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Comparison of FibroTouch and FibroScan for staging fibrosis in chronic liver disease: Single-center prospective study

Yumin Xu[a,1], Yuhan Liu[a,1], Zhujun Cao[a,1], Lin Wang[a], Ziqiang Li[a], Zike Sheng[a], Wei Cai[a], Hui Wang[a], Shisan Bao[b,*], Qing Xie[a,*]

[a] Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] Discipline of Pathology, School of Medical Sciences and Bosch Institute, Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia

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ABSTRACT

Background: The aim of this study was to compare the diagnostic accuracy of the FibroTouch and FibroScan in patients with chronic liver disease (CLD) for staging fibrosis.
Methods: A prospective study was conducted in 435 CLD patients between 2014 and 2017. Index tests (FibroTouch, FibroScan, APRI, and FIB-4 score) and a reference standard (liver biopsy) were performed within one week.
Results: The area under the receiver operating curve (AUROC) of the FibroTouch was similar with that of the FibroScan for the diagnosis of significant fibrosis, severe fibrosis, or cirrhosis; however, the AUROC of the FibroTouch was higher than that of APRI or FIB-4 ($p < 0.001$). There was a significant correlation ($rho = 0.85$, $p < 0.001$) between the FibroTouch and FibroScan for liver stiffness. The overall diagnostic accuracy of FibroTouch for significant fibrosis, severe fibrosis, or cirrhosis was 73.3%, 83.2%, or 84.1%, respectively. No significant differences between the FibroTouch and FibroScan were detected regarding the sensitivity, specificity, negative predictive value, positive predictive value, and accuracy. The optimal cut-off values for each stage of fibrosis were similar between the FibroTouch and FibroScan.
Conclusion: The FibroTouch is a valuable diagnostic tool for diagnosing liver fibrosis with good diagnostic accuracy which was comparable with that of the FibroScan, but superior to that of the APRI and FIB-4.

Key Summary

What is the established knowledge on this subject?

Without effective management, patients with chronic liver disease (CLD) are at increased risk for the development of liver fibrosis, cirrhosis, and end-stage liver disease. The early identification and subsequent monitoring of fibrosis are important to impede disease progression. The FibroScan is a reliable and non-invasive tool to measure liver stiffness (LS) reflecting the degree of fibrosis.

What are the significant and/or new findings of this study?

The FibroTouch is a valuable diagnostic tool for assessing LS in patients with CLD, and its accuracy is comparable with that of the FibroScan in the staging of liver fibrosis. The success rate was 100% for LS measurements obtained by the FibroTouch, with only eight (1.8%) measurements being potentially unreliable. The LS cut-off values generated by the FibroTouch were comparable with those generated by the FibroScan, indicating its enormous potential in clinical settings.

1. Introduction

Chronic liver disease (CLD) is a major health burden with increasing morbidity worldwide [1]. Viral hepatitis was responsible for 1.34 million deaths in 2015 [2]. The incidence of alcoholic liver disease and non-alcoholic fatty liver disease is also on the rise [3–7]. Without effective management, individuals with CLD are at increased risk of developing liver fibrosis, cirrhosis, and end-stage liver disease. Thus, the early identification of liver fibrosis is critical for the management of CLD before the condition can no longer be successfully reversed.

The gold standard for staging fibrosis is the histopathological analysis of liver biopsies. However, due to the invasive nature of the procedure, serious complications can arise [8,9]. Therefore, the last

* Corresponding authors.
E-mail addresses: bob.bao@sydney.edu.au (S. Bao), xieqingrjh@163.com (Q. Xie).
[1] Authors have contributed equally.

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two decades have witnessed an increase in the development of non-invasive diagnostic techniques that are as effective as liver biopsies. The FibroScan (Echosens, Paris, France) is an instrument that measures liver stiffness (LS) using mechanical and/or ultrasound shear wave propagation through hepatic parenchyma with high accuracy. The FibroScan is recommended as a non-invasive tool to assess fibrosis according to the European Association for the Study of the Liver guidelines [10] and World Health Organization guidelines [11,12]. However, the approximate rates of failed measurements and non-interpretable results are 5% and 15%, respectively, for the FibroScan, which decreases its applicability. Furthermore, different types of probes (S, M, or XL) are needed to adjust for the thoracic perimeter and skin capsule distance of different individuals to increase its diagnostic performance. The diagnostic accuracy of the FibroScan can be compromised in the presence of inflammation and obesity or ascites [13]. Another limitation of the FibroScan is the relatively high cost of the instrument (US $50,000) as well as the associated annual maintenance fees (US $8500) [10] and the relatively high cost for patients.

In 2013, the FibroTouch (Wuxi Hisky Medical Technology Co., Ltd., Wuxi, China) was introduced for clinical application [14]. The FibroTouch is an integrated two-dimensional image guiding system that allows precise positioning and depth of measurement after automatic adjustment of the dynamic probes according to the thickness of the subcutaneous fat [15]. In 2017, more than 600 hospitals across Asia, including China, Korea, Singapore, India, and Thailand, have reported use of the FibroTouch. Furthermore, several studies have demonstrated promising results generated by the FibroTouch with a successful measurement rate of 100% [16–18]. However, its use in the diagnosis of fibrosis in CLD patients with different etiologies is limited.

The aim of this study was to compare the diagnostic accuracy of the FibroTouch and FibroScan for the staging of fibrosis in CLD patients with different etiologies using the histopathology of liver biopsies as the reference standard.

2. Materials and methods

2.1. Study design

This study was performed in the frame of the Rui Jin (RJ)-Touch Project, in which consecutive adult patients with liver disease who received FibroTouch measurements between June 2014 and July 2017 from Ruijin Hospital, a tertiary academic center for liver and infectious diseases, were prospectively enrolled. The results of this study were reported in accordance with the Standards for Reporting of Diagnostic Accuracy (STARD) (2015) [19].

The inclusion criterion was patients with liver disease, who agreed to undergo a liver biopsy and to receive LS measurements with both the FibroScan and FibroTouch. The exclusion criteria were patients younger than 16 years old; those with evidence of hepatocellular carcinoma, intrahepatic cholangiocarcinoma, or extra-hepatic neoplasia; those with histopathology results but no fibrosis staging information; those whose biopsy specimens were less than 10 mm; and those whose time between the liver biopsy and LS measurements was more than 7 days. A flowchart of the study design and the patient enrollment approach is illustrated in Fig. 1.

Various parameters were collected from all patients at the time of LS measurement. The clinical parameters included age, gender, and body mass index (BMI). Blood was collected to quantify the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), gamma-glutamyl transpeptidase (GGT), and albumin. The platelet count was also obtained.

This study was approved by the *Institutional Ethics Review Committee at Ruijin Hospital* (TG1310FT, 2014-04-21). Written, informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the *1975 Declaration of Helsinki*, as reflected in a priori approval by the institution's human research committee.

2.2. Histopathological staging of liver fibrosis biopsy specimens

The histopathological staging of liver fibrosis biopsy specimens served as the reference standard. Percutaneous needle biopsies were performed by experienced clinicians using the Bard® MAGNUM™ biopsy instrument (C.R. Bard, Inc., Covington, GA, USA) with a 16-gauge needle following ultrasound guidance as previously described [20–22]. All specimens were fixed immediately in formalin for subsequent embedding in paraffin wax. At least six serial sections were processed for hematoxylin–eosin, Masson's trichrome, and reticular fiber staining. Histopathological analysis was performed by two independent pathologists in a double-blind fashion using Scheuer's scoring system for grading inflammation and staging fibrosis [23].

Fibrosis was staged as stage 0 (S0), absence of fibrosis; stage 1 (S1), enlarged, fibrotic portal tracts; stage 2 (S2), periportal or portal-portal septa, but intact architecture; stage 3 (S3), fibrosis with architectural distortion, but no obvious cirrhosis; or stage (S4), cirrhosis. Significant fibrosis was defined as fibrosis stage $S \geq 2$. Necro-inflammation was graded as grade 0 (G0), none or minimal portal/periportal inflammation without lobular activity; grade 1 (G1), portal and lobular inflammation without lobular necrosis; grade 2 (G2), mild piecemeal necrosis with focal necrosis or acidophil bodies; grade 3 (G3), moderate piecemeal necrosis with severe focal cell damage; or grade 4 (G4), severe piecemeal necrosis with bridging necrosis. Hepatic steatosis was graded based on the percentage of hepatocytes containing fat droplets as F0 (1–5%), F1 (6–33%), F2 (34–66%) and F3 (≥67%) [24].

2.3. FibroScan

Transient elastography was performed using the FibroScan (Echosens, Paris, France) with a standard probe (M probe) as previously described [25]. Before the liver biopsy, FibroScan measurements were carried out by two independent and experienced nurses without knowledge of the FibroTouch results. The objective was to obtain ten acceptable measurements (defined as a successful LS measurement), with the maximum number of attempts set at 20. Each measurement was considered "very reliable" (IQR/M ≤0.1), "reliable" (0.1 < IQR/M ≤ 0.3 or IQR/M > 0.3 with LS median <7.1 kPa), or "poorly reliable" (IQR/M >0.3 with LS median ≥7.1 kPa) based on the criteria proposed by Boursier [26].

2.4. FibroTouch

The FibroTouch elicits a controlled low-frequency shear wave to vibrate the liver and tracks the shear wave propagation through the liver tissue *via* a high-frequency signal. By measuring the speed of the shear wave propagation, LS can be measured with specific scientific algorithms, which indirectly assesses the degree of liver fibrosis. FibroTouch measurements were performed by two independent and experienced nurses without knowledge of the FibroScan results. During the measurements, each patient was laid in a standardized supine position, with the right hand placed underneath the head. A coupling agent was smeared over the region of the right 7th–9th intercostal spaces. The probe was applied to the skin in a vertical position, with pressure maintained within the permitted range. The median value of the ten acceptable FibroTouch measurements (with their interquartile range) was expressed in

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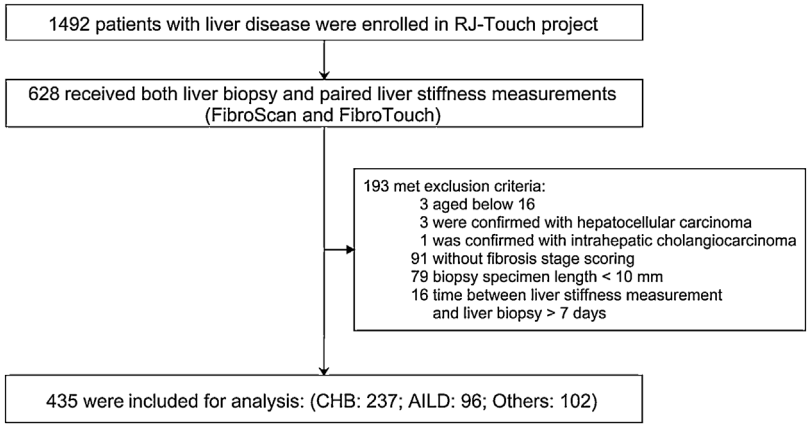

Fig. 1. Flow chart of the study design and patient enrollment. Abbreviations: RJ-Touch: Ruijin-Touch; CHB: chronic hepatitis B; AILD: autoimmune liver disease.

kilopascals (kPa) as the representative measurement. Due to the lack of reliability criteria to validate the FibroTouch, we applied the reliability criteria of the FibroScan to the FibroTouch [26].

2.5. APRI and FIB-4 scores

The aspartate aminotransferase to platelet ratio index (APRI) [27] and the fibrosis index based on the four factors (FIB-4) [28] were calculated upon patient enrollment as follows: APRI = ([AST/ULN*]/platelet count (10^9/L)) × 100 and FIB-4 = (age (years) × AST (U/L)/(platelet count (10^9/L) × ALT (U/L)$^{1/2}$). In our laboratory, the ULN of AST was 40 IU/L.

2.6. Standardization of AUROCs according to the prevalence of each fibrosis stage

The AUROCs were adjusted according to the prevalence of each fibrosis stage based on the DANA method proposed by Poynard et al. [29]. DANA was calculated as follows: DANA = [(prevalence F2 × 2 + prevalence F3 × 3 + prevalence F4 × 4)/(prevalence F2 + prevalence F3 + prevalence F4)] − [prevalence F1/(prevalence F0 + prevalence F1)]. The adjusted AUROC (adjAUROCs) was calculated as follows: adjAUROC = observed AUROC (obAUROC) + (0.1056) × (2.5–DANA).

2.7. Statistical analysis

Comparisons among multiple groups were performed using ANOVA or the Kruskall–Wallis test for continuous variables. Comparisons between two groups were performed using the *t*-test, Mann–Whitney U test for continuous variables, and Chi-square test for categorical variables, as appropriate. The correlation coefficient between the FibroTouch and FibroScan was calculated and plotted based on the Spearman method. Bland–Altman analysis was used to evaluate the agreement between the FibroTouch and FibroScan, and the limits of the agreement (mean ± 1.96 times the SD of the differences) were determined. The diagnostic performance of LS, APRI, and FIB-4 was determined with receiver operating curve (ROC) analyses, followed by calculations of the 95% CI using the binomial exact method. The area under the ROC (AUC) of different diagnostic methods was compared using the DeLong method [30]. Optimal cut-off values were determined for the FibroTouch and FibroScan to predict significant fibrosis, severe fibrosis, and cirrhosis according to at least 90% sensitivity or at least 90% specificity. McNemar's test was used for side-by-side comparison of the diagnostic accuracy of the FibroTouch and FibroScan. All statistical analyses were performed and graphs were prepared using R 3.4.3 (http://www.r-project.org/) or MedCalc (Version 11.4.2.0). A two-tailed $p < 0.05$ was considered statistically significant.

Table 1
Patient characteristics.

Characteristics	All
Patient, no.	435
Age, (years), median (IQR)	41 (32.5, 53)
Male sex, n (%)	216 (49.7%)
BMI, kg/m^2, median (IQR)	22.9 (20.8, 25)
Etiology of liver disease, n (%)	
HBV infection	237 (54.5%)
HCV infection	10 (2.3%)
Non-alcoholic fatty liver disease	15 (3.4%)
Autoimmune liver diseases	96 (22.1%)
Drug induced liver injury	13 (3.0%)
Unknowns & others	58 (13.3%)
More than one etiology	6 (1.4%)
Alanine aminotransferase (IU/L), median (IQR)	58 (33, 97.2)
Aspartate aminotransferase (IU/L), median (IQR)	41.5 (28, 70)
Alkaline phosphatase (IU/L), median (IQR)	75 (60, 115)
Gamma-glutamyl transpeptidase (IU/L), median (IQR)	34 (19, 98.8)
Platelets (10 × 9/L), median (IQR)	176 (142, 214.8)
Serum Albumin (g/L), median (IQR)	42 (38, 45)
APRI, median (IQR)	0.6 (0.4, 1.2)
FIB-4, median (IQR)	1.4 (0.8, 2.5)
Specimen length (mm)	15 (12, 20)
Inflammation grade, n (%)	
G0/G1/G2/G3/G4	81 (18.6%)/102 (23.4%)/125 (28.7%)/108 (24.8%)/19 (4.4%)
Fibrosis stages, n (%)	
S0/S1/S2/S3/S4	102 (23.4%)/92 (21.1%)/128 (29.4%)/60 (13.8%)/53 (12.2%)
Steatosis, n (%)	
F0 (<5%)/F1 (5%–33%)/F2 (34%-66%)/F3 (>66%)	344 (79.1%)/60 (13.8%)/21 (4.8%)/10 (2.3%)

Abbreviations: BMI, body mass index, IQR, interquartile range APRI, aspartate aminotransferase to platelet ratio index, FIB-4, fibrosis index based on the four factors.

3. Results

3.1. Patient enrollment and characteristics

A total of 1492 CLD patients received FibroTouch measurements. Among the entire cohort, 628 patients also received FibroScan measurements and liver biopsies, and 193 out of 628 patients were excluded (Fig. 1). Therefore, 435 patients were analyzed with clinical and histopathological characteristics (Table 1). The main etiology of these patients was HBV infection (54.5%), followed by

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Table 2
Success and Reliability of the FibroTouch (Type B) and FibroScan (M Probe).

Success and Reliability	FibroTouch	FibroScan	*p*-Value
All patients (n = 435)			
Failure, n (%)	0 (0%)	4 (0.9%)	0.12
Poorly reliable, n (%)	8 (1.8%)	3 (0.7%)	0.22
Reliable, n (%)	208 (47.8%)	306 (70.0%)	<0.001
Very reliable, n (%)	219 (50.3%)	122 (27.1%)	<0.001
Measurement duration (s), median (IQR)	48.8 (37.5, 190.4)	118 (105, 153.5)	<0.001
Patients with BMI ≤25 (n = 325)			
Failure, n (%)	0 (0%)	2 (0.6%)	0.50
Poorly reliable, n (%)	4 (1.2%)	1 (0.3%)	0.38
Reliable, n (%)	144 (44.3%)	228 (70.2%)	<0.001
Very reliable, n (%)	177 (54.5%)	94 (28.9%)	<0.001
Measurement duration (s), median (IQR)	47.8 (37.4, 189)	117 (104, 153)	<0.001
Patients with BMI >25 (n = 110)			
Failure, n (%)	0 (0%)	2 (1.8%)	0.50
Poorly reliable, n (%)	4 (3.6%)	2 (1.8%)	0.69
Reliable, n (%)	64 (58.2%)	78 (70.9%)	0.07
Very reliable, n (%)	42 (38.2%)	28 (25.5%)	0.06
Measurement duration (s), median (IQR)	57.6 (38.5, 192.9)	125 (109.2, 155)	<0.001

The proportions were compared using the Chi-square test, followed by Fisher's exact test, if necessary.
Failure indicates no valid measurements.
Abbreviation: BMI, body mass index.

autoimmune liver diseases (22.1%), non-alcoholic fatty liver disease (3.4%), drug-induced liver injury (3.0%), HCV infection (2.3%), and unknown or other etiology (13.3%). The median size of the liver biopsies in the entire cohort was 15 mm (IQR: 12–20 mm).

The prevalence of the inflammation grades, fibrosis stages, and steatosis was enumerated (Table 1). There were 53 patients with cirrhosis (12.2%), and no patient had decompensated cirrhosis upon enrollment.

3.2. Failed measurements, unreliable results, or time-consuming examination

The measurement failure rate was 0% for the FibroTouch and 0.9% for the FibroScan (Table 2). No differences were observed in the rates of failed measurements and "poorly reliable" measurements between the FibroScan and FibroTouch. The proportion of "very reliable" (IQR/M ≤0.1) measurements was significantly higher for the FibroTouch than that for the FibroScan ($p < 0.001$) in patients with a BMI ≤25, but not in patients with a BMI >25. Among the patients with "poorly reliable" or "reliable" results, 49% of patients received "very reliable" measurements using the FibroTouch. The measurement duration was significantly shorter for the FibroTouch than that for the FibroScan (median 48.8 vs 118 s). These results were validated in patients with a BMI ≤25 or >25.

3.3. Measurement of liver stiffness as determined by the FibroTouch and FibroScan

There was a significant direct correlation between the FibroTouch and FibroScan with regard to LS measurements (*rho* = 0.85, $p < 0.001$, Supplementary Fig. 1A). Bland–Altman analysis revealed a mean difference of 0.4 between the FibroTouch and FibroScan, with the lower 95% limit of agreement being −8.9 and the upper 95% limit of agreement being 9.6 (Supplementary Fig. 1B).

3.4. Diagnostic accuracy of transient elastography

The results of LS and two other established scores (APRI and FIB-4) from all patients with different stages of fibrosis (S0–S4) are shown in Supplementary Fig. 2. The distribution of the LS measurements, as determined with the FibroTouch or FibroScan, differed significantly between each of the two compared fibrosis stages ($p < 0.001$). The diagnostic accuracy of the FibroTouch, FibroScan, APRI, and FIB-4 is shown in Fig. 2 and Supplementary Figs. 3 and 4 for the entire cohort and the subgroups, according to the vari-

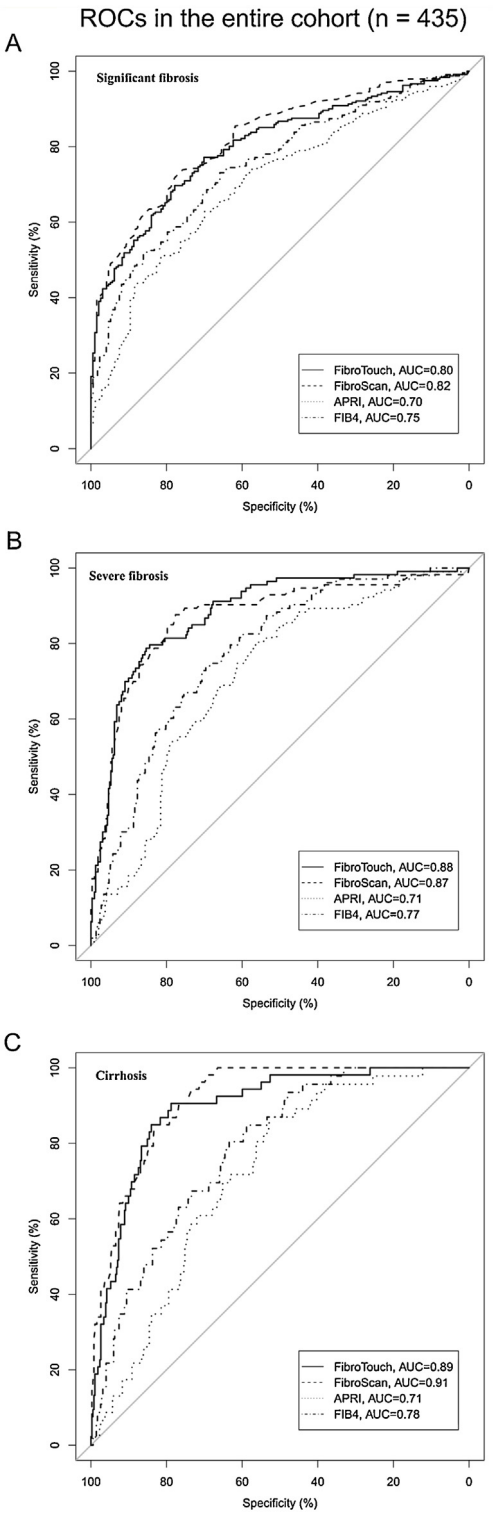

Fig. 2. ROC analysis of four non-invasive methods for the diagnosis of patients with significant fibrosis (A), severe fibrosis (B), and cirrhosis (C). Abbreviations: AUC: area under the receiver operating characteristic curve; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis index based on the four factors.

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Table 3
Diagnostic values for all patients and CHB patients generated by the FibroTouch (type B) and FibroScan (M probe).

Fibrosis Stage	ObAUC (95%CI)	DANA	AdjAUC (95%CI)	Aim	Cut-off	Sensitivity	Specificity	NPV	PPV	Accuracy
All patients (n = 435)										
FibroTouch, kPa										
≥S2	0.80 (0.76–0.84)	2.1	0.84 (0.80–0.88)	Sensitivity ≥90	>6.14	90.04%	37.11%	74.74%	63.82%	66.21%
				Specificity ≥90	>10.8	51.87%	90.21%	60.20%	87.94%	69.20%
≥S3	0.88 (0.85–0.91)	2.1	0.92 (0.89–0.95)	Sensitivity ≥90	>8.5	90.27%	68.01%	95.61%	49.76%	73.79%
				Specificity ≥90	>13.2	70.80%	90.06%	89.51%	71.17%	84.83%
S4	0.89 (0.86–0.92)	2.1	0.93 (0.90–0.96)	Sensitivity ≥90	>11.5	90.57%	78.80%	98.36%	36.92%	80.00%
				Specificity ≥90	>18.2	66.04%	90.05%	95.01%	47.30%	86.90%
FibroScan, kPa										
≥S2	0.82 (0.78–0.86)	2.1	0.86 (0.82–0.90)	Sensitivity ≥90	>5.8	90.04%	46.91%	79.65%	67.81%	70.90%
				Specificity ≥90	>10	55.19%	90.21%	62.09%	87.50%	71.10%
≥S3	0.87 (0.83–0.90)	2.1	0.91 (0.87–0.94)	Sensitivity ≥90	>8.2	90.27%	71.12%	95.38%	52.31%	75.98%
				Specificity ≥90	>11.8	68.14%	90.06%	88.89%	70.64%	84.30%
S4	0.92 (0.88–0.94)	2.1	0.96 (0.92–0.98)	Sensitivity ≥90	>10.4	90.57%	76.70%	98.29%	35.04%	78.09%
				Specificity ≥90	>16.5	66.04%	90.05%	95.00%	47.95%	87.07%
CHB patients (n = 237)										
FibroTouch, kPa										
≥S2	0.77 (0.71–0.82)	2.21	0.80 (0.74–0.85)	Sensitivity ≥90	>5.8	90.32%	30.97%	75.00%	61.04%	63.22%
				Specificity ≥90	>10.0	41.94%	90.27	61.54%	83.95%	69.89%
≥S3	0.87 (0.82–0.91)	2.21	0.90 (0.85–0.94)	Sensitivity ≥90	>7.6	91.23%	62.78	97.37%	44.08%	67.36%
				Specificity ≥90	>10.7	66.67%	90%	92.01%	61.22%	81.61%
S4	0.90 (0.85–0.93)	2.21	0.93 (0.88–0.96)	Sensitivity ≥90	>8.1	92.86%	61.72%	99.04%	22.57%	59.31%
				Specificity ≥90	>12.5	78.57%	90.43%	97.79%	38.98%	81.84%
FibroScan, kPa										
≥S2	0.81 (0.75–0.86)	2.21	0.84 (0.78–0.89)	Sensitivity ≥90	>5.8	91.13%	51.33%	79.65%	67.81%	70.90%
				Specificity ≥90	>10	42.74%	91.15%	62.09%	87.50%	71.10%
≥S3	0.88 (0.83–0.91)	2.21	0.91 (0.86–0.94)	Sensitivity ≥90	>6.9	91.23%	61.67%	95.43%	41.02%	63.11%
				Specificity ≥90	>10.3	68.42%	90%	91.67%	62.24%	81.90%
S4	0.94 (0.91–0.97)	2.21	0.97 (0.94–1.00)	Sensitivity ≥90	>9.1	92.86%	77.99%	99.26%	30.91%	73.27%
				Specificity ≥90	>11.3	78.57%	90.43%	97.46%	37.82%	81.11%

Abbreviations: ObAUC, observed area under the receiver operating characteristic curve; DANA, difference between advanced and non-advanced fibrosis; AdjAUC, adjusted area under the receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value; CI, confidence interval; CHB, chronic hepatitis B.

ous etiologies. The AUC was significantly higher for the FibroTouch and FibroScan than that for the APRI or FIB-4 in predicting significant fibrosis, severe fibrosis, or cirrhosis in the entire cohort (Fig. 2 and Supplementary Table 2), which was supported by the results of liver biopsies with a median size of ≥20 mm (Supplementary Fig. 5). No significant differences in the AUC, sensitivity, specificity, negative predictive value, positive predictive value, or accuracy were observed between the FibroScan and FibroTouch for the diagnosis of significant fibrosis, severe fibrosis, or cirrhosis (Fig. 2 and Supplementary Table 2). Furthermore, no significant differences were observed for the aforementioned diagnostic values of the FibroTouch between patients with a BMI ≤ 25 and a BMI < 25 (Supplementary Table 3).

3.5. Optimal LS cut-off values

The optimal LSM cut-off values for the FibroTouch and FibroScan, which were based on a sensitivity of at least 90% and a specificity of at least 90% for the diagnosis of significant fibrosis, severe fibrosis, or cirrhosis, are shown in Table 3 and Fig. 3. The cut-off values for the FibroTouch and FibroScan for ruling out disease with at least 90% sensitivity were very close at 6.1 kPa and 5.8 kPa for significant fibrosis, 8.5 kPa and 8.2 kPa for severe fibrosis, and 11.5 kPa and 10.4 kPa for cirrhosis, respectively. However, the FibroTouch produced LS measurements that were lower than those of the FibroScan for ruling in disease with a specificity of at least 90% at 10.8 kPa and 10 kPa for significant fibrosis, 13.2 kPa and 11.8 kPa for severe fibrosis, and 18.2 kPa and 16.5 kPa for cirrhosis, respectively. In chronic hepatitis B (CHB) patients, the cut-off values for the FibroTouch and FibroScan were similar for ruling in and ruling out significant fibrosis, severe fibrosis, or cirrhosis.

Using these specific cut-off values, the diagnostic accuracy for ruling in significant fibrosis, severe fibrosis, or cirrhosis was similar between the FibroTouch and FibroScan. For the purpose of ruling out these diseases, the accuracy of the FibroScan was higher than that of the FibroTouch, especially for ruling out cirrhosis in CHB patients (Supplementary Table 4).

4. Discussion

In this single-center prospective cohort of CLD patients who underwent liver biopsies, FibroTouch and FibroScan out-performed APRI and FIB-4 in diagnosing the different stages of liver fibrosis. The FibroTouch provided an accuracy comparable to that of the FibroScan with AUROC values of 0.80 vs 0.82, 0.88 vs 0.87, 0.89 vs 0.92 in diagnosing significant fibrosis, severe fibrosis, and cirrhosis, respectively. There was no difference in the overall accuracy of the FibroTouch when analyzing the entire CLD or CHB population, CHB patients with ALT ≤2-fold of ULN, and CHB patients with normal ALT, AILD or CLD with other etiologies. The cut-off values for the FibroTouch and FibroScan were similar, suggesting that the FibroTouch could be anothor ideal instrument for routine practice.

The FibroTouch is an integrated two-dimensional (2D)-image guiding system that allows precise positioning and depth of measurement after automatically adjusting the dynamic probes according to the thickness of the subcutaneous fat. The diagnostic accuracy of the FibroTouch in staging fibrosis has been investigated earlier in several retrospective studies with relatively small sample sizes (66–313 patients) [31–37]. However, most of the studies are published in the local language [31–33,35,36]; only two out of five studies compared results between two systems [31,36], and none of them reported unsuccessful and reliable results. Therefore, data on the FibroTouch in staging fibrosis are not easily translated into clinical practices worldwide. This prospective study enrolled the largest number of patients (n = 432) to investigate both the accuracy and applicability of the FibroTouch. The good diagnostic accuracy of

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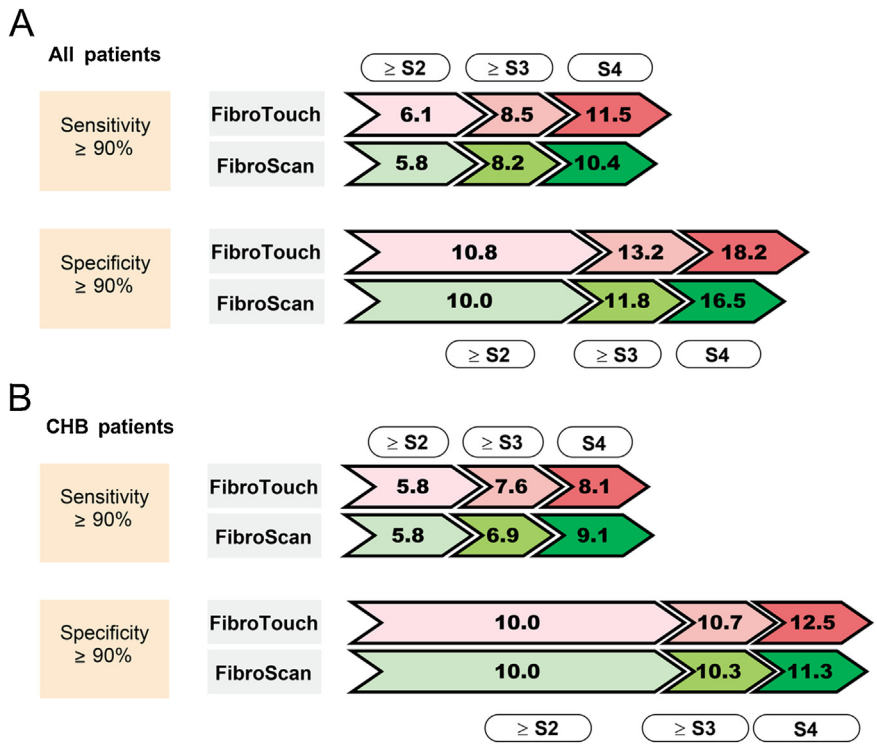

Fig. 3. Optimal cut-off values of LS for all (A) and CHB (B) patients generated by the FibroTouch and FibroScan.

the FibroTouch was consistent with previous studies (Supplementary Table 5). The results from our study clearly demonstrated that the FibroTouch was comparable to the FibroScan and significantly better than the APRI and FIB-4 in diagnosing the various fibrosis stages. Similar to the limitation of the FibroScan [10], the FibroTouch was moderately accurate in diagnosing significant fibrosis with an AUROC of 0.80 in the general CLD population and 0.77 in the CHB population. However, the diagnosis of severe fibrosis and cirrhosis with the FibroTouch was excellent with an AUROC of almost 0.90.

The unreliable results of the FibroTouch or FibroScan in our study were 1.8% or 0.9%, respectively, which were lower than those of other reports [38]. This discrepancy can be explained by the low prevalence (3%) of obesity (BMI > 30) and the highly experienced performer for the measurements (experience of LS measurements >10,000 times) in our cohort, which might have reduced the unsuccessful and unreliable rates [10,38,39]. Moreover, the FibroTouch can automatically adjust the dynamic probes according to the thickness of the subcutaneous fat to increase the rate of reliable measurements [15], which supports our study in the sense that there were no unsuccessful measurements. The FibroTouch was less time-consuming to operate compared to the FibroScan, as suggested by our data, which might be an added advantage of the FibroTouch in centers with a large volume of patients.

We acknowledge that there are several limitations in our study. First, although the reference standard used for staging fibrosis was liver biopsy, the diagnostic accuracy of biopsy was limited by sampling error as well as inter- and intra-observer variability. We excluded all the unqualified specimens to reduce the sampling error, but the inter- and intra-observer variability was not well addressed. Second, the XL probe for the FibroScan was not available during the study period, and we were unable to make comparisons with the FibroTouch in terms of reliability and applicability. Thus, subgroup analysis was performed according to the BMI, which allowed us to compare the FibroScan (M probe) with the FibroTouch in patients with a BMI <25. Among these patients, the FibroTouch provided more "very reliable" measurements compared to the FibroScan with the M probe. Third, the diagnostic performance of the FibroTouch was not analyzed in the non-alcoholic fatty liver disease population due to the limited number of patients enrolled in this study. A future study on this cohort should be performed. Fourth, the performance of the controlled attenuation parameter of the FibroTouch compared to the FibroScan was not performed in our study, which will be pursued in a future study.

In conclusion, our prospective study confirmed that the FibroTouch is a valuable diagnostic tool for the staging of liver fibrosis in CLD patients. The diagnostic accuracy of the FibroTouch was comparable with that of the FibroScan and superior to that of the APRI and FIB-4. Most of the cut-off values for the FibroTouch for the diagnosis of the various stages of liver disease were close with those for the FibroScan, which is critical for the applicability of this tool in various clinical settings.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.02.009.

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