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Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: Comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores☆

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***Background/Aims*: To assess prospectively the accuracy of transient elastography (TE, FibroScan) for the detection of cirrhosis and oesophageal varices (OV) in chronic hepatitis C (CHC), as compared with currently available non-invasive methods (AST/ALT ratio (AAR), APRI, prothrombin index (PI), platelet count (PC), FibroTest (FT) and Lok index).**

***Methods*: All tests were performed the day of liver biopsy (LB), taken as reference, in 298 consecutive CHC patients (cirrhosis: 70; Child-Pugh A: 70; OV: 25).**

***Results*: TE had the best diagnostic accuracy for detection of cirrhosis (AUROCs: TE 0.96 vs. FT 0.82, Lok and APRI 0.80, PC 0.79, PI 0.73, AAR 0.61, respectively; $p < 0.0001$). Overall, the percentage of saved LB was: TE (cut-off: 12.5 kPa) 90%, PC 82%, FT 79%, PI 77%, AAR 76%, APRI 70%, and Lok 45%, respectively. At a cut-off of 21.5 kPa, TE predicted the presence of OV with 76% sensitivity and 78% specificity and correctly classified 73% of patients vs. AAR 81%, Lok 77%, FT, PI 70%, PC 69%, and APRI 66%, respectively.**

***Conclusions*: TE is currently the most accurate non-invasive method for early detection of cirrhosis in CHC (cut-off: 12.5 kPa), as compared with other available methods, but cannot replace endoscopy for OV screening.**

***Keywords*: Cirrhosis; Oesophageal varices; Chronic hepatitis C; Non-invasive measurement**

1. Introduction

Hepatitis C virus infection, with an estimated prevalence of more than 170 million worldwide, is a major public health care problem [1]. Chronic hepatitis C (CHC) is the most common cause of cirrhosis and hepatocellular carcinoma (HCC), and the leading indication for liver transplantation in the United States and many Western countries. In patients with compensated cirrhosis, the annual incidence of decompensation, HCC, and death reach approximately 4%, 3% and 3%, respectively [2,3].

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Early diagnosis of cirrhosis is important in patients with CHC not only because it prompts screening for HCC and oesophageal varices (OV) but also because these patients have the most urgent need for antiviral therapy.

Liver biopsy (LB) is still considered as the gold standard and is recommended in the majority of patients with CHC for fibrosis evaluation and treatment indication [4]. However, its accuracy for the diagnosis of cirrhosis has been questioned, in relation to sampling errors and intra- and inter-observer variability that may lead to understaging [5–10]. In addition, LB is an invasive and painful procedure [11,12], with rare but potentially life-threatening complications [13]. Thus, many patients with CHC are reluctant to undergo LB and may be discouraged from starting therapy for this reason.

These limitations have prompted the search for new approaches [14–16]. Several laboratory tests and scores have been proposed for the non-invasive prediction of cirrhosis in patients with CHC. Among these, prothrombin index (PI) [17], platelet count [18], AST/ALT ratio (AAR) [19,20], and AST-to-platelet ratio index (APRI) [21] are based on routine laboratory parameters and therefore readily available in clinical practice. Among scores calculated from statistical models, the FibroTest (FT; Biopredictive, Paris, France) is based on a mathematical formula combining five variables (total bilirubin, γGT, haptoglobin, α2-macroglobulin and apoliprotein A1) [22] and the Lok index (combining platelet count, AST/ALT ratio, and international normalized ratio, INR) has been specifically designed for the diagnosis of HCV-cirrhosis [23]. The latest technological advance in the setting of non-invasive diagnosis is the measurement of liver stiffness by means of transient elastography, TE (FibroScan®, Echosens, Paris, France) [24,25]. TE has been recently demonstrated to be a reliable tool for assessing hepatic fibrosis in patients with CHC [26,27] with achieving the greatest accuracy for detecting severe fibrosis and cirrhosis [28,29]. In addition, in patients with cirrhosis, TE may be of prognostic value in predicting OV [30,31]. However, these different methods have not been compared against each other yet in a single and independent study.

The aim of this prospective study was to assess the accuracy of TE for the detection of cirrhosis and OV in patients with CHC, as compared with standard laboratory tests (AAR, APRI, PI and platelet count) and non-invasive scores (FT and Lok index).

2. Patients and methods

2.1. Patients

The study cohort included 333 consecutive patients with CHC who underwent percutaneous LB at our center between June 2003 and April 2007. CHC was defined by detectable serum anti-HCV antibodies and HCV RNA with chronically elevated serum alanine aminotransferase (ALT) levels. Exclusion criteria were: co-infection with hepatitis B virus, HBV ($n = 3$) or human immunodeficiency virus, HIV ($n = 4$), other causes of liver disease ($n = 6$), decompensated liver disease ($n = 7$), liver transplantation ($n = 2$), anticoagulant treatment ($n = 1$), inadequate LB specimen (length <10 mm and/or portal tracts <6) ($n = 12$).

Finally, 298 patients were studied. All patients underwent liver ultrasound examination before LB. Also in patients with cirrhosis, upper GI endoscopy was performed systematically.

The study protocol conformed to the ethical guidelines of the 1975 Helsinki declaration and was approved by our institutional review board. Patients were enrolled after giving their written informed consent.

2.2. Liver histology and quantification of liver fibrosis

Liver biopsy was performed by senior operators using the Menghini technique with a 1.6-mm-diameter needle (Hepafix®, Braun, Melsungen, Germany). Biopsy specimens were fixed in formalin and embedded in paraffin. All biopsy specimens were analyzed by the same trained pathologist blinded to the results of non-invasive methods. Liver fibrosis was staged on a 0–4 scale according to the METAVIR scoring system [32] as follows: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis.

2.3. Liver stiffness measurement

Liver stiffness measurements were performed the same day as LB using TE (FibroScan, Echosens, Paris, France). Details of the technical background and examination procedure have been previously described [24]. Ten validated measurements were performed for each patient. The success rate was calculated as the number of validated measurements divided by the total number of measurements. The results were expressed in kilopascals (kPa). The median value was considered representative of the elastic modulus of the liver. Only procedures with at least 10 successful acquisitions and a success rate of at least 60% were considered reliable. In addition, the median value of successful measurements was considered representative of the liver stiffness in a given patient, only if the interquartile range (IQR) of all validated measurements was less than 30% of the median value. Cirrhosis was defined according to the two published cut-offs in patient with hepatitis C: 12.5 kPa [26] and 14.6 kPa [27], respectively.

2.4. Serum fibrosis markers

The parameters (aspartate aminotransferase, ALT, γ-glutamyltranspeptidase, total bilirubin, α2-macroglobulin, apolipoprotein A1, haptoglobin, INR, PI and platelet count) allowing to calculate FT, APRI, AAR and Lok index were determined in the same laboratory on blood sampled the day of LB.

The FT score was purchased from Biopredicitve website (www.biopredictive.com). Formulas for calculating other scores (APRI and Lok index) were taken from the original publications [21,23].

2.5. Statistical analysis

Patients' characteristics are given as mean ±1 SD or as median and IQR as appropriate. Receiver operating characteristics (ROC) curves were constructed. Sensitivity (Se), specificity (Sp), positive and negative predictive values (PPV and NPV), positive likelihood ratio (+LR) and negative likelihood ratio (−LR) were calculated using cut-offs previously described for cirrhosis for each serum index (FibroTest value $\geqslant 0.75$ [22]; platelet count $<150 \times 10^9\ L^{-1}$ [18]; PI $\leqslant 85\%$ [17]; AST/ALT ratio >1 [20]; APRI <1 or $\geqslant 2$ [21]; Lok index <0.2 or $\geqslant 0.5$ [23]) and the two reported TE cut-offs (12.5 and 14.6 kPa) [26,27].

Regarding diagnostic performances for the detection of OV, as serum indexes have not been designed for this purpose, cut-offs were established using ROC curves to calculate Se, Sp, PPV, NPV, +LR and −LR. The following cut-offs have been chosen: fibrotest value

$\geqslant$0.78; platelet count <140 × 10^9 L^{-1}; PI $\leqslant$80%; AST/ALT ratio >1; APRI $\geqslant$1.3; Lok index $\geqslant$0.6. As for TE, optimized cut-offs established using ROC curves (21.5 and 30.5 kPa), were compared to the published cut-offs for detection of OV (13.9 and 17.9 kPa) [30,31] and detection of large OV (19 kPa) [30].

Areas under ROC curves (AUROCs) were calculated using the trapezoidal rule. Comparisons of AUROCs were done using the method described by Hanley and McNeil for correlated data. Initially, we compared all AUROCs, and in case of rejection of the null hypothesis (all AUROCs are equal), differences were searched for by two-by-two comparisons, using Bonferroni adjustement for multiple pairwise comparisons. Analyses were performed using Stata V8.0 (StataCorp 2003. Stata Statistical Software: release 8.0. College Station TX).

3. Results

3.1. Patients

The characteristics of the 298 patients at the time of LB are shown in Table 1. There were 171 men and 127 women, and their mean age was 51.7 ± 11.8 years. The mean LB length was 19.5 ± 7.8 mm and the mean number of portal tracts was 14.6 ± 7.5. Biopsy length was greater than 15 mm in 210 patients (69%) and than 25 mm in 75 patients (25%). Cirrhosis (F4) was present in 70 patients (23%). As expected, these patients had lower platelet count, PI and albumin, higher INR and bilirubin levels than patients without cirrhosis. All patients had compensated cirrhosis (Child-Pugh A: 70). OV were present on upper gastrointestinal endoscopy in 25 patients (36%) and were large (grades 2–3) in 13 (19%). Splenomegaly and/or portal hypertension signs were present on ultrasound in 25 patients (35%).

3.2. Comparative performance of TE and serum indexes for detection of cirrhosis

Liver stiffness measurement could not be obtained in 10 patients (3%). These patients did not differ from the others for age (55.4 ± 10.5 vs. 51.6 ± 11.8 years, respectively, $p = 0.32$) and gender (male 70% vs. 57%, respectively, $p = 0.37$) but had significantly higher BMI (31.2 ± 5.4 vs. 24.9 ± 4.2 kg/m^2, respectively, $p <$ 0.0001).

Analysis was conducted in "intention-to-treat", thus these 10 patients were considered as not correctly classified when calculating the number of patients correctly classified by TE.

Fig. 1 shows box plots of TE, FT, Lok index, APRI, AAR, PI and platelet count in patients with and without cirrhosis and Fig. 2 shows ROC curves for the diagnosis of cirrhosis. AUROCs (95% CI) for the diagnosis of cirrhosis are given in Table 2. TE had a significantly better AUROC than all the other tests ($p < 0.0001$).

The diagnostic performances of TE and serum markers are shown in Table 3. TE had the highest positive likelihood ratios (+LR) values (ranging between 16.6 and 35.5 as compared with values ranging from 1.59 to 6.83 for serum markers) and the lowest negative likelihood ratios (−LR) values (ranging between 0.18 and 0.29 as compared with values ranging from 0.30 to 0.77 for serum markers).

At a cut-off of 12.5 kPa, cirrhosis could be predicted with 85% certainty and excluded with 95% certainty. A total of 21 patients (7%) were misclassified: 16% of patients with cirrhosis (11 out of 70) and 4% without cirrhosis (10 out of 228). When analysing these 21

Table 1
Baseline characteristics of the 298 patients according to the presence of cirrhosis.

	Total $n = 298$	Cirrhosis $n = 70$	No cirrhosis $n = 228$	p
Gender (male)	171 (57%)	42 (60%)	129 (57%)	0.71
Age (years)	51.7 ± 11.8	54.1 ± 11.8	51.1 ± 11.7	0.05
BMI (kg/m^2)	25.1 ± 4.3	25.9 ± 4.1	24.9 ± 4.4	0.09
AST (×ULN)	1.6 ± 1.3	2.2 ± 1.7	1.5 ± 1.2	<0.001
ALT (×ULN)	2.2 ± 1.9	2.6 ± 2.2	2.0 ± 1.8	0.03
Platelets (10^9 L^{-1})	216 ± 75	164 ± 77	232 ± 67	<0.0001
Total bilirubin (μmol/L)	11.3 ± 5.1	14.4 ± 6.4	10.3 ± 4.1	<0.0001
Albumin (g/L)	40.1 ± 4.7	38.2 ± 4.4	40.8 ± 4.6	0.0003
Prothrombin index (%)	94 ± 9	87 ± 12.4	96 ± 7	<0.0001
INR	1.05 ± 0.08	1.11 ± 0.13	1.03 ± 0.06	<0.0001
Liver biopsy				
Length (mm)	19.5 ± 7.8	17.4 ± 6.3	20.3 ± 8.0	<0.01
Number of fragment	2.9 ± 3.2	3.4 ± 3.2	2.6 ± 3.0	<0.05
Fibrosis stage (Metavir) (%)				
F0–F1			74 [32]	
F2			97 [43]	
F3			54 [25]	

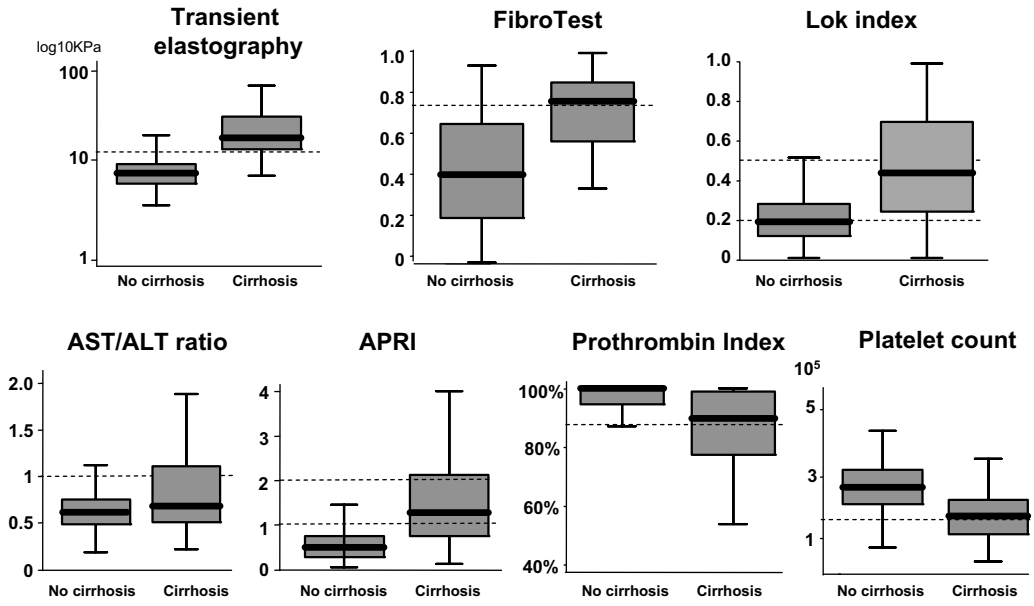

Fig. 1. Box plots of transient elastography, FibroTest, Lok index, AST/ALT ratio, APRI, prothrombin index and platelet count for cirrhosis. The top and bottom of the boxes are the first and third quartiles, respectively. The length of the box thus represents the IQR within which 50% of the values were located. The line through the middle of each box represents the median. The error bars show the minimum and maximum values (range). The dashed lines represent the cut-offs for the detection of cirrhosis.

misclassified patients, they did not differ from the others for gender (male 71% vs. 56%, respectively, $p = 0.24$), age (51 ± 11 vs. 51 ± 12 years, respectively, $p = 0.99$), BMI (26.3 ± 6.1 vs. 24.8 ± 4.0 kg/m^2, respectively, $p = 0.11$), ALT levels (2.6 ± 1.9 vs. 2.3 ± 2.3 ULN, respectively, $p = 0.48$), the mean LB length (18.7 ± 4.5 vs. 19.9 ± 7.9 mm, respectively, $p = 0.50$), the mean success rate for TE (77% vs. 86%, respectively, $p = 0.15$), the mean IQR (2.4 vs. 2.3, respectively, $p = 0.89$), and the mean number of measurements per patient (10.1 vs. 10.9, respectively, $p = 0.20$). Interestingly, in the 10 patients without cirrhosis classified by TE as having cirrhosis, all were F3 on LB.

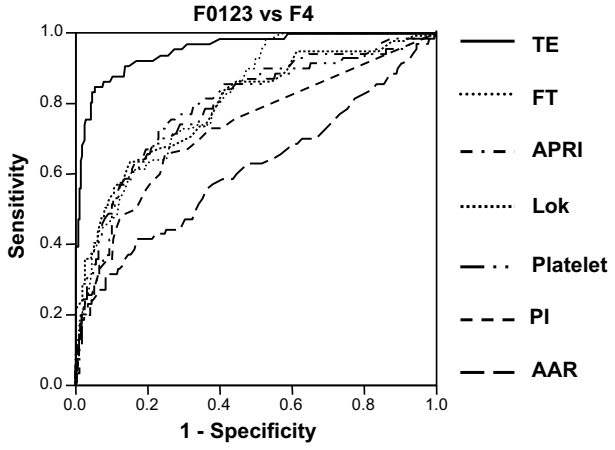

Fig. 2. ROC curves for transient elastography (TE), FibroTest (FT), Lok index, AST/ALT ratio (AAR), APRI, prothrombin index (PI) and platelet count for the prediction of cirrhosis (F0123 vs F4) in the 298 patients. Corresponding AUROC values are shown in Table 2.

At a cut-off of 14.6 kPa, cirrhosis could be predicted with 90% certainty and excluded with 92% certainty. A total of 24 patients (8%) were misclassified: 27% of patients with cirrhosis (19 out of 70) and 2% without cirrhosis (5 out of 228).

Overall, the percentage of correctly classified patients in whom LB could have been avoided was as follows: TE (12.5 kPa) 90% and (14.6 kPa) 89%; platelet count 82%; FT 79%; PI 77%; AAR 76%; APRI 70%, and Lok index 45%, respectively.

3.3. Discordant results between transient elastography and serum indexes for detection of cirrhosis

Results are summarized in Table 4. Prevalence of discordant results between TE and serum indexes ranged between 13.5% (APRI) and 23.6% (PI). It must be stressed, however, that due to the high proportion of unclassified cases, only 152 and 236 patients could be analysed with Lok index and APRI, respectively. When discrepant cases were analysed taking LB as the reference, the diagnosis of cirrhosis was confirmed for TE in 71% (APRI) to 81% (AAR) of cases. Overall, TE results were confirmed in most cases (80–88%), whatever the serum index used.

Table 2
Comparison of AUROCs (95% CI) of the different methods for detecting cirrhosis in the 298 patients and for discriminating the presence of oesophageal varices (OV: none vs grades 1–2–3) and the presence of large OV (none-grade 1 vs grades 2–3) in the 70 patients with cirrhosis.

	Cirrhosis	Presence of OV	Large OV
Transient elastography	0.96 (0.93-0.98)[a]	0.84 (0.75–0.94)	0.87 (0.77–0.97)
FibroTest	0.82 (0.73–0.86)	0.72 (0.60–0.85)	0.75 (0.62–0.87)
APRI	0.80 (0.74–0.86)	0.62 (0.48–0.75)[b]	0.71 (0.55–0.86)[c]
Lok index	0.80 (0.73–0.86)	0.81 (0.71–0.92)	0.87 (0.79–0.95)
Platelet count	0.79 (0.72–0.85)	0.69 (0.55–0.83)	0.79 (0.64–0.94)
Prothrombin index	0.73 (0.66–0.80)	0.68 (0.55–0.81)	0.77 (0.62–0.91)
AST/ALT ratio	0.61 (0.53–0.70)	0.83 (0.72–0.94)	0.79 (0.64–0.94)

p value for comparison between all tests.
[a] $p < 0.0001$ (difference due to higher AUROC of TE).
[b] $p < 0.0006$ (due to lower AUROC of APRI).
[c] $p < 0.04$ (due to lower AUROC of APRI); not significant when not specified.

3.4. Diagnostic performance of transient elastography and serum indexes for detection of oesophageal varices

As shown in Fig. 3, liver stiffness values increased with the grade of OV ($p < 0.0001$ using Kruskal–Wallis test). The AUROC of TE for the presence of OV did not differ from others except for APRI ($p < 0.0006$) (Table 2). Similarly, the AUROC of TE for the presence of large OV did not differ from others, except for APRI ($p < 0.04$).

Diagnostic performances for the presence of OV and large OV are given in Tables 5 and 6.

At a cut-off of 21.5 kPa, TE predicted the presence of OV with 76% Se and 78% Sp as compared with 96% Se and 39% Sp, using the 13.9 kPa cut-off proposed by Kazemi et al. [30], and 84% Se and 61% Sp, using the 17.6 kPa cut-off proposed by Vizzuti et al. [31]. Overall, the percentage of correctly classified patients was as follows: TE (13.9 kPa) 57%, (17.6 kPa) 66% and (21.5 kPa) 73%; AAR 81%; Lok index 77%; FT and PI 70%, platelet count 69%, and APRI 66%, respectively.

At a cut-off of 30.5 kPa, TE predicted the presence of large OV with 77% Se and 85% Sp as compared with 84% Se and 62% Sp, using the 19 kPa cut-off proposed by Kazemi et al. [30]. Overall, the percentage of correctly classified patients was as follows: TE, (19.0 kPa) 63%, (21.5 kPa) 67% and (30.5 kPa) 79%; PI 79%; Lok

Table 3
Comparative performance of non-invasive tests for the diagnosis of cirrhosis in the 298 patients (for a 23% prevalence).

Non-invasive tests	Cut-offs	Patients with cirrhosis ($n = 70$)	Patients without cirrhosis ($n = 228$)	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	−LR	Correctly classified
Transient elastography (kPa)	<12.5	11	212							
(failure $n = 10$)	⩾12.5	55	10	83	95	85	95	16.60	0.18	267 (90%)
	<14.6	19	217							
	⩾14.6	47	5	71	98	90	92	35.50	0.29	264 (89%)
Platelet count (10^9 L^{-1})	⩾150	41	214							
	<150	29	14	41	94	67	84	6.83	0.63	243 (82%)
FibroTest	<0.75	31	197							
	⩾0.75	39	31	55	86	55	86	3.93	0.52	236 (79%)
Prothrombin index	>85%	45	205							
	⩽ 85%	25	23	35	90	52	82	3.50	0.72	230 (77%)
AST/ALT ratio	<1	48	203							
	⩾ 1	22	25	31	89	47	81	2.81	0.77	225 (70%)
APRI	<1.0	25	186	64	81	52	88	3.37	0.44	
	Unclassified	24	29							
	⩾2.0	21	13	30	94	62	81	5.00	0.74	207 (70%)
Lok index	<0.2	10	105	86	46	32	91	1.59	0.30	
	Unclassified	32	110							
	⩾0.5	28	13	40	94	68	84	6.66	0.64	133 (45%)

Se sensitivity; Sp specificity; PPV and NPV positive and negative predictive values; +LR positive likelihood ratio; −LR negative likelihood ratio.

Table 4
Analysis of discordant results between transient elastography and the different serum markers for the diagnosis of cirrhosis as compared to liver biopsy (LB) taken as reference.

Non-invasive tests	Prevalence of discordance	Number of patients diagnosed as cirrhosis by non-invasive tests	Number of diagnosis of cirrhosis confirmed by LB	Total number of diagnosis confirmed by LB
Transient elastography (TE) and prothrombin index (PI) ($n = 288$)	68 (23.6%)	TE: 43 PI: 25	TE: 34/43 (79%) PI: 4/25 (16%)	TE: 55/68 (81%) PI: 13/68 (19%)
Transient elastography (TE) and AST/ALT ratio (AAR) ($n = 288$)	65 (22.6%)	TE: 42 AAR: 23	TE: 34/42 (81%) AAR: 0/23 (0%)	TE: 57/65 (88%) AAR: 8/65 (12%)
Transient elastography (TE) and FibroTest (FT) ($n = 288$)	56 (19.4%)	TE: 27 FT: 29	TE: 20/27 (74%) FT: 2/29 (7%)	TE: 47/56 (84%) FT: 9/56 (16%)
Transient elastography (TE) and platelet count (PC) ($n = 288$)	51 (17.7%)	TE: 37 PC: 14	TE: 29/37 (78%) PC: 2/14 (14%)	TE: 41/51 (80%) PC: 10/51 (20%)
Transient elastography (TE) and Lok index ($n = 152$)	25 (16.4%)	TE: 11 Lok: 14	TE: 8/11 (73%) Lok: 2/14 (14%)	TE: 20/25 (80%) Lok: 5/25 (20%)
Transient elastography (TE) and APRI ($n = 236$)	32 (13.5%)	TE: 21 APRI: 11	TE: 15/21 (71%) APRI: 0/11 (0%)	TE: 26/32 (81%) APRI: 6/32 (19%)

index 77%; AAR and platelet count 76%; FT 64%, and APRI 63%, respectively.

4. Discussion

The results of the present prospective study, comparing seven non-invasive methods to LB, show that TE is currently the most accurate method for detection of cirrhosis in patients with CHC. Diagnostic accuracy of TE for detecting cirrhosis was significantly better than those of all the other tests with an AUROC of 0.96 (95%CI 0.93–0.98). In addition, using more discriminating criteria independent of cirrhosis prevalence, such as the likelihood ratios (LR), which describe how many times more likely a person with the disease will receive a particular test result than a person without the disease, TE had the highest +LR values (ranging between 16.6 and 35.5 as compared with values ranging from 1.6 to 6.8 for serum markers) and the lowest −LR values (ranging between 0.18 and 0.29 as compared with values ranging from 0.30 to 0.77 for serum markers). Finally, TE use would have resulted in avoiding the need for LB in up to 90% of patients, a finding in keeping with those of a recent French multicenter study [29]. It must be stressed, however, that in contrast to that study and most studies so far, we analysed TE performance in "intention-to-treat" analysis. Thus, patients with TE failure (3%) were not excluded and LB was deemed necessary, a condition closer to "real life". As previously reported [33], TE failure was associated with increased BMI.

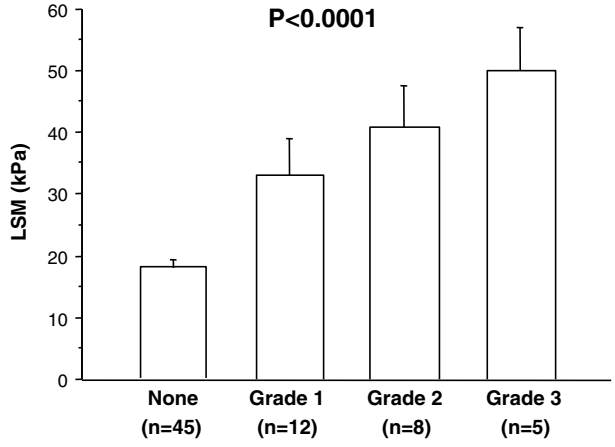

Fig. 3. Liver stiffness measurement (LSM) values for each oesophageal varices grade. The vertical axis presents LSM values in kiloPascal. The top of the boxes are the mean value in each group. The ended lines represent the standard deviation.

Optimal TE cut-off for the diagnosis of cirrhosis remains debated as reported cut-offs for cirrhosis range from 10.3 kPa in chronic hepatitis B to 17.3 kPa in chronic cholestatic diseases [25]. In the largest series to date of patients with chronic liver diseases of various etiologies (with around 35% with CHC), Ganne-Carrie et al. proposed a cut-off of 14.6 kPa [29] and suggested that TE cut-off values could be optimized if specifically defined for each etiology. In the present study, we evaluated the two published cut-offs for cirrhosis in CHC: 12.5 kPa [26] and 14.6 kPa [27]. At a cut-off of 12.5 kPa, cirrhosis could be predicted with 85% certainty and excluded with 95% certainty whereas at a cut-off of 14.6 kPa, cirrhosis could be predicted with 90% certainty and excluded with 92% certainty. These performances are similar to those previously reported [26,27]. Using the 14.6 kPa cut-off instead of 12.5 kPa resulted in decreasing the number of false-positive (5 vs. 10, respectively) but increased the number of false-negative (19 vs, 11, respectively). Interestingly, in the

Table 5
Comparative performance of non-invasive tests for the diagnosis of eosophageal varices (OV) (none vs. grades 1–2–3) in the 70 patients with cirrhosis (for a 36% prevalence).

Non-invasive tests	Cut-offs	Patients with OV ($n = 25$)	Patients without OV ($n = 45$)	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	−LR	Correctly classified
Transient elastography (kPa)	<13.9	1	16							
(failure $n = 4$)	⩾13.9 (30)	24	25	96	39	49	94	1.57	0.10	40 (57%)
	<17.6	4	25							
	⩾17.6 (31)	21	21	84	61	57	86	2.15	0.26	46 (66%)
	<21.5	6	32							
	⩾21.5	19	9	76	78	68	84	3.46	0.31	51 (73%)
Platelet count (10^9 L^{-1})	⩾140	11	34							
	<140	14	11	56	76	56	76	2.29	0.58	48 (69%)
FibroTest	<0.78	7	31							
	⩾0.78	18	14	72	69	56	82	2.31	0.41	49 (70%)
Prothrombin index	>80%	14	38							
	⩽80%	11	7	44	84	61	73	2.83	0.66	49 (70%)
AST/ALT ratio	<1.0	8	40							
	⩾1.0	17	5	68	89	77	83	5.10	0.37	57 (81%)
APRI	<1.3	8	29							
	⩾1.3	17	16	68	64	51	78	1.91	0.50	46 (66%)
Lok index	<0.6	8	37							
	⩾0.6	17	8	68	82	68	82	3.83	0.39	54 (77%)

Se, sensitivity; Sp, specificity; PPV and NPV, positive and negative predictive values; +LR, positive likelihood ratio; −LR, negative likelihood ratio.

10 patients without cirrhosis classified by TE (12.5 kPa) as having cirrhosis, all were F3 on LB. We used LB as the "gold standard" for the diagnosis of cirrhosis in the present study despite its limitations because it is still recommended in patients with CHC [4]. However, it has been demonstrated that cirrhosis is missed on a single blind LB in between 10% and 30% of cases [7,9,10]. Thus, we cannot exclude that these 10 patients may represent false-negative of LB. Indeed, liver specimens in our cirrhotic patients were significantly smaller and more fragmented than in the other patients. However, biopsy quality criteria used in the present study (mean length of 19.5 ± 7.8 mm with 70% of specimen >15 mm and reading by a single pathologist blinded to the results of non-invasive methods) can be considered to be satisfactory and in accordance with recent recommendations for accurate fibrosis staging [34].

A major strength of the present study is that we compared TE to a large panel of non-invasive serum markers including simple and routinely available laboratory tests such as PI, platelet count, AAR, and APRI but also more complex scores such as FT and the Lok index. Overall, diagnostic performances for cirrhosis of these markers were very similar to those originally reported. The poor diagnostic accuracy of AAR in our study (AUROC: 0.61) is in keeping with the findings of Lackner et al. [35]. PI, platelet count, APRI, Lok index, and FT had similar AUROCs ranging from 0.73 to 0.82. The performance of FT and APRI are in keeping with those reported in the most recent independent validation studies [36–38]. However, it must be stressed that each of these tests was more suited for exclusion of cirrhosis than for its prediction. For instance, using the reported cut-off values of <0.2 (Lok), <1.0 (APRI), <0.75 (FT), $\geqslant 150 \times 10^9$ L^{-1} (platelet count) and >85% (PI), each test excluded cirrhosis with a negative predictive value of 91%, 88%, 86%, 84% and 82%, respectively. Conversely, prediction of cirrhosis using a cut-off value of >0.5 (Lok), >2.0 (APRI), >0.75 (FT), $<150 \times 10^9$ L^{-1} (platelet count) and ⩽85% (PI), prediction of cirrhosis was much less reliable (PPV 68%, 62%, 55%, 67% and 52%, respectively). As already pointed out by Lackner et al. [35], platelet count *per se* had a similar diagnostic accuracy as the APRI and Lok index comprising platelet count among other laboratory parameters. However, platelet count was much more accurate for correctly classifying patients than APRI and Lok (82% vs 70% and 45%, respectively). This may be related to the fact that, in contrast to other tests, APRI and Lok index use two different cut-off values for exclusion and prediction of cirrhosis.

When TE results were compared with those of the different serum indexes, discrepancies were observed with a prevalence ranging between 13.5% for APRI and 23.6% for PI. It must be stressed, however, that around 20% of patients could not be classified with APRI. Interestingly, when discrepant cases were analysed, taking LB as the reference, TE results were confirmed in most cases (80–88%), whatever the serum index used. These results suggest that, given the high

Table 6
Comparative performance of non-invasive tests for the diagnosis of eosophageal varices (OV) (none – grade 1 vs. grades 2–3) in the 70 patients with cirrhosis (for a 19% prevalence).

Non-invasive tests	Cut-offs	Patients with large OV ($n = 13$)	Patients without large OV ($n = 57$)	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	−LR	Correctly classified
Transient elastography (kPa)	<19.0	2	33							
(failure $n = 4$)	⩾19.0	11	20	85	62	35	94	2.24	0.24	44 (63%)
	<21.5	2	36							
	⩾21.5	11	17	85	68	39	95	2.65	0.22	47 (67%)
	<30.5	3	45							
	⩾30.5 (30)	10	8	77	85	56	94	5.13	0.27	55 (79%)
Platelet count (10^9 L^{-1})	⩾140	3	43							
	<140	10	14	77	75	42	93	3.08	0.31	53 (76%)
FibroTest	<0.78	3	35							
	⩾0.78	10	22	77	61	31	92	1.98	0.38	45 (64%)
Prothrombin index	>80%	5	47							
	⩽80%	8	10	62	82	44	90	3.44	0.46	55 (79%)
AST/ALT ratio	<1.0	4	44							
	⩾1.0	9	13	69	77	41	92	3.00	0.40	53 (76%)
APRI	<1.3	3	34							
	⩾1.3	10	23	77	60	30	92	1.92	0.38	44 (63%)
Lok index	<0.6	2	43							
	⩾0.6	11	14	85	75	44	96	3.40	0.20	54 (77%)

Se, sensitivity; Sp, specificity; PPV and NPV, positive and negative predictive values; +LR, positive likelihood ratio; −LR, negative likelihood ratio.

accuracy of TE alone, combining TE with serum indexes does not increase diagnostic accuracy for cirrhosis.

TE has certain advantages over indices based on laboratory tests, in that it provides more direct measurement of fibrosis and is not affected by intercurrent health disorders. Indeed, the serum markers performance may be influenced by changes in their clearance and excretion [16] and the reproducibility of measurement of some parameters, such as, for instance AST levels or platelet count, is questionable [39]. On the contrary, TE has been shown to be a highly reproducible and operator-independent technique [40,41]. Another advantage of TE is that it could be a valuable tool for the detection of OV in patients with cirrhosis [28,30,31]. The AUROCs of TE for the detection of OV and large OV in the present study (0.84 and 0.87, respectively) are similar to those previously reported [30,31]. Importantly, except for APRI, TE did not perform better than serum indexes for both the detection of OV and large OV. The diagnostic performances of serum indexes in our study are consistent with those previously published [42–44], except for platelet count for which diagnostic value has been recently questioned [45]. However, optimal cut-offs vary from study to study. Similarly, optimal TE cut-off remains to be defined. In the present study, we compared our optimized cut-offs for detection of OV (21.5 kPa) and large OV (30.5 kPa) with those previously published (13.9 kPa [30] and 17.6 kPa [31], and 19 kPa [30], respectively). Overall, the rates of correctly classified patients were 73%, 66% and 57%, using 21.5, 17.6 and 13.9 kPa cut-offs, respectively, for detection of OV and 79%, 66% and 63%, using 30.5, 21.5 and 19.0 kPa cut-offs, respectively, for detection of large OV. As stated previously for cirrhosis, differences in cut-off may be related to differences in prevalence of OV in the studied populations. It must be stressed, however, that patients in our population all had compensated cirrhosis and prevalence of OV and large OV (36% and 19%, respectively) in keeping with the most recent reports [43]. Further studies are needed to address this issue. Finally, the performances of both TE and serum indexes remain currently insufficient to confidently predict the presence of OV in clinical practice and to screen cirrhotic patients without endoscopy [46,47].

In conclusion, our results suggest that TE is currently the most accurate non-invasive method for early detection of cirrhosis in CHC, as compared with other available methods, avoiding the need for LB in 90% of cases but cannot replace endoscopy for OV screening.

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