	0.15	0.38	0.94	0.89	0.99	0.78	0.56	
MELD	7 <sup>a</sup>	0.93	0.86	0.98	0.16	0.08	0.24	0.43	0.34	0.35
	13 <sup>b</sup>	0.54	0.41	0.66	0.82	0.73	0.90	0.67	0.53	
	19 <sup>c</sup>	0.18	0.09	0.29	0.95	0.90	0.99	0.71	0.50	
LSM	9.3 <sup>a</sup>	0.96	0.90	1.00	0.16	0.08	0.25	0.43	0.34	0.34
	49.7 <sup>b</sup>	0.47	0.33	0.61	0.87	0.79	0.93	0.70	0.55	
	65.2 <sup>c</sup>	0.35	0.22	0.49	0.95	0.89	0.99	0.81	0.62	
ABT	9.71 <sup>a</sup>	0.95	0.88	1.00	0.21	0.13	0.30	0.44	0.35	0.34
	2.23 <sup>b</sup>	0.52	0.39	0.64	0.83	0.74	0.91	0.66	0.52	
	1.17 <sup>c</sup>	0.21	0.11	0.32	0.95	0.91	0.99	0.75	0.50	
APRI	0.35 <sup>a</sup>	0.95	0.88	1.00	0.16	0.08	0.24	0.43	0.34	0.27
	0.57 <sup>b</sup>	0.84	0.73	0.93	0.43	0.33	0.54	0.50	0.40	
	2.82 <sup>c</sup>	0.21	0.11	0.32	0.95	0.90	0.99	0.75	0.50	

ABT, <sup>13</sup>C-aminopyrine breath; APRI, aspartate aminotransferase-to-platelet ratio index; CI, confidence interval; ICG, indocyanine green; LSM, liver stiffness measurement; MELD, Model for End-stage Liver Disease; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

<sup>a</sup>Se=95%.

<sup>b</sup>Maximum Youden index.

<sup>c</sup>Sp=95%.

**Table 6** Diagnostic indices for occurrence of severe complications according to a combination of C–P score and APRI score, and C–P score and ABT

		Se	95% CI		Sp	95% CI		PPV	95% CI		NPV	95% CI		Youden
C-P cutoff	APRI cutoff													
6	0.35	0.75	0.63	0.86	0.72	0.63	0.82	0.65	0.52	0.75	0.81	0.72	0.89	0.47
C-P cutoff	ABT cutoff													
6	9.42	0.75	0.63	0.86	0.70	0.60	0.80	0.63	0.51	0.75	0.81	0.71	0.89	0.45

ABT, <sup>13</sup>C-aminopyrine breath; APRI, aspartate aminotransferase-to-platelet ratio index; CI, confidence interval; C–P, Child–Pugh score; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

performances in previous studies [30–33]. In this study including 296 patients, we assessed the accuracy of LSM, APRI score, ABT test, and ICG plasma clearance, for the diagnosis of cirrhosis and the prediction of severe complications in cirrhotic patients. Our results suggest that both LSMs, APRI score, and metabolic liver function tests, are accurate methods for the diagnosis and/or the exclusion of cirrhosis, whatever the cause of CLD. Diagnostic accuracy of LSM was significantly higher than APRI score and ABT, and a cutoff of 14.1 kPa would identify cirrhosis with a positive predictive value of 92% (and a negative predictive value of 80%). Our study also suggests that these tools are relevant to predict severe complications among patients with cirrhosis.

The results of this study conducted in a large cohort of patients with CLD of various causes confirm that transient elastography is a very efficient technique for the diagnosis of cirrhosis, whatever the cause of CLD. Using a cutoff value of 10.5 kPa, negative and positive predictive values were 90 and 86%, respectively. With a cutoff value of 7.4 kPa, negative predictive value was 95% (and positive predictive value was 73%), and with a cutoff value of 14.1 kPa, positive predictive value was 92% (and negative predictive value was 80%). In clinical daily practice, such results could be of major relevance, both for excluding and/or identifying cirrhosis in patients with CLD of various causes. In our study, cutoff values of LSM for the diagnosis of cirrhosis are consistent with those previously reported: cutoff values ranging from 10.3 to 17.6 kPa [7–18,34]. In 1007 patients with CLD of all causes, Ganne-Carrié *et al.* [17] reported a cutoff value of 14.6 kPa for the diagnosis of cirrhosis, with a specificity of 95%. In our study, the cutoff with a specificity of 95% was 14.1 kPa, which is similar. The cutoff value that maximizes the Youden index was 11.7 kPa in their study, and 10.5 kPa in ours, which is also quite similar. In our patients with chronic hepatitis C, the optimal cutoff value of 12.6 kPa is similar to the cutoff value reported by Castera *et al.* [13] in 183 patients. The cutoff values of elastometry for the diagnostic of cirrhosis in patients with alcoholic liver disease were lower than in patients with chronic hepatitis C, in opposition to previous reports [15,17]. In our cohort, the lack of alcoholic noncirrhotic patients can explain this finding, according to the fact that median value for LSM in cirrhotic patients with alcoholic liver disease was higher than in other patients.

In our study, the diagnostic accuracy of APRI score, a very simple index, was good, as a score less than 0.27 could exclude cirrhosis with a negative predictive value of 85% (and a positive predictive value of 62%), and a score over 1 could assess it with a predictive positive value of 90% (and a negative predictive value of 58%). These cutoff values of APRI score for the diagnosis of cirrhosis were lower than those reported in previous studies, in which a cutoff value of 2 identified cirrhosis with a specificity of 85% or more [27,35–37]. All previous reports included exclusively patients with chronic hepatitis C, in whom median aspartate aminotransferase levels were higher than in our patients, which probably led to higher cutoff values. In this study, among all the noninvasive tests, only APRI score was affected by active alcohol consumption, probably because of a more important liver inflammation and therefore a higher aspartate aminotransferase level in these patients. ABT could also be very relevant for diagnosing cirrhosis, as a cutoff of 14.57% dose/h could exclude cirrhosis with a negative predictive value of 84% (and a positive predictive value of 54%), and a cutoff of 4.15% dose/h could assess it with a predictive positive value of 90% (and a negative predictive value of 67%). Our results are comparable with those of Giannini *et al.* [23] who defined a cutoff value of 5.6% dose/h for diagnosing cirrhosis. Combining APRI score or ABT with LSM did not increase diagnostic value of LSM much, probably because the diagnostic performance of FS is self-sufficient.

The second part of our study was focused on the evaluation of prognosis in the group of cirrhotic patients. Our results show that Child–Pugh score and MELD score are good prognostic indicators for the occurrence of severe complications, especially when over 9 for Child–Pugh and 19 for MELD. We report here that LSM, ABT, ICG plasma clearance and APRI score could also predict severe complications among these patients when over 49.7 kPa for LSM, 2.82 for APRI, 51.1 for ICG, and less than 1.17% dose/h for ABT. The prognostic value of ABT was similar to Child–Pugh score in our study, as reported in previous studies [19,38,39], but cutoff values were not comparable because of technical discrepancies (results expressed in % dose/2 h). As described in a previous study [40], ICG is also a reliable tool for assessing prognosis in cirrhotic patients, and our cutoff points are comparable with those reported earlier; its prognostic value is

similar to Child–Pugh score. As shown in previous studies [19,26,41–43], Child–Pugh score and MELD score are closely related to the occurrence of severe complications among cirrhotic patients, and our cutoff values are slightly lower than those reported earlier. Degre *et al.* [19] determined their cutoffs points for predicting mortality, while we aimed at the occurrence of complications, which explains this deviation. Our results also show that both LSM and metabolic liver function tests seem to be more accurate for excluding the risk for severe complications rather than identifying it. Persistent alcohol consumption has been widely reported as a robust prognostic indicator [44]. In our cohort, there was no significant difference between active drinkers and others, probably because of a lack of patients with active alcohol consumption in our study.

In conclusion, all the noninvasive methods evaluated in this study, especially elastometry, are very efficient for the diagnosis of cirrhosis and are consistent predictors of complications in patients with cirrhosis. These diagnostic performances could even be refined if specific cutoff values of LSM according to the cause of LCD were used. As needle LB carries a risk of severe complications and implies well-known limitations such as false-negative results, our study strongly confirms that these noninvasive methods could be a reliable alternative to identify liver cirrhosis. However, there is a need for prospective studies to validate the diagnostic accuracy of these resources, especially for metabolic liver function tests, and to predict the complications of cirrhosis using FS so that a close and long follow-up could be performed.

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