Assessment of Liver Fibrosis With Elastography Point Quantification vs Other Noninvasive Methods

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BACKGROUND & AIMS: **Elastography point quantification (ElastPQ) is a non-invasive method for assessing liver fibrosis based on liver stiffness. We evaluated the accuracy of ElastPQ for the staging of liver fibrosis in patients with chronic liver disease (CLD) compared with aspartate transaminase to platelet ratio index, fibrosis-4 index, and transient elastography (TE), using liver biopsy as reference standard.**

METHODS: **We performed a retrospective study of 406 patients with CLD of any etiology who underwent liver biopsy analysis from September 2012 through June 2017 at a clinic in Bologna, Italy. We obtained liver stiffness measurements, made by ElastPQ and TE, for 361 patients. Liver fibrosis stage was assessed by the METAVIR scoring system. Areas under the receiver operating characteristic curve (AUROC) were used to assess the diagnostic performance of ElastPQ.**

RESULTS: **ElastPQ values correlated with histologic detection of fibrosis ($r = 0.718$; $P < .001$). The AUROC values were 0.856 for detection of significant fibrosis (F≥2), 0.951 for advanced fibrosis (F≥3), and 0.965 for cirrhosis. The best cut-off values identified for classifying patients with F≥2, F≥3, or cirrhosis were 6.0 kPa, 6.2 kPa, and 9.5 kPa, respectively: these were lower than those for TE. Comparison of ElastPQ with TE data resulted in superimposable diagnostic accuracy of both methods for each stage of liver fibrosis. Both elastography techniques performed better than aspartate transaminase to platelet ratio index or fibrosis-4 index scores ($P < .05$ for all AUROC comparisons).**

CONCLUSIONS: **ElastPQ has good to excellent performance for the non-invasive staging of liver fibrosis in patients with CLD. ElastPQ identified patients with fibrosis or cirrhosis with levels of accuracy that were not inferior to those of TE, and outperformed serum fibrosis indexes in identifying each stage of liver fibrosis.**

Keywords: Fibrosis; Liver Biopsy; Liver Stiffness; Noninvasive Assessment.

The degree of liver fibrosis is the most important predictor of disease outcome in chronic liver disease (CLD) and influences the prognosis and therapeutic management.[1,2] For years, liver biopsy has been considered the reference method for the staging of liver fibrosis, even though it is invasive, often painful, and with limitations in diagnostic accuracy, such as sampling error and/or intraobserver and interobserver variability.[3–6] To overcome these limitations, the noninvasive approaches based on serologic methods or imaging techniques were increasingly developed for the evaluation of liver fibrosis.[7]

Transient elastography (TE) is the first available and most extensively evaluated shear wave elastography method for liver fibrosis assessment in various CLD and its usefulness was confirmed by several meta-analyses.[8–11] However, in the clinical practice this method is limited by a high rate of unreliable results.[12,13] More recently, several manufactures of ultrasound systems

Abbreviations used in this paper: APRI, aspartate aminotransferases-to-platelets ratio index; AST, aspartate aminotransferases; AUROC, area under the receiver operating characteristic curve; CLD, chronic liver disease; ElastPQ, elastography point quantification; FIB-4, fibrosis-4; HCV, hepatitis C virus; IQR, interquartile range; LSM, liver stiffness measurement; PPV, positive predictive value; TE, transient elastography.

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have implemented shear wave-based measurement methods that have become rapidly available in clinical practice. As well as TE, these techniques are based on shear waves but have the advantage of being able to measure real-time liver stiffness during an abdominal ultrasound scan.[7,14] The shear wave measurement software available on the Philips ultrasound system is an elastography point quantification (ElastPQ). As reported in the current guidelines,[7,14] evidence regarding accuracy of ElastPQ for fibrosis staging is limited, both because of its relatively recent release on the market (in 2012 in the United States) and the decrease in the number of liver biopsies in current clinical practice.

The aim of this study was to prospectively compare the diagnostic accuracy of ElastPQ, TE, and biochemical markers of fibrosis for the staging of liver fibrosis in a large cohort of patients with CLD using METAVIR histology scoring system as reference standard.

What You Need to Know

Background

Noninvasive methods had rapidly replaced percutaneous liver biopsy in the assessment of liver fibrosis.

Findings

ElastPQ has high diagnostic accuracy for the staging of liver fibrosis and performing better than other noninvasive methods in the assessment of liver fibrosis.

Implications for patient care

ElastPQ can be considered a useful tool for optimizing the diagnostic and therapeutic approaches used for liver diseases and a promising alternative in the assessment of liver fibrosis.

Patients and Methods

Patients

All consecutive patients with CLD of any cause scheduled to liver biopsy from September 2012 to June 2017 at the Diagnostic and Interventional Ultrasound Unit of Policlinico S. Orsola-Malpighi, Bologna, Italy, were evaluated. For all patients, clinical parameters including age, sex, body mass index, standard liver blood tests, abdominal ultrasonography, and ElastPQ were determined at the time of liver biopsy. The patients who had undergone liver stiffness measurement (LSM) using TE within 2 weeks from liver biopsy were included. All physicians who performed LSM were blinded to the results of other noninvasive methods and liver biopsies. Exclusion criteria were: (1) age less than 18 years, (2) previous liver transplantation, (3) decompensated cirrhosis and/or evidence of hepatocellular carcinoma and/or biliary obstruction, (4) acute liver injuries of any cause on CLD, (5) LSM not assessed or time between liver biopsy and TE >2 weeks, and (6) liver biopsy samples smaller than 20 mm or having less than 11 portal tracts.

This study was performed on ethics approval from the institutional regulatory board of the hospital as part of a global approval for elastography studies (code number: 025/2013/O/Sper). Written informed consent was obtained from each enrolled patient before enrolment.

Serum Liver Fibrosis Indexes

Blood samples were obtained from all patients after an overnight fast to quantify the number of platelets in the blood, serum aspartate aminotransferases (AST), alanine transaminases, and γ-glutamyltransferase. AST-to-platelets ratio index (APRI)[15] and fibrosis-4 (FIB-4)[16] were calculated.

Liver Biopsy and Histologic Examination Criteria

Liver biopsies were performed under ultrasound guidance by an attending physician (C.S.). As for the diagnostic protocol not less than one 16-gauge 2-cm long core biopsy from the right liver lobe was considered satisfactory. The liver biopsy specimens were fixed in formalin and embedded in paraffin as preparation procedure. A senior pathologist (A.D.), with >10 years of experience, who was unaware of the biochemical parameters and ElastPQ and TE values examined the tissue samples and reported *ad hoc* the liver fibrosis stage according to the METAVIR scoring system.[17] The histologic fibrosis stage was used as gold standard for the analysis.

Elastography Point Quantification

LSM was assessed with ElastPQ technique by 1 physician (C.S.), using an iU22 scanner with a convex probe C5-1. Investigator had more than 5 years of experience in real-time elastography studies. The examinations were performed in the right lobe of the liver through intercostal spaces, with the patient lying supine with the right arm in maximal abduction and suspended normal respiration. Using a real-time B-mode image, the rater selected a vessel-free area, at least 1.5 cm below Glisson capsule, where a fixed region of interest of 0.5 × 1.5 cm was placed by moving a trackball. Using the software provided by the manufacturer (version 6.3.2.2), we calculated LSM expressed in kilopascal. Ten successful measurements of ElastPQ were obtained in the same location for every patient. Mean value and standard deviation within the region of interest were recorded. In absence of specific quality criteria indicated by the manufacturer of the ElastPQ, we considered as "unreliable measurement" the inability to obtain 10 successful LSM and as "failure" when no measurements were obtained.

Liver Stiffness Measurement

TE was performed with FibroScan (Echosens, Paris, France), using the M and XL probe (the latter available from January 2017). Two physicians (F.C. and S.G.), with experience of at least 500 TE procedures, performed all the examinations. Liver stiffness was assessed through the intercostal spaces during breath hold, with the patient in the supine position, right arm above the head. Results were expressed as the median value of the total measurements in kilopascal. The success rate of LSM was calculated as the ratio between validated and total measurements. TE was considered reliable when 10 validated measurements were acquired with a success rate of at least 60% and interquartile range (IQR) <30% of the median (in patients with LSM ≥7.1 kPa). Unsuccessful LSM was defined as either the presence of valid measurements that did not meet the above criteria (unreliable) or total absence of valid measurements (failure).

Statistical Analysis

The results were reported as median ± IQR for continuous variables and as frequency and percentage for categorical variables. The Mann-Whitney and chi-square tests were used to compare continuous and categorical variables as appropriate. Correlations between the results of ElastPQ, TE, FIB-4, APRI, and histologic fibrosis stage were analyzed using Spearman correlation coefficients. A correlation was considered to be strong if the correlation coefficient was 0.7–1.0 and moderate if correlation coefficient was 0.4–0.7. Multivariate regression analysis using backward, step-wise elimination, was performed using linear regression to identify independent variables influencing ElastPQ. Receiver operating characteristic curves for APRI, FIB-4, TE, and ElastPQ were built. Area under the receiver operating characteristic curve (AUROC) and the 95% confidence intervals of the AUROC values were calculated for detection of any degree of histologic fibrosis. The AUROCs were categorized as excellent if higher than 0.9, as good for values between 0.8 and 0.9, and as fair for values between 0.7 and 0.8. Significant differences between AUROCs were tested using the Hanley and McNeil method.[18] A $P < .05$ was considered significant. The AUROC for differentiating significant (F2-F4) fibrosis from nonsignificant (F0-F1) fibrosis (DANA) was standardized according to the prevalence of fibrosis stage in the present study population, as previously described.[19] Cutoff values were determined for noninvasive tests to predict degree of fibrosis using an optimization step that maximized the Youden index. Furthermore, descriptions of the operating characteristics (sensitivity, specificity, positive predictive value [PPV], negative predictive value, positive likelihood ratio, and negative likelihood ratio) of noninvasive tests for the detection of fibrosis were calculated assuming that gold standard for the diagnosis of fibrosis was the histologic examination. All analyses were performed using SPSS for Windows (Statistical Package for the Social Sciences, version 21.0, Armonk, NY).

Results

Patients' Characteristics

A total of 491 patients underwent liver biopsy and ElastPQ. No biopsy-related bleeding complications were identified. Eighty-five (17.3%) did not meet the eligibility criteria and were excluded (Figure 1). TE was not performed in 33 patients because of equipment maintenance. Among 406 patients enrolled, unsuccessful LSM were obtained in 45 (11.1%): TE was unreliable in 18 and failed in 27 patients of whom 3 also failed ElastPQ (all with body mass index >25 kg/m^2). Finally, 361 patients with valid LSM using TE and ElastPQ were included for the analysis. The main clinical and demographic characteristics of the study cohort are summarized in Table 1.

Liver Stiffness Measurement Characteristics and Factors Influencing Elastography Point Quantification Measurements

The overall median LSM was 5.0 kPa (IQR, 4.2; range, 2.4–40.4) using ElastPQ and 6.9 kPa (IQR, 6.4; range, 2.5–61.5) using TE. The 2 elastography techniques

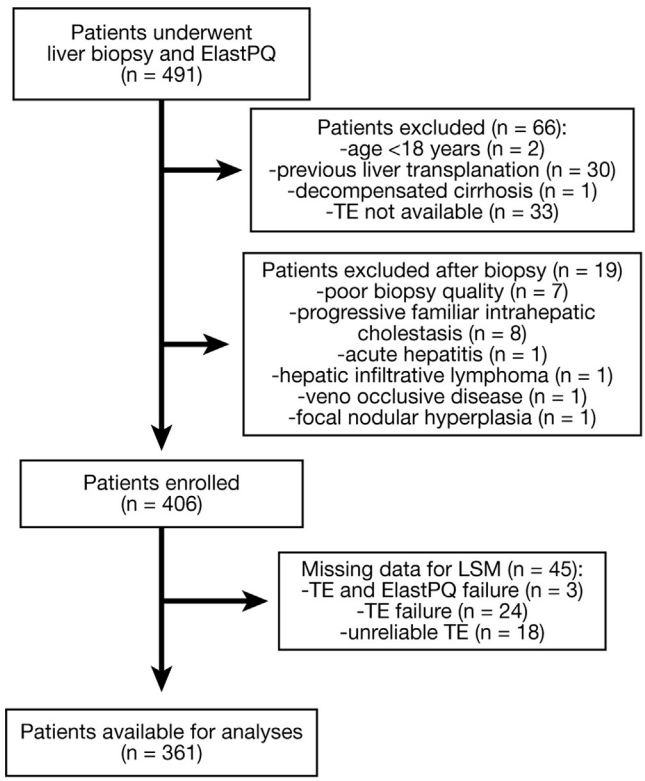

Figure 1. Flow chart of patients included in the study.

Table 1. Main Clinical and Demographic Characteristics of the 361 Patients With Chronic Liver Disease Enrolled

Variable	All patients (n = 361)	HCV patients (n = 173)	*P* value
Age, *y*	51 ± 17	52 ± 12.5	.485
Male gender	192 (53.2)	90 (52)	.853
BMI, kg/m^2	25.2 ± 5.6	24.7 ± 4.8	.067
AST, *U/L*	36 ± 35.5	41 ± 42	.190
ALT, *U/L*	46 ± 53	53 ± 55	.097
gGT, *U/L*	47.5 ± 63.3	39 ± 40.8	.022
PLT, $\times 10^3/mmc$	197 ± 92	187 ± 97	.232
Biopsy length, *mm*	30.3 ± 8.4	29.5 ± 7.6	.874
Aetiology			
HCV	173 (47.9)		
HBV	40 (11.1)		
NASH/ASH	66 (18.3)		
PBC/AIH/overlap	62 (17.2)		
cryptogenetic	20 (5.5)		
Histologic fibrosis stage (METAVIR score)			.660
F0–1	191 (52.9)	92 (53.1)	
F2	68 (18.8)	39 (22.5)	
F3	57 (15.8)	24 (13.9)	
F4	45 (12.5)	18 (10.4)	

NOTE. Data are given as median ± interquartile range or as number of cases (%).
AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ASH, alcoholic steatohepatitis; AST, aspartate aminotransferase; BMI, body mass index; gGT, γ-glutamyltransferase; HBV, hepatitis B virus; HCV, hepatis C virus; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; PLT, platelet count.

covaried linearly ($r = 0.784$; $P < .001$). Supplementary Figure 1 shows the plot of the correlation between TE and ElastPQ. The median values of ElastPQ, such as TE, APRI, and FIB-4, increased with increasing degree of fibrosis (Table 2). ElastPQ and TE demonstrated a strong correlation with histologic fibrosis stage ($r = 0.718$ and $r = 0.776$, respectively). A lower coefficient of correlation was found for serum liver fibrosis indexes. Multivariate regression analysis, including sex, age, AST, alanine transaminases, γ-glutamyltransferase, platelets, etiology, and METAVIR stage, confirmed the correlation of ElastPQ with fibrosis stage (B = 4.289; standard error, 0.196; $P < .001$), but not with all other variables.

Comparison of the Diagnostic Performances of Elastography Point Quantification, Transient Elastography, Aspartate Aminotransferases-to-Platelets Ratio Index, and Fibrosis-4

Pairwise comparisons of AUROC values among ElastPQ, TE, APRI, and FIB-4 were performed (Table 3 and Figure 2). Diagnostic performance according to the AUROC values for the detection of both advanced fibrosis and cirrhosis was excellent for ElastPQ and for TE. For the diagnosis of significant fibrosis, TE showed only a slight improvement in the AUROC compared with ElastPQ. However, both elastography techniques performed better than APRI and FIB-4 ($P < .05$ for all receiver operating characteristic curve comparisons).

The difference between the mean fibrosis stage of significant fibrosis and the mean fibrosis stage of nonsignificant fibrosis (DANA) for our patient cohort was 2.92. Hence, the adjusted AUROCs were 0.811.

Optimal cutoff values assessed by ElastPQ for predicting the different degree of fibrosis ranged from 6.0 kPa (for significant fibrosis) to 9.5 kPa (for cirrhosis) and were closer and lower than those assessed by TE (Table 3). When we performed analyses according to a sensitivity of at least 90% and a specificity of at least 90%, the optimal cutoff values of ElastPQ for the diagnosis of F2 or greater, F3 or greater, and F4 were also very close (Supplementary Table 1).

With respect to TE, ElastPQ showed a lower sensitivity in the detection of significant fibrosis, whereas in the assessment of cirrhosis ElastPQ had a slightly higher sensitivity than TE. However, ElastPQ showed a higher specificity than TE in assessing significant fibrosis but had a lower specificity for the assessment of advanced fibrosis.

A similar negative predictive value was found between ElastPQ and TE for the diagnosis of significant fibrosis, whereas PPV was higher for ElastPQ, with a risk of misclassification caused by false positives of 6.6%. Conversely, for the diagnosis of advanced fibrosis, TE had a significantly higher PPV than ElastPQ. For the diagnosis of cirrhosis, negative predictive values were high in both elastography techniques with a negligible

Table 2. ElastPQ, TE, APRI, and FIB-4 Values According to Fibrosis Stage

Variable	Fibrosis stage (METAVIR)				Correlation coefficient
	F0–1	F2	F3	F4	
ElastPQ	4.2 ± 1.5	4.9 ± 2.7	9.3 ± 7.7	17.5 ± 10.7	0.718 ($P < .001$)
TE	5.4 ± 2.3	7.5 ± 3.0	15.4 ± 10.2	25.1 ± 14.0	0.776 ($P < .001$)
APRI	0.33 ± 0.27	0.53 ± 0.65	1.02 ± 1.09	1.31 ± 1.38	0.583 ($P < .001$)
FIB-4	1.04 ± 0.76	1.52 ± 1.28	2.60 ± 2.13	4.45 ± 4.16	0.623 ($P < .001$)

NOTE. Data are expressed as the median ± IQR. Correlation among APRI, FIB-4, TE, ElastPQ, and fibrosis stage was tested using the nonparametric Spearman correlation coefficient.
APRI, aspartate aminotransferases-to-platelets ratio index; ElastPQ, elastography point quantification; FIB-4, fibrosis-4; TE, transient elastography.

Table 3. Analysis of Diagnostic Performance Between ElastPQ, TE, APRI, FIB-4, and METAVIR Stage

	All patients								
Fibrosis stage	Cutoff	AUROC (95% CI)	Accuracy, %	Sens, %	Spec, %	PPV (95% CI)	NPV (95% CI)	LR+	LR-
ElastPQ									
F ≥2	6.0	0.856 (0.816–0.896)	83.1	71.8	93.2	90.4% (84.2–94)	78.8% (73–83.6)	10.544	0.303
F ≥3	6.2	0.951 (0.925–0.977)	88.1	94.1	85.7	72.2% (64–79.1)	97.4% (94.4–98.8)	6.588	0.069
F = 4	9.5	0.965 (0.948–0.982)	90.9	97.8	89.9	57.9% (46.7–68.4)	99.6% (98–99.9)	9.656	0.025
TE									
F ≥2	7.6	0.900 (0.869–0.931)	81.4	77.6	84.8	82% (75.3–87.2)	81% (75–85.8)	5.114	0.263
F ≥3	9.5	0.969 (0.948–0.990)	92.8	94.1	92.3	82.8% (74.9–88.6)	97.6% (94.8–98.9)	12.188	0.064
F = 4	13.9	0.959 (0.939–0.978)	89.8	95.6	88.9	55.1% (44.1–65.7)	99.3% (97.5–99.8)	8.627	0.050
APRI									
F ≥2	0.53	0.801 (0.756–0.846)	74.2	70	78	73.9% (66.6–80.1)	74.5% (68–80)	3.183	0.385
F ≥3	0.62	0.844 (0.802–0.887)	77.6	82.4	75.7	57.1% (49.1–64.9)	91.6% (87.1–94.6)	3.386	0.233
F = 4	0.63	0.855 (0.812–0.899)	70.9	93.3	67.7	29.2% (22.4–37.1)	98.6% (96–99.5)	2.892	0.098
FIB-4									
F ≥2	1.54	0.814 (0.769–0.858)	75.6	74.1	77	74.1% (67.1–80.1)	77% (70.5–82.4)	3.217	0.336
F ≥3	1.67	0.878 (0.8141–0.916)	78.1	88.2	74.1	57.3% (49.5–64.8)	94.1% (90–96.6)	3.411	0.159
F = 4	2.23	0.907 (0.872–0.941)	79.8	91.1	78.2	37.3% (28.8–46.6)	98.4% (96–99.4)	4.173	0.114

APRI, aspartate aminotransferases-to-platelets ratio index; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ElastPQ, elastography point quantification; FIB-4, fibrosis-4; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; TE, transient elastography.

risk of misdiagnosis caused by false negatives: cirrhosis was assessed by biopsy in less than 1% of patients with liver stiffness lower than the cutoff. However, PPV for cirrhosis was considerably lower with a risk of misclassification caused by false positives of 42.1% using ElastPQ and 44.9% using TE.

Overall, using AUROC cutoffs, ElastPQ correctly classified 247 of 361 (68.4%) patients, whereas TE correctly classified 244 of 361 (67.6%) patients. Cohen kappa was similar for ElastPQ and TE (0.488 and 0.493, respectively). Both techniques showed a lower rate of correctly classified patients in F2 stage with respect to the others. Among patients misclassified with ElastPQ, only 8 of 114 (7%) had standard deviation/mean >0.30 ($P = .824$).

Concordance Between Elastography Point Quantification and Transient Elastography

ElastPQ and TE agreed on the diagnosis of <F2 versus ≥F2 in 297 patients (82.3%). In the 64 patients in whom they disagreed, ElastPQ agreed with liver biopsy results in 35 cases and TE in 31 cases. ElastPQ and TE agreed on the diagnosis of <F3 versus ≥F3 in 316 patients (87.5%). Among the 45 patients in whom they disagreed, ElastPQ agreed with liver biopsy results in 14 cases and TE in 31 cases. Finally, ElastPQ and TE agreed on the diagnosis of <F4 versus F4 in 339 patients (93.9%). Among the 22 patients in whom they disagreed, ElastPQ agreed with liver biopsy results in 13 cases and TE in 9 cases.

Subgroup Analysis of Hepatitis C Virus Cohort

From analysis of 173 patients with chronic hepatitis C, the best cutoff values of ElastPQ for diagnosing significant fibrosis, advanced fibrosis, and cirrhosis were 6.2 (AUROC, 0.860), 7.5 (AUROC, 0.976) and 9.7 (AUROC, 0.976) kPa, respectively (Supplementary Table 2 and Supplementary Figure 2). For each stage of fibrosis, the diagnostic performance of ElastPQ was significantly better than those of APRI and of FIB-4 but was not significantly different from TE.

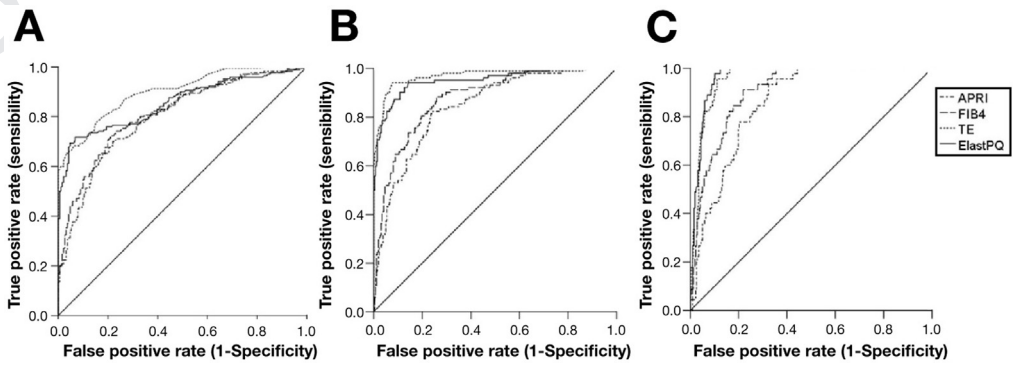

Figure 2. Receiver-operating characteristic curves for ElastPQ, TE, APRI, and FIB-4 for the diagnosis of (*A*) significant fibrosis (F2 or greater), (*B*) advanced fibrosis (F3 or greater), and (*C*) cirrhosis (F4).

Intention-to-Diagnose Analysis

An intention-to-diagnose analysis using per-protocol cutoff values was performed to evaluate the stability of our results. Failures and unreliable results were included as false negatives. The analysis showed a negative effect on the correct classifications and sensitivity of the 2 elastography techniques (Supplementary Table 3).

Discussion

During the last years, the number of ultrasound-based elastography techniques has rapidly increased and shear wave elastography devices from several companies are now on the market. When it comes to Philips ElastPQ technology, only a few studies were published so far,[20–25] mainly examining small series and without having liver histology as reference standard because of the decreasing number of liver biopsies performed in many hepatologic centers.

To our knowledge, this is the largest biopsy-controlled study comparing ElastPQ with TE and others serum fibrosis indexes having histology as a reference standard. In line with previous findings,[20–26] our data showed that liver stiffness measured with ElastPQ was directly and linearly correlated with the stages of fibrosis, and the values increased with the extent of liver fibrosis.

Furthermore, our results strongly support that ElastPQ has high diagnostic accuracy for the staging of liver fibrosis. As previously reported for TE[26–30] and ARFI,[31–34] the diagnostic accuracy of ElastPQ assessed by AUROC was more than 95% for the diagnosis of advanced fibrosis and cirrhosis and about 85% for the diagnosis of significant fibrosis. According to these results, ElastPQ can be used in clinical practice as a good diagnostic tool for the diagnosis of significant fibrosis and as an excellent tool for the diagnosis of advanced fibrosis and cirrhosis. Interestingly, the performance of ElastPQ for the staging of fibrosis was similar in the hepatitis C virus (HCV) subgroup as compared with the overall group.

In our cohort ElastPQ showed a noninferior performance compared with TE for each stage of fibrosis. This suggests that both methods may be used in the noninvasive work-up of patients with liver disease. Nevertheless, several advantages of ElastPQ over TE exist. ElastPQ is integrated in a routine ultrasound machine, which provides both B-mode imaging and quantitative liver stiffness assessment. Although the size of the region of measurement is indeed smaller than in TE, it can be selectively placed in real-time and the LSM can benefit from the guidance of anatomic and tissue information.

ElastPQ and TE outperformed APRI and FIB-4 in identifying each stage of liver fibrosis. Differently from the stiffness that directly depends on internal structure of the liver, the serum markers calculated using AST and alanine transaminases reflect alterations of hepatic function but not of the extracellular matrix metabolism.

The best cutoff values identified in our series for predicting significant fibrosis, advanced fibrosis, and cirrhosis were 6.0, 6.2, and 9.5 kPa, respectively. As reported in another study[35] comparing ElastoPQ with TE in a smaller cohort of patients with CLD, cutoff values for ElastPQ were lower than those for TE for the same fibrosis stages. Furthermore, liver fibrosis assessed by METAVIR turned out to be the only independent determinant of LSM obtained with ElastPQ without interference of usual TE confounders, such as transaminases, age, or body mass index. However, our thresholds are slightly closer to each other and lower than those from Fraquelli et al,[35] both in the overall cohort and in the HCV subgroup, although patients' characteristics and fibrosis stage distribution were superimposable between 2 studies.

In our study, LSM failed in less than 1% of patients using ElastPQ and in more than 6% using TE. However, the lack of the XL probe during the first part of the study reduced the rate of reliable results for TE and likely prevented a proper comparison of feasibility between 2 elastography techniques. When this study was performed, no published data suggesting usefulness of reliability criteria for ElastPQ were available and to date there is no agreement on objective quality criteria. However, only 8 of 114 misclassified patients had standard deviation/mean >0.30 suggesting that this criterion results in a negligible improvement in the accuracy of this technique.

Our study has some limitations. First, the different stages of fibrosis were not uniformly balanced in our series and this uneven distribution may have affected the optimal cutoff values obtained with the receiver operating characteristic curves. Second, our cohort included patients with CLD from various causes, in whom fibrosis is commonly staged using different scoring systems. However, all biopsy specimens were classified according METAVIR scoring system. Furthermore, an appropriate subgroup analysis for patients with HCV was reported and we did not find significant difference in the diagnostic accuracy of the technique between patients with HCV and without HCV. In other etiologies, the small sample size prevents us from reaching any conclusion. Finally, we did not analyze separately the data obtained with M and XL probe because the latter was available only in the last 4 months of the enrolment and was effectively used only in 2 subjects.

In conclusion, ElastPQ is an accurate and reliable noninvasive method for the staging of liver fibrosis in patients with CLD. This technique provides similar diagnostic performance compared with TE in identification of all stages of fibrosis but, with respect to TE, is implemented on conventional ultrasound systems and has the advantage of B-mode imaging. Further prospective studies are needed to validate the thresholds obtained with ElastPQ for the different fibrosis stages and

to evaluate their prognostic value toward the prediction of clinically relevant so-called hard outcomes, such as development of portal hypertension, hepatic decompensation, and mortality.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.06.027.

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Reprint requests
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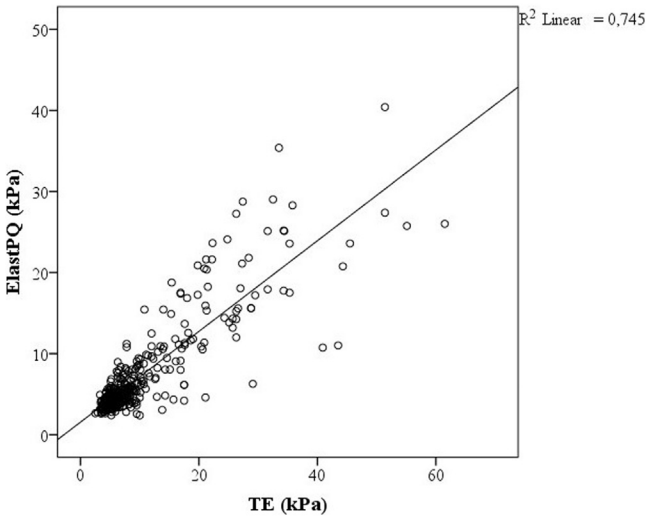
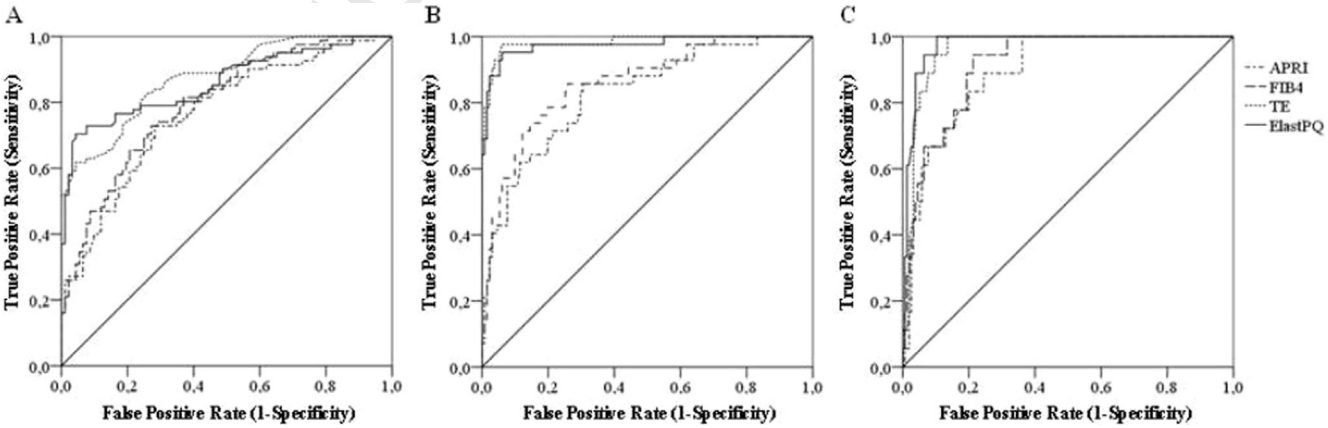
Conflicts of interest Q2
The authors disclose no conflicts.



Supplementary Figure 1. Plot show the correlation between liver stiffness values by using ElastPQ and TE.



Supplementary Figure 2. Receiver operating characteristic curves for ElastPQ, TE, APRI, and FIB-4 for the diagnosis of (*A*) significant fibrosis (F2 or greater), (*B*) advanced fibrosis (F3 or greater), and (*C*) cirrhosis (F4) in HCV cohort.

Supplementary Table 1. Analysis of Diagnostic Performance Between ElastPQ and METAVIR Stage According to a Sensitivity ≥90% and a Specificity ≥90%

Fibrosis stage	Cutoff	Accuracy, %	Sens, %	Spec, %	PPV, % (95% CI)	NPV, % (95% CI)	LR+	LR-
F ≥2	4.2	69.3	90	50.8	61.9 (58.3–65.5)	85.1 (78.1–90.1)	1.83	0.20
	5.8	82	71.8	90.6	87.8 (81.9–92)	78.4 (74–82.2)	8.06	0.31
F ≥3	6.6	89.5	90.2	89.2	76.7 (69.7–82.4)	95.9 (92.8–97.7)	8.34	0.11
	6.9	89.5	87.3	90.3	78.1 (70.9–83.9)	94.7 (91.5–96.8)	9.04	0.14
F = 4	10.7	91.4	91.1	91.5	60.3 (51.1–68.8)	98.6 (96.6–99.5)	10.66	0.10
	9.7	90.9	95.6	90.2	58.1 (49.7–66.1)	99.3 (97.4–99.8)	9.74	0.05

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ElastPQ, elastography point quantification; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

Supplementary Table 2. Analysis of Diagnostic Performance Between ElastPQ, TE, APRI, FIB-4, and METAVIR Stage in HCV Cohort

	HCV cohort							
Fibrosis stage	Cutoff	AUROC (95% CI)	Accuracy, %	Sens, %	Spec, %	PPV, % (95% CI)	NPV, % (95% CI)	LR+	LR-
ElastPQ									
F ≥2	6.2	0.860 (0.803–0.917)	83.8	70.4	95.7	93.4 (84.3–97.4)	78.6 (70.1–85.2)	16.185	0.310
F ≥3	7.5	0.976 (0.948–1.000)	94.2	95.2	93.9	83.3 (70.4–91.3)	98.4 (94.4–99.6)	15.595	0.051
F = 4	9.7	0.976 (0.955–0.997)	92.8	100	89.7	52.9 (36.7–68.5)	100 (97.3–100)	9.688	0
TE									
F ≥2	8.8	0.874 (0.824–0.925)	79.8	61.7	95.7	92.6 (82.4–97.1)	73.9 (65.4–81)	14.198	0.400
F ≥3	9.5	0.983 (0.963–1.000)	94.8	97.6	93.9	83.7 (71–91.5)	99.2 (95.6–99.9)	15.985	0.025
F = 4	11.2	0.962 (0.935–0.990)	87.9	100	86.5	46.2 (31.6–61.4)	100 (97.2–100)	7.381	0
APRI									
F ≥2	0.53	0.768 (0.698–0.838)	72.3	72.8	71.7	69.4 (59–78.2)	75 (65–82.9)	2.577	0.379
F ≥3	0.62	0.829 (0.758–0.901)	73.4	85.7	69.5	47.4 (36.5–58.5)	93.8 (87.2–97.1)	2.807	0.206
F = 4	1.03	0.895 (0.834–0.956)	76.9	88.9	75.5	29.6 (19.1–42.8)	98.3 (94.1–99.5)	3.626	0.147
FIB-4									
F ≥2	1.53	0.796 (0.731–0.861)	72.8	72.8	72.8	70.2 (59.8–79)	75.3 (65.4–83.1)	2.681	0.373
F ≥3	1.87	0.861 (0.796–0.925)	76.9	85.7	74.1	51.4 (40–62.8)	94.2 (87.9–97.3)	3.303	0.193
F = 4	2.45	0.915 (0.865–0.966)	80.3	94.4	78.7	34 (22.4–47.8)	99.2 (95.5–99.9)	4.436	0.071

APRI, aspartate aminotransferases-to-platelets ratio index; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ElastPQ, elastography point quantification; FIB-4, fibrosis-4; HCV, hepatitis C virus; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; TE, transient elastography.

Supplementary Table 3. Intention-to-Diagnose Analysis

	F0–1 vs F2–4		F0–2 vs F3–4		F0–3 vs F4	
Fibrosis	ElastPQ	TE	ElastPQ	TE	ElastPQ	TE
Correctly classifies	335/406 (82.5%)	294/406 (72.4%)	358/406 (88.2%)	335/406 (82.5%)	361/406 (88.9%)	324/406 (79.8%)
Sensitivity	139/192 (72.4%)	132/215 (61.4%)	109/112 (97.3%)	96/147 (65.3%)	51/55 (92.7%)	43/90 (47.8%)
Specificity	196/214 (91.6%)	162/191 (84.8%)	249/294 (84.7%)	239/259 (92.3%)	310/351 (88.3%)	281/316 (88.9%)
PPV	139/157 (88.5%)	132/161 (82%)	109/154 (70.8%)	96/116 (82.8%)	51/92 (55.4%)	43/78 (55.1%)
NPV	196/249 (78.7%)	162/245 (66.1%)	249/252 (98.8%)	239/290 (82.4%)	310/314 (98.7%)	281/328 (85.7%)

ElastPQ, elastography point quantification; NPV, negative predictive value; PPV, positive predictive value; TE, transient elastography.