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CLINICAL STUDIES

Direct comparison of diagnostic performance of transient elastography in patients with chronic hepatitis B and chronic hepatitis C

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Keywords
cirrhosis – hepatitis B – hepatitis C – liver fibrosis – liver stiffness – transient elastography

Abbreviations
BMI, body mass index; LB, liver biopsy; LR(−), negative likelihood ratio; LR(+), positive likelihood ratio; NPV, negative predicitive value; PPV, positive predictive value; ×ULN, times the upper limit of normal.

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Abstract

Background/Aims: Accuracy of transient elastography (TE) in hepatitis B virus (HBV) infection has not been well established. We aimed to compare the performances of TE for the assessment of liver fibrosis in patients with chronic HBV or hepatitis C virus (HCV) infection. A secondary analysis was performed to assess whether or not alanine aminotransferase (ALT) levels would impact on the accuracy of TE. *Methods:* This cross-sectional study, carried out in a single centre, included treatment-naïve patients with compensated chronic HBV or HCV infection, consecutively admitted between 2006 and 2008 for a liver biopsy and TE measurement on the same day. *Results:* A total of 202 HBV patients and 363 HCV subjects were evaluated. Overall diagnostic accuracy of TE in the HBV group was comparable to that observed in HCV patients [area under the receiver-operating characteristics (AUROCs) 0.867 ± 0.026 vs. 0.868 ± 0.019 for predicting $F \geq 2$, $P = 0.975$; 0.902 ± 0.029 vs. 0.894 ± 0.020 for $F \geq 3$, $P = 0.820$; and 0.935 ± 0.024 vs. 0.947 ± 0.027 for F4, $P = 0.740$ respectively]. TE exhibited comparable accuracies, sensitivities, specificities, predictive values and likelihood ratios in HBV and HCV groups. AUROC analysis showed no influence of ALT levels on the performance of TE in HBV individuals. ALT-specific cut-off values did not exhibit significantly higher diagnostic performances for predicting fibrosis in HBV patients with elevated ALT. *Conclusions:* In HBV patients, TE measurement accurately predicts the absence or presence of significant fibrosis, advanced fibrosis or cirrhosis and shows similar performances as compared to HCV patients. The use of TE cut-off values adjusted to ALT level did not improve performances for estimating liver fibrosis in HBV patients.

Prognosis and management of patients with chronic hepatitis B virus (HBV) infection or chronic hepatitis C virus (HCV) infection are directly related to the stage of liver fibrosis. Subjects who have advanced liver fibrosis represent the group at greatest risk for developing liver-related complications and mortality and are therefore in need of therapy for the underlying aetiology (1, 2). This emphasizes the need for a safe and effective diagnostic tool for the assessment of liver fibrosis. Percutaneous liver biopsy (LB) has long remained the gold standard method for fibrosis staging (3). However, it is an invasive technique with associated morbidity and potentially life-threatening complications (4, 5). Furthermore, the accuracy of LB has also been questioned because of the sampling errors and intra- and inter-observer variability, which may lead to over-staging or under-staging of fibrosis (6–8).

These limitations have encouraged the search for new non-invasive markers of hepatic fibrosis. Direct and indirect blood tests, as well as innovative imaging techniques have been developed as alternatives to LB (9). Even though many of these are relatively low-cost tests and easy-to-perform methods, significant drawbacks persist, such as imperfect methodological standardization, random fluctuations over time and suboptimal accuracies, frequently influenced by the presence of other hepatic and non-hepatic conditions. Transient elastography (TE) is a procedure developed to assess more directly liver fibrosis through a physical method, with a similar performance for predicting significant

fibrosis and higher accuracy to identify cirrhosis, as compared to blood tests (10).

In contrast to chronic hepatitis C, there are few studies with appropriate methodology on the accuracy of TE in patients with chronic hepatitis B (11, 12). Moreover, different cut-offs for predicting the presence of significant/advanced fibrosis have been proposed, as compared to those used for HCV subjects. Specific characteristics of chronic hepatitis B, such as a macronodular pattern of cirrhosis and fluctuating hepatic necroinflammatory activity, could conceivably influence the accuracy of TE.

The aim of this study was to evaluate and directly compare the performances of TE for estimating hepatic fibrosis in a series of consecutive patients with chronic hepatitis B or chronic hepatitis C, followed-up in a single centre. A secondary objective was to look for different cut-offs to improve accuracy of TE according to alanine aminotransferase (ALT) levels in chronic hepatitis B.

Materials and methods

Study population

This cross-sectional study included treatment-naïve patients with chronic hepatitis B or chronic hepatitis C who were consecutively admitted in the Service d'Hepatologie de l'Hôpital Beaujon between 2006 and 2008 for a liver biopsy (LB) and transient elastography (TE) measurement, after giving their written informed consent. Chronic hepatitis B was defined by the presence of hepatitis B surface antigen (HBsAg) and detectable serum hepatitis B virus DNA (HBV-DNA) for at least 6 months. Chronic hepatitis C was defined by the presence of anti-HCV antibodies and detectable serum HCV-RNA by PCR (>50 IU/ml). Subjects with one or more of the following conditions were excluded: excessive alcohol consumption (>30 g/day for men, >20 g/day for women); co-infection with human immunodeficiency virus and/or hepatitis delta virus; other causes of liver disease; decompensated liver disease or hepatocellular carcinoma; and previous liver surgery or liver transplantation.

This study protocol was conformed to the ethical guidelines of the Helsinki Declaration and was approved by our institutional review board.

Liver biopsy

Percutaneous liver biopsies were performed under ultrasound guidance using the Menghini technique with disposable 16-gauge diameter needles. A single, experienced pathologist, who was unaware of the clinical data, evaluated all slides. Histological features were analysed using the METAVIR group scoring system (13). Significant fibrosis was defined by the presence of F2, F3, or F4 METAVIR stage and the presence of F3 or F4 stages characterized advanced fibrosis. Steatosis was categorized as absent (<5% of hepatocytes affected); mild (5–10%); moderate (11–30%); severe (>30%). The length of each liver fragment and the number of portal tracts were recorded and only patients with LB length $\geq$ 15 mm and/or at least six portal tracts were included.

Transient elastography

Transient elastography examinations were performed prior to LB, on the same day of the procedure, and by a single experienced operator (AC). Measurements were performed by using the standard technique, as previously described (10). Only patients with at least 10 valid measurements, with an interquartile range of less than 30% of the median stiffness, and with at least 60% success rate were included in the final analysis. According to previous studies, the following cut-off values were used (10, 11): (a) HCV infection: 7.1 kPa for significant fibrosis ($F \geq 2$), 9.5 kPa for advanced fibrosis ($F \geq 3$) and 12.5 kPa for cirrhosis (F4); (b) HBV infection: 7.2 kPa for $F \geq 2$, 8.1 kPa for $F \geq 3$ and 11 kPa for F4. A secondary analysis was performed to assess whether alternative cut-offs, adjusted according to ALT levels, would improve the accuracy of TE measurement for the estimation of fibrosis staging in HBV carriers (12): (a) normal ALT level: 6.0 kPa for $F \geq 2$, 9.0 kPa for $F \geq 3$ and 12.0 kPa for F4; (b) ALT level between 1 and 5 times the upper limit of normal (ULN): 7.5 kPa for $F \geq 2$, 12.0 kPa for $F \geq 3$ and 13.4 kPa for F4.

Laboratory tests

Complete physical examination and laboratory tests (complete blood count, biochemical tests, alpha-fetoprotein and virological markers) were assessed on the same day that LB and TE were performed. Serum HCV-RNA was measured with the VERSANT HCV 3.0 Assay (bDNA; Siemens Medical Solutions, Puteaux, France) with a quantification range of 615–7 690 000 IU/ml. HCV genotype was assessed by the Line Probe Assay (InnoLiPA HCV; Innogenetics, Ghent, Belgium). HBsAg, hepatitis B e antigen (HBeAg) and antibodies were measured using standard enzyme-linked immunosorbent assays (Abbott Diagnostics, Abbott Park, IL, USA). HBV DNA levels were measured using COBAS Ampliprep/COBAS TaqMan HBV (CAP/CPM, Roche Molecular System Inc., Branchburg, NJ, USA).

Statistical analysis

Continuous variables were compared using the Student's *t*-test, the Mann–Whitney test, or the Kruskal–Wallis test when appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. Test results with *P* values of less than 0.05 were considered statistically significant. Statistical analysis was

performed by SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). The diagnostic performance of TE in HCV and HBV subjects was assessed by comparison with liver histology and by measuring the area under the receiver-operating characteristics (AUROC). ROC curve comparisons were performed using the MEDCALC software package version 9.3 (MedCalc Software, Mariakerke, Belgium), which employs calculation of the AUROC and 95% confidence intervals by the technique described by DeLong *et al.* (14). Diagnostic accuracy was also evaluated by comparing the sensitivity, specificity, positive and negative predictive values (PPV and NPV respectively), and likelihood ratios of TE measurement to predict the absence or presence of significant fibrosis, advanced fibrosis and cirrhosis in each group (HCV and HBV), by using the appropriate set of cut-offs points, as described above.

Results

Patients

From January 2006 to December 2008, 613 subjects were considered for enrollment. Among these, 48 patients (7.8%) were excluded because of unreliable results (40 cases) or unsuccessful transient elastography (TE) measurements (8 cases) (Fig. 1). Therefore, 565 patients (202 HBV and 363 HCV) were included and analysed in the present study. Demographic, clinical, laboratorial and histological features were not significantly different between included and excluded subjects (data not shown), except for a higher BMI in those who were excluded (25.8 ± 4.0 vs. 24.4 ± 3.5 kg/m² respectively; $P = 0.05$).

Table 1 summarizes the characteristics of the 363 HCV and of the 202 HBV consecutive patients fulfilling the entry criteria. The mean age was 46.1 ± 11.2 years with a male predominance (67%). HBV patients were significantly younger and were more frequently men, as compared to HCV subjects (80 vs. 60%, $P < 0.001$). As expected, HCV patients were mainly Caucasian (87%) and Asian ethnicity was more prevalent among HBV individuals (26%). In all, 58% of HCV subjects were genotype 1 and 24% of HBV patients were HBeAg positive. As for blood parameters, slight differences were observed between groups, with higher ALT levels and lower albumin levels being observed in HCV subjects, and lower mean platelet count and lower prothrombin activity identified in HBV patients.

Histology

In the studied population, the mean biopsy length was 19.7 ± 6.4 mm, with a median of 20 mm [interquartile range (IQR) 17–22 mm]. The median number of portal tracts was 12 (IQR 10–20). As shown in Figure 2, HBV patients presented with less severe histological findings according to the METAVIR group scoring system as compared with HCV subjects. All HBV patients showed liver lesions (at least A1 or F1) and were not inactive carriers. Significant fibrosis ($F \geq 2$) was observed in 54% of HCV and in 42% of HBV patients ($P = 0.005$), and advanced fibrosis ($F \geq 3$) was identified in 24 and 17% of HCV and HBV subjects respectively ($P = 0.048$). Likewise, significant steatosis (>30% of hepatocytes) was found to be significantly more prevalent among HCV patients (23 vs. 11%, respectively; $P < 0.001$). Figure 3 depicts TE value distribution in relation to METAVIR activity grades and fibrosis stages, as well as its relationship with the degree of hepatic steatosis. TE values significantly increased in the presence of significant necroinflammatory activity and with higher fibrosis stages, both in HCV and HBV patients ($P < 0.001$, Fig. 3A–D). Medians of TE for each fibrosis stage in HCV patients were comparable to those found in HBV subjects (F0: 4.3 vs. 5.1 kPa, $P = 0.592$; F1: 5.4 vs. 5.3 kPa, $P = 0.640$; F2: 7.3 vs. 7.8 kPa, $P = 0.233$; F3: 9.8 vs. 10.8 kPa, $P = 0.601$; F4:

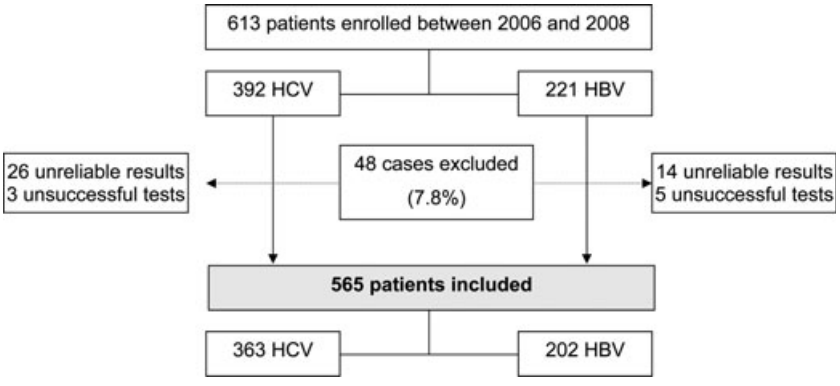

Fig. 1. Flow diagram of candidates. Flow diagram of the potential candidates for participation in this study, reasons for the exclusion and subjects enrolled.

Table 1. Demographic, clinical and laboratorial features of included patients

Characteristic	All patients (n = 565)	HCV (n = 363)	HBV (n = 202)	P
Age, years*	46.1 ± 11.2	49.0 ± 10.2	41.0 ± 11.0	<0.001
Male gender	67%	60%	80%	<0.001
Origin				<0.001
Caucasian	25%	87%	21%	
Asiatic	25%	12%	26%	
Other	50%	1%	53%	
BMI, kg/m²*	24.4 ± 3.5	24.6 ± 3.6	24.2 ± 3.4	0.199
Obesity†	6%	6%	7%	0.838
Diabetes mellitus	5%	5%	5%	0.700
Insulin resistance‡	25%	27%	20%	0.215
ALT, ×ULN§	2.3 (1.0–2.8)	2.5 (1.2–3.1)	2.1 (0.9–2.0)	<0.001
Platelet count, 10^9/L*	211 ± 63	214 ± 63	206 ± 62	0.154
Prothrombin activity, %*	93 ± 10	94 ± 10	90 ± 11	<0.001
Albumin, g/dl*	4.3 ± 1.2	4.2 ± 0.5	4.4 ± 0.5	<0.001
Viral load, logUI/ml*	NA	5.60 ± 0.69	4.90 ± 1.90	NA
HCV genotype 1	NA	58%	NA	NA
HBeAg positive	NA	NA	24%	NA

*Mean ± SD.

†BMI > 30 kg/m².

‡HOMA-IR > 3.0; available for 180 HCV patients and 80 HBV subjects.

§Median (interquartile range).

BMI, body mass index; NA, not applicable; ×ULN, times the upper limit of normal.

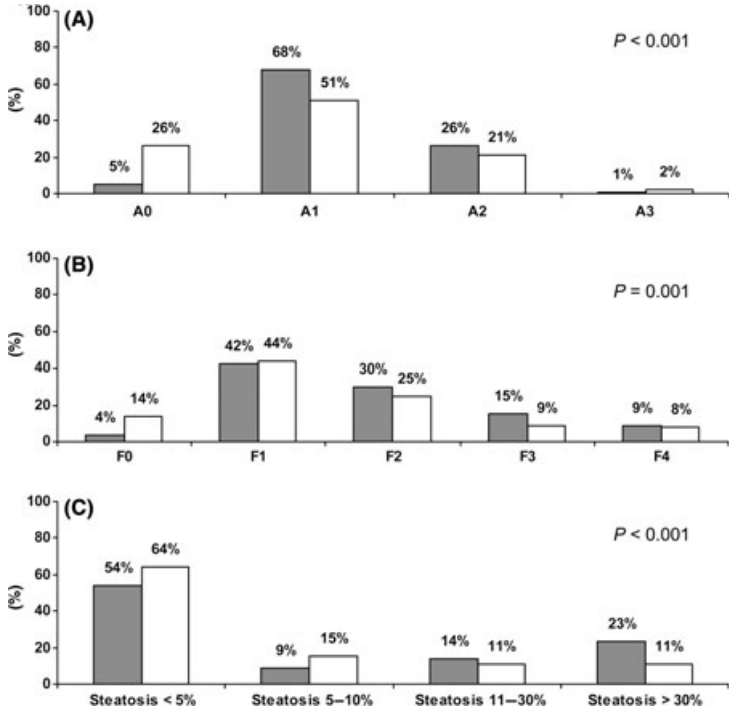

Fig. 2. Histological findings. Distribution of histological findings, including METAVIR necroinflammatory grading (A), METAVIR fibrosis score (B) and steatosis classification (C). Grey bars represent HCV patients, and white bars represent HBV subjects.

20.9 vs. 14.5 kPa, P = 0.248). HCV subjects with moderate to severe steatosis exhibited higher TE values (Fig. 3E); this association was not observed among HBV patients (Fig. 3F).

Diagnostic accuracy of transient elastography

In HCV patients, median TE values were significantly higher when comparing the F2/F3/F4 group to the F0–

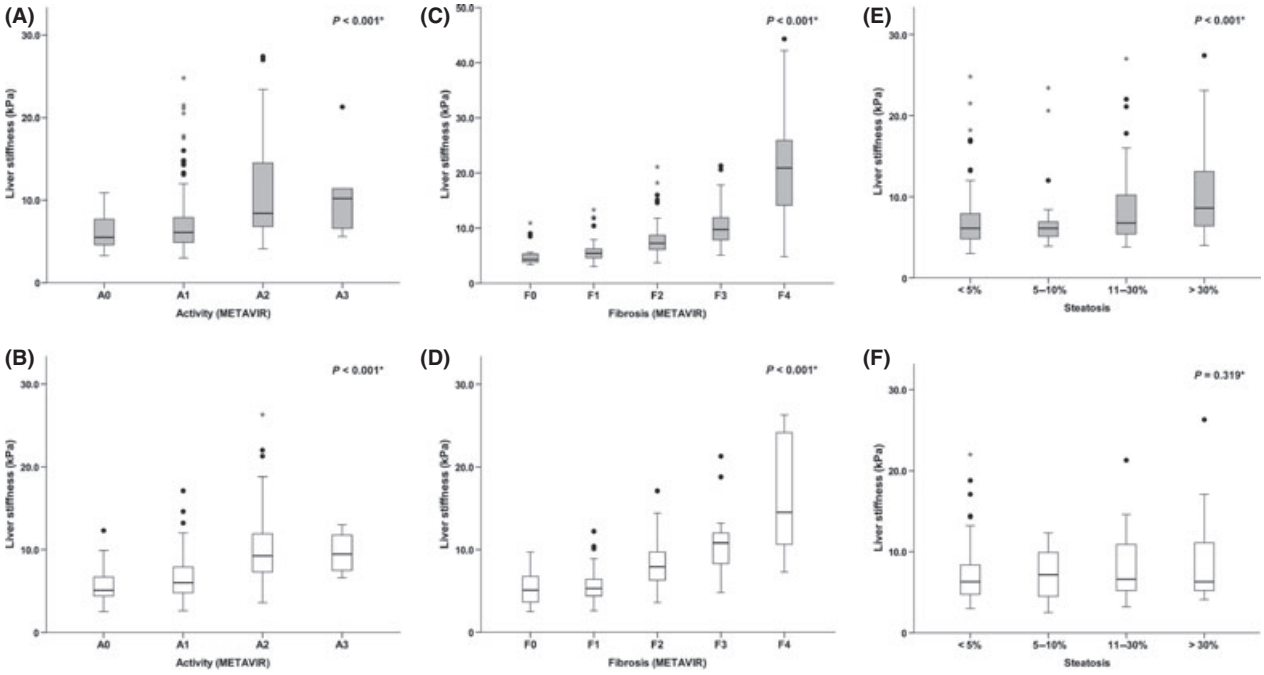

Fig. 3. Box-plots in HCV and HBV patients. Box-plots of transient elastography measurements in HCV (in grey; A, C and E) and HBV patients (in white; B, D and F) for METAVIR necroinflammatory grading (A and B), METAVIR fibrosis score (C and D) and steatosis classification (E and F). The line across the box indicates the median value; the box contains the 25–75% interquartile range and the whiskers represent the highest and the lower values. *Kruskal–Wallis test.

F1 group (8.6 vs. 5.3 kPa, $P < 0.001$), the F3/F4 and the F0/F1/F2 groups (11.5 vs. 6.1 kPa, $P < 0.001$), and cirrhotics and non-cirrhotics patients (20.9 vs. 6.3 kPa, $P < 0.001$). Liver stiffness was also highly discriminative of those with fibrosis scores F $\geq$ 2, F $\geq$ 3 and F4 among HBV patients (8.9 vs. 5.2 kPa, 11.7 vs. 5.9 kPa, and 14.5 vs. 6.1 kPa, respectively; $P < 0.001$ for all comparisons).

As shown in Figure 4, no differences were observed between the area under the receiver-operating characteristics (AUROCs) of the TE measurement for predicting significant fibrosis in HCV and HBV patients (0.868 ± 0.019 vs. 0.867 ± 0.026, $P = 0.975$; Fig. 4A). Likewise, TE exhibited comparable AUROCs for both HCV and HBV subjects in discriminating those with advanced fibrosis (0.894 ± 0.020 vs. 0.902 ± 0.029, $P = 0.820$; Fig. 4B). Finally, AUROCs were not significantly different in HCV and HBV patients for the detection of cirrhosis (0.947 ± 0.027 vs. 0.935 ± 0.024, $P = 0.740$; Fig. 4C). In HBV subjects, HBeAg status had no significant impact on the diagnostic performance of TE in predicting F $\geq$ 2 (0.876 ± 0.032 in HBeAg-negative vs. 0.875 ± 0.059 in HBeAg-positive subjects, $P = 0.988$), F $\geq$ 3 (0.872 ± 0.048 vs. 0.926 ± 0.040, $P = 0.387$) or F4 (0.966 ± 0.024 vs. 0.907 ± 0.055, $P = 0.326$).

Table 2 shows the diagnostic accuracies of the TE in discriminating significant liver fibrosis, advanced fibrosis and cirrhosis by applying the proposed *a priori* cut-offs for HCV and HBV patients. In HCV patients with TE <7.1 kPa, 147 of 209 (70%) exhibited no or mild fibrosis. In all, 135 of 197 HCV patients (68%) with significant fibrosis exhibited TE $\geq$7.1 kPa, and only 11% of the patients without significant fibrosis exhibited TE $\geq$7.1 kPa. Ninety per cent of HCV patients with TE <9.5 kPa showed F0, F1 or F2, and 73% of those with values $\geq$9.5 kPa had F3 or F4 on liver biopsy (LB). By comparison with LB, in HCV subjects, concordant results were found in 78% of cases (282/363) for significant fibrosis, 86% (313/363) for advanced fibrosis, and 93% (339/363) for cirrhosis.

In HBV patients (Table 2), 103 of 125 (82%) of those with TE <7.2 kPa showed F0 or F1. In all, 63 of 85 patients (74%) with significant fibrosis displayed TE $\geq$7.2 kPa, and 12% of those with F0/F1 on LB were incorrectly expected to have F $\geq$ 2. For the prediction of advanced fibrosis, only 4 patients of 140 HBV subjects showed F3/F4 on LB in spite of having TE measurements <8.1 (negative predictive value = 97%). In all, 30 of 62 patients (48%) with TE $\geq$8.1 kPa actually had F3 or F4 on LB. Hence, in HBV patients, concordant results between TE and LB were found in 82% of cases (166/202) for significant fibrosis, 82% (166/202) for advanced fibrosis and 89% (179/202) for cirrhosis.

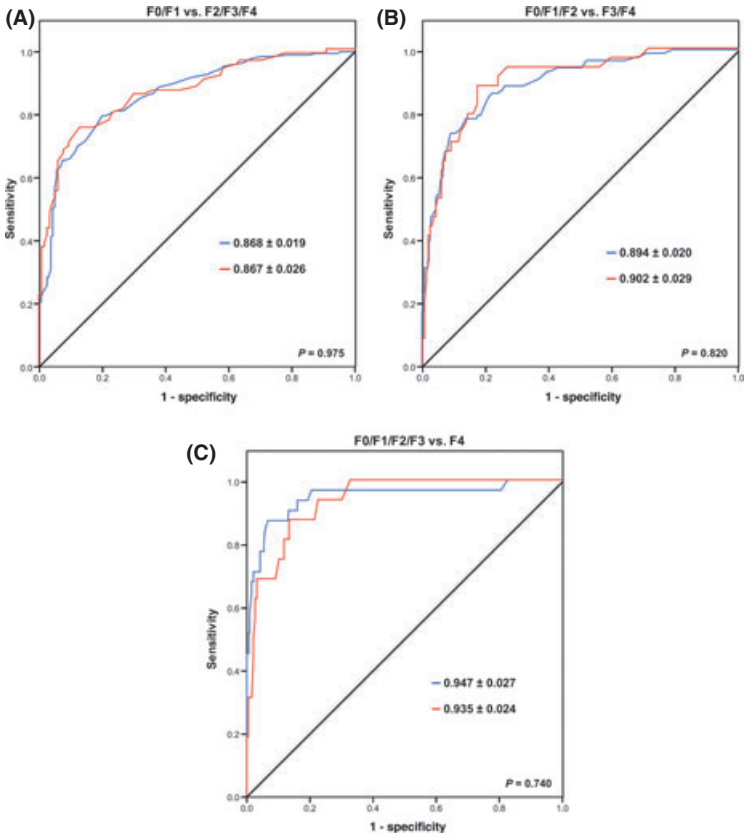

Fig. 4. ROC curves in HCV and HBV patients. Receiver-operating characteristic curves of transient elastography for the diagnosis of significant fibrosis [F0/F1 vs. F2/F3/F4, (A)], advanced fibrosis [F0/F1/F2 vs. F3/F4, (B)] and cirrhosis [F0/F1/F2/F3 vs. F4, (C)] in HCV (blue lines) and HBV (red lines) patients.

Performance of transient elastography in HBV patients according to ALT level

In the HBV group, 35% of subjects showed ALT levels <1 ×ULN, 57% had ALT 1–5 ×ULN, and 8% exhibited ALT values >5 ×ULN. A positive correlation was observed between ALT level and liver stiffness ($r = 0.365$, $P < 0.001$), and patients with elevated ALT presented with higher median TE values (5.5, 6.7, and 9.5 kPa in subjects with ALT <1 ×ULN, 1–5 ×ULN, and >5 ×ULN respectively; $P < 0.001$). Patients with F0/F1 and normal ALT showed TE values not significantly different from those with F0/F1 with elevated ALT levels ($P = 0.153$). Likewise, F3/F4 subjects with normal ALT exhibited TE values not significantly different from those with F3/F4 with elevated ALT levels ($P = 0.945$). Among subjects with significant fibrosis, those with elevated ALT tended to exhibit higher TE measurement as compared to those with normal ALT (8.3 vs. 7.1 kPa respectively; $P = 0.072$). However, this seems not to produce a significant impact on diagnostic accuracy of TE measurement since the AUROCs for the prediction of significant fibrosis, advanced fibrosis and cirrhosis in subjects with normal ALT and in those with elevated ALT were not statistically different (0.830 ± 0.062 vs. 0.868 ± 0.032, 0.904 ± 0.081 vs. 0.883 ± 0.035, 0.984 ± 0.015 vs. 0.907 ± 0.039, respectively; $P \geq 0.05$ for all comparisons).

Table 3 shows the analysis of the accuracy of TE in predicting liver fibrosis in HBV patients by using two different sets of cut-offs, according to distinct ALT levels. Owing to the small number of patients with ALT >5 ×ULN, these subjects were excluded from the analysis. For diagnosing significant fibrosis, comparable diagnostic performances were identified whether using the fixed cut-off points proposed by Marcellin *et al.* (11) or the ALT-specific values defined by Chan *et al.* (12). For estimating the presence or absence of advanced fibrosis and cirrhosis, the cut-off values suggested by Chan *et al.* exhibited slightly better performances, as compared to those proposed by Marcellin *et al.* However, differences were not significant.

Finally, comparable AUROCs were observed for the prediction of all fibrosis ranges in patients with and without significant necroinflammatory activity and significant hepatic steatosis, both in HCV and HBV patients (data not shown; $P > 0.05$ for all comparisons).

Table 2. Diagnostic accuracy of transient elastography in predicting significant fibrosis (METAVIR F2/F3/F4), advanced fibrosis (METAVIR F3/F4) and cirrhosis (METAVIR F4) in 363 HCV and 202 HBV patients, according to classical cut-off values

		Cut-off (kPa)	All patients	F0/F1	F2/F3/F4	PREV (%)	ACC (%)	SEN (%)	SPE (%)	PPV (%)	NPV (%)	LR (+)	LR (−)
Significant fibrosis	HCV		***n* (%)**	***n* = 166**	***n* = 197**	54	78	68	89	88	70	6.00	0.35
		<7.1	209 (58)	147 (89)	62 (31)								
		≥7.1	154 (42)	19 (11)	135 (69)								
	HBV			***n* = 117**	***n* = 85**	42	82	74	88	82	82	6.20	0.30
		<7.2	125 (62)	103 (88)	22 (26)								
		≥7.2	77 (38)	14 (12)	63 (74)								
		Cut-off (kPa)	All patients	F0/F1/F2	F3/F4	PREV (%)	ACC (%)	SEN (%)	SPE (%)	PPV (%)	NPV (%)	LR (+)	LR (−)
Advanced fibrosis	HCV		***n* (%)**	***n* = 276**	***n* = 87**	24	86	68	92	73	90	8.51	0.35
		<9.5	282 (78)	254 (92)	28 (32)								
		≥9.5	81 (22)	22 (8)	59 (68)								
	HBV			***n* = 168**	***n* = 34**	17	82	88	81	48	97	4.63	0.15
		<8.1	140 (69)	136 (81)	4 (12)								
		≥8.1	62 (31)	32 (19)	30 (88)								
		Cut-off (kPa)	All patients	F0/F1/F2/F3	F4	PREV (%)	ACC (%)	SEN (%)	SPE (%)	PPV (%)	NPV (%)	LR(+)	LR (−)
Cirrhosis	HCV		***n* (%)**	***n* = 332**	***n* = 31**	9	93	84	94	58	98	14.65	0.17
		<12.5	318 (88)	313 (94)	5 (16)								
		≥12.5	45 (12)	19 (6)	26 (84)								
	HBV			***n* = 186**	***n* = 16**	8	89	75	90	39	98	7.34	0.28
		<11.0	171 (85)	167 (90)	4 (25)								
		≥11.0	31 (15)	19 (10)	12 (75)								

ACC, accuracy; LR(+), positive likelihood ratio; LR(−), negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; PREV, prevalence of the evaluated fibrosis staging; SEN, sensitivity; SPE, specificity.

Table 3. Comparison of diagnostic accuracy of transient elastography in predicting significant fibrosis (METAVIR F2/F3/F4), advanced fibrosis (METAVIR F3/F4) and cirrhosis (METAVIR F4) in 186 HBV patients with distinct ALT levels, according to the cut-off values proposed by Marcellin *et al.* (11) and by Chan *et al.* (12)

	ALT	Proposed cut-offs (kPa)		PREV (%)	ACC (%)	SEN (%)	SPE (%)	PPV (%)	NPV (%)	LR (+)	LR (−)
Significant fibrosis	≤1 ×ULN	Marcellin	7.2	27	84	61	92	73	87	7.49	0.42
		Chan	6.0		72	78	69	48	89	2.54	0.32
	1–5 ×ULN	Marcellin	7.2	48	80	74	86	83	78	5.34	0.31
		Chan	7.5		79	70	88	84	76	5.78	0.34
Advanced fibrosis	≤1 ×ULN	Marcellin	8.1	10	93	86	93	60	98	12.86	0.15
		Chan	9.0		93	71	95	63	97	14.29	0.30
	1–5 ×ULN	Marcellin	8.1	17	78	90	76	44	97	3.74	0.14
		Chan	12.0		88	53	96	71	91	12.11	0.50
Cirrhosis	≤1 ×ULN	Marcellin	11.0	5	96	67	97	50	98	21.33	0.34
		Chan	12.0		97	67	98	67	98	42.67	0.34
	1–5 ×ULN	Marcellin	11.0	10	87	73	88	40	97	6.06	0.31
		Chan	13.4		92	55	96	60	95	13.64	0.47

ACC, accuracy; LR(+), positive likelihood ratio; LR(−), negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; PREV, prevalence of the evaluated fibrosis staging; SEN, sensitivity; SPE, specificity; ×ULN, times the upper limit of normal.

Discussion

This study was specifically designed to evaluate and compare the diagnostic performance of transient elastography (TE) for the assessment of liver fibrosis in HBV and HCV subjects and was carried out in a single centre and included a large cohort of consecutive subjects who underwent a liver biopsy (n = 565). Its results confirm that TE measurement is an accurate tool for the non-invasive diagnosis of liver fibrosis in patients with chronic viral hepatitis, either related to HBV or HCV.

As expected, TE values significantly increased with higher fibrosis stages, both in HCV and HBV patients (Fig. 3), with TE values being not significantly different between groups for a given fibrosis stage. Specifically regarding HCV patients, TE exhibited a good diagnostic performance in predicting significant fibrosis, and an excellent performance for the diagnosis of advanced fibrosis and cirrhosis, as previously shown in previous studies (10, 15), with area under the receiver-operating characteristics (AUROCs) comparable to these studies (0.868 ± 0.019, 0.894 ± 0.020 and 0.947 ± 0.027 respectively).

In contrast to chronic hepatitis C, there are few studies with appropriate methodology on the accuracy of TE in patients with chronic hepatitis B (11, 12, 16, 17). In a multicentre French study, Marcellin *et al.* (11) evaluated 173 HBV patients and found AUROCs of 0.810 (95% CI 0.730–0.860) for predicting significant fibrosis, and 0.930 (95% CI 0.820–0.980) for estimating the presence of cirrhosis, by using 7.2 and 11.0 kPa as cut-offs respectively. In the present study, performed in a different cohort of patients, TE showed a diagnostic performance comparable to that previously observed, being highly accurate in discriminating patients with significant fibrosis (0.867 ± 0.026), with even higher AUROCs for predicting the presence of advanced fibrosis (0.902 ± 0.029) and cirrhosis (0.935 ± 0.024).

It has been shown that TE exhibits a similar performance for predicting significant fibrosis and higher accuracy to identify cirrhosis, as compared to other non-invasive tests (18–20). This has been further confirmed by Castéra *et al.* (21) in a recent study with 298 HCV patients, in which the performances of TE and of several serum non-invasive biomarkers for predicting the presence of cirrhosis were compared. In this study, TE was the most accurate method for identifying cirrhosis (METAVIR F4). In addition, the highly validated TE cut-off of 12.5 kPa exhibited a positive predictive value (PPV) of 85% to predict the presence of cirrhosis and a negative predictive value (NPV) of 95% to exclude cirrhosis, with LR(+) and LR(−) of 16.6 and 0.18 respectively.

Likewise, Chan *et al.* (12) observed in HBV patients a PPV of 82% for predicting cirrhosis and a NPV of 87% to exclude cirrhosis when using a cut-off of 12.0 kPa for patients with ALT <1 ×ULN [LR(+) = 12.9 and LR (−) = 0.42], and a PPV of 78% and a NPV of 92% when using a cut-off of 13.4 kPa for subjects with ALT 1–5 ×ULN (LR(+) = 11.1 and LR(−) = 0.27). As compared to the results of these two studies, the TE cut-off values used in our study (12.5 kPa for HCV patients and 11.0 kPa for HBV subjects) had similar and high NPVs for excluding cirrhosis (98%), although these cut-offs showed lower PPVs to predict F4 stage (58% for HCV and 39% for HBV, Table 2). This might be attributable to different prevalences of cirrhosis in the study by Castéra *et al.* (23%) (19), in the study by Chan *et al.* (25%) (12), and in this study (8%) (Fig. 2). In fact, this hypothesis is further emphasized by the observation, in our study, of very similar likelihood ratios [LR (+) = 14.65 and LR(−) = 0.17 for HCV; LR(+) = 7.34 and LR(−) = 0.28 for HBV], diagnostic parameters known to be less susceptible to the prevalence of the target disorder (e.g. a given fibrosis stage) in the study population.

An issue that has been a matter of dispute is whether or not TE would reveal a similar diagnostic performance in patients with chronic hepatitis B as compared with patients with chronic hepatitis C. Theoretically, interferences in TE accuracy could be exerted by a macronodular pattern of cirrhosis and by the fluctuation of hepatic necroinflammatory activity (often expressed by exacerbations in serum aminotransferases levels), features more frequently observed in chronic hepatitis B. In addition, in HBV infection, a more precise fibrosis staging is desirable for therapeutic decisions, particularly to identify proper candidates for antiviral therapy [septal fibrosis (F2) is usually required], as well as to select the most adequate drug to be used (interferon is generally not indicated for cirrhotic subjects). In a study published by Ogawa *et al.* (22) they evaluated TE in 68 patients with chronic HBV hepatitis and 161 with chronic HCV hepatitis. These authors found a statistically significant correlation of TE values with liver fibrosis in both HBV and HCV hepatitis ($r = 0.559$ and $r = 0.686$ respectively). However, a direct comparison of accuracies between groups has not been done in that study. In 2010, Sporea *et al.* (23) assessed TE in 140 patients with HBV infection and 317 patients with HCV infection. These authors found a significant correlation between liver stiffness and fibrosis in both groups, with a higher correlation coefficient in HCV patients ($r = 0.578$ vs. $r = 0.408$, $P = 0.02$). Nevertheless, the small number of cirrhotic HBV patients might have biased the comparison (7 vs. 39 HCV). In addition, likelihood ratios have not been presented, making it difficult to draw any firm conclusions. In the present study, by direct comparison, the AUROCs of TE were not significantly different for predicting significant fibrosis, advanced fibrosis and cirrhosis in HBV and HCV patients (Fig. 4). In addition, as shown in Table 2, TE displayed comparable accuracy parameters in both groups. Taken together, these results show that TE exhibits similar overall diagnostic performance in HBV infection as compared to HCV patients.

It is well known that the accumulation of extracellular matrix is the major determinant of liver stiffness. However, it is conceivable that cellular oedema and necroinflammatory changes could also influence TE measurement. This concept is supported by prior studies that observed increasing values of liver stiffness in the presence of high grades of necroinflammatory activity (12, 24–26). In the present study, as expected, HBV subjects with elevated ALT showed higher TE values. This could be explained, at least in part, by an association between higher ALT levels and significant

necroinflammatory activity or steatosis. In fact, we observed an increase of TE values in parallel with the degree of necroinflammatory activity in both HCV and HBV patients (Fig. 3), as well as higher TE values in the presence of more significant hepatic steatosis. Nevertheless, the comparison of diagnostic accuracies of TE in subjects with different ALT levels, as assessed by AUROC analysis, showed no influence of ALT activity on the overall performance of TE in predicting significant fibrosis, advanced fibrosis and cirrhosis. Likewise, comparable AUROCs were found for the diagnosis of significant fibrosis, advanced fibrosis and cirrhosis irrespective of the presence of significant activity or significant hepatic steatosis, in both HCV and HBV patients. However, we cannot exclude the possibility that the association between TE values and steatosis in HBV subjects might have been attenuated by the lower prevalence of moderate/significant steatosis as compared to HCV patients. In fact, in a recently published study by Fraquelli *et al.* (27), severe/moderate necroinflammatory activity was associated with fibrosis overestimation in HBV patients, while severe/moderate steatosis and severe/moderate necroinflammatory activity were independently associated with fibrosis overestimation in HCV subjects.

To evaluate whether the use of fixed cut-off points proposed by Marcellin *et al.* (11) would exhibit the same accuracy of TE measurement for the prediction of fibrosis stage in HBV carriers with normal or elevated ALT levels, we performed a comparison with the ALT-specific values defined by Chan *et al.* (12). For predicting significant fibrosis, both cut-off sets performed similarly in estimating the severity of liver fibrosis in HBV patients with either normal or elevated ALT (Table 3). The cut-off values proposed by Chan *et al.* did not exhibit higher performances for predicting fibrosis stage. The performances were slightly higher for predicting advanced fibrosis and cirrhosis in patients with ALT between 1 and 5 $\times$ULN, however, the differences were not significant. This discrepancy between our results and those of Chan *et al.* might be because of different populations studied. The use of cut-offs more adapted to the interference of necroinflammatory activity (expressed by higher ALT levels) on TE measurement, instead of fixed values, needs to be validate in further studies, in different populations.

In conclusion, in HBV patients, TE measurement reliably predicts the absence or the presence of significant fibrosis, advanced fibrosis or cirrhosis, and exhibits similar diagnostic performance as compared to HCV subjects. In patients with chronic hepatitis B, the use of TE cut-off values adjusted to ALT level for estimating liver fibrosis needs to be validated.

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