Research Article

Diagnostic of FibroTouch and six serological models in assessing the degree of liver fibrosis among patients with chronic hepatic disease: A single-center retrospective study

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Abstract

Background and aims
The aim of this study was to evaluate the diagnostic value of FibroTouch and serological models on staging hepatic fibrosis in chronic liver diseases.

Methods
We recruited 850 patients undergoing liver biopsy and received FibroTouch test before or after liver biopsy within one week, blood was taken for the routine inspection before the operation within one week. The serological models were calculated by the blood results and routine clinical information. The diagnostic value of FibroTouch and six serological models was analyzed by receiver operating characteristic curve (ROC).

Results
Patients with severe liver fibrosis had significantly higher AST, ALT, GGT, RDW, ALP, and FT-LSM. The area under the receiver operating characteristic curve (AUROC) of FT-LSM for the liver diagnosis of $S \geq 2$, $S \geq 3$ and $S = 4$ was 0.75 (95% confidence interval [CI]: 0.72–0.78), 0.83 (95% CI: 0.80–0.86), and 0.85 (95% CI: 0.81–0.89), respectively. The optimal cut-off of FT-LSM for diagnosing $S \geq 2$, $S \geq 3$ and $S = 4$ was 8.7, 10.7, and 12.3, respectively.

Conclusions
Our study showed the FibroTouch has a higher diagnostic value compared with the non-invasive serological models in staging the fibrosis stage. The cut-off of FibroTouch and five
serological models (APRI, FIB-4, S-index, Forns, and PRP) increased with the severe of fibrosis stage.

1. Introduction

Chronic liver disease (CLD) is affecting millions of people worldwide with increasing mortality and morbidity, and it is still a huge burden for the global health [1]. Liver fibrosis is a pathophysiological process, which refers to the abnormal hyperplasia of connective tissue in liver caused by various pathogenic reasons. Although Chronic hepatitis B virus (CHB) dominates the liver fibrosis [2] in China, the Alcoholic liver disease (ALD), Nonalcoholic fatty liver disease (NAFLD), Drug induced liver injury (DILI), and Autoimmune hepatitis (AIH) are at a rising stage in recent years [2]. CLD leads to progressive liver fibrosis, which could develop into liver cirrhosis and hepatocellular carcinoma. Therefore, early identification of fibrosis grade can effectively prevent to progress disease. However, liver biopsy is still the "gold standard" for the diagnosis of liver fibrosis, which is hardly to complete in the real clinical for its trauma, observer error and sampling error.

FibroTouch, a self-made instrument in China, has achieved good clinical effect which can evaluate the degree of liver fibrosis by detecting liver stiffness measurement (LSM). Previous studies [3, 4] have showed the FibroTouch was an effective tool with high sensitivity and specificity for the diagnosis of liver fibrosis which was comparable with that of Fibroscan. Considering the high cost of Fibroscan, we prefer FibroTouch to stage the degree of fibrosis in our research.

The researchers have tried to explore the serological model of liver fibrosis, such as aspartate transaminase-to-platelet ratio index (APRI), FIB-4, S-Index, Forns, PRP, and Fib-5. APRI is a most common noninvasive diagnostic model for hepatic fibrosis which first applied in HCV patients [5]. FIB-4 first applied in the HCV patients but then extended to other CLD for its simple, widely application, and easy to obtain [6]. Kun Zhou [7] suggested a S-index mathematical model consisting of routine laboratory markers with a high degree of accuracy, possible reducing the need for liver biopsy. Other researchers [8–10] explored some serological models such as Forns, PRR, and Fib-5, which was also effective in the stage of fibrosis. Although the serological models of liver fibrosis can obtain by conventional serological signs, the accurate of the models need to interpret more carefully. The aim of this study was to evaluate the diagnostic value of FibroTouch and serological models on staging hepatic fibrosis in chronic liver diseases.

2. Material and methods

2.1. Patient

Patients who underwent liver biopsy recruited in our analysis from September 1, 2015 to June 10, 2021, and they treated in the hepatology department of Hangzhou Xixi Hospital with CLD. The inclusion criteria were as follows: (1) age older than 16; (2) chronic liver disease; (3) underwent liver biopsy; (4) written informed consent. The exclusion criteria were: (1) co-infection with HIV; (2) cancer; (3) schistosomiasis liver disease; (4) hereditary diseases; (5) unknown liver disease; (6) incomplete information of patients. A flowchart of patient enrollment illustrated in Fig 1. All patients received FibroTouch test before or after liver biopsy within one week, and blood was taken for the routine inspection before the operation within one week.

The study approved by the institutional ethics review committee at Hangzhou Xixi Hospital.
The study protocol was in accordance with the ethics guidelines of the 1975 Declaration of Helsinki. Written informed consent was unwanted for the retrospective nature of the study (2021 Science Ethic No.02).

2.2. Blood test

Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Glutamyl transpeptidase (GGT), Cholesterol (CHO), Albumin (ALB), and Alkaline phosphatase (ALP) tested by the Beckman Coulter au5831 automatic biochemical analyzer at laboratory department in Xixi hospital. Platelet (PLT) and Red Cell volume Distribution Width (RDW) detected using the automatic blood cell analyzer.

2.3. FibroTouch

During the measurement, the patient was in the supine position, right hand raised and placed on the head, and the detection points were selected from the right axillary front to the 7th, 8th and 9th ribs of the axillary midline, close to the rib space. The FibroTouch liver stiffness (FT-LSM) value was measured at a fitting time for 10 consecutive effective tests. Finally, the median was taken as the F value to mark the degree of fibrosis of liver tissue. The results with deviation greater than one third of the median data and operation success rate less than 60% considered invalid. All operations were completed by the same doctor who had received professional training.

2.4. Histopathological staging of liver fibrosis

After being reviewed and approved by the ethics committee of Hangzhou Xixi Hospital, the patients signed the informed consent form and used the ultrasound-guided adjustable ejection.
biopsy gun for percutaneous liver biopsy. The length of liver tissue was 1.5–2.0 cm, fixed with 4% formaldehyde, embedded in paraffin, and sectioned with a thickness of 5 um for HE and Masson staining. The liver tissue section contained at least 6 portal areas. Hepatic fibrosis performed by two pathologists in a double-blind manner using the Scheuer scoring system [3, 11], S0: no fibrosis; S1: fibrosis enlarged in the portal tracts; S2: fibrous septum formation in the portal area, but intact architecture; S3: fibrosis with lobular structure disorder, but no obvious cirrhosis; S4: cirrhosis.

2.5. The calculation formula of serological model

\[
\text{APRI} = \frac{\text{AST}}{\text{ULN}} \times 100/\text{PLT};
\]

\[
\text{FIB-4} = \frac{\text{age} \times \text{AST}}{\text{PLT} \times \sqrt{\text{ALT}}};
\]

\[
\text{S-Index} = \frac{1000 \times \text{GGT}}{\text{PLT} \times \text{ALB}^{2}};
\]

\[
\text{Forns} = 7.811 - 3.131 \times \ln(\text{PLT}) + 0.781 \times \ln(\text{GGT}) + 3.467 \times \ln(\text{age}) - 0.014 \times \text{CHO};
\]

\[
\text{PRP} = \frac{\text{RDW}}{\text{PLT}};
\]

\[
\text{Fib-5} = 0.3 \times \text{ALB} + 0.05 \times \text{PLT} - 0.014 \times \text{ALP} + 6 \times (\text{AST}/\text{ALT}) + 14.
\]

2.6. statistical analysis

SAS 9.4 (SAS Institute Inc., Cary, NC) statistical software was used for analysis. The continuous skewed data were expressed by median (interquartile range, IQR). Spearman correlation analysis was used for the correlation between fibrosis stage and other evaluation methods. The diagnostic value of FibroTouch and six serological models was analyzed by receiver operating characteristic curve (ROC). The closer of AUROC to 1, the better diagnostic value it can provide. The comparison of AUROC among different models and FT-LSM was analyzed by the Delong test. P value < 0.05 considered as statistically significant for all the tests.

3. Results

3.1. Patient characteristics

A total of 850 CLD patients who underwent liver biopsy, received FibroTouch measurement and blood test included in the final analysis, and the detail information were shown in Table 1. There were 344 patients with mild fibrosis or no fibrosis (S<2), including 206 males and 138 females, with a median age of 42.5 years.

410 patients had moderate to severe fibrosis (2≤S<4), including 200 males and 210 females, with a median age of 45.0 years. 96 patients had cirrhosis, with a median age of 46.0 years. There were no significant differences between chronic HBV disease and other CLD, but age and gender were significantly different among different grades of liver fibrosis. Patients with severe liver fibrosis had significantly higher AST, ALT, GGT, RDW, ALP, and FT-LSM; a significantly lower ALB, CHO, and PLT was seen in the high grade of liver fibrosis. All the serological models were significantly different among different grades of hepatic fibrosis, and only the FIB-5 negative correlated with the liver fibrosis (Table 1).
3.2. Correlations among fibrosis stage, serological model, and FT-LSM

We used the fibrosis stage, serological models, and FT-LSM to build a Spearman’s correlation coefficient in Table 2. All the correlations between any two were statistically significant, but

### Table 2. The correlation among fibrosis stage, serological model, and FT-LSM.

| Variable      | FT-LSM | Fibrosis stage | APRI | FIB-4 | S-Index | Forns | PRP | FIB-5 |
|---------------|--------|----------------|------|-------|---------|-------|-----|-------|
| FT-LSM        | 1      | 0.54*          | 0.35*| 0.33* | 0.44*   | 0.34* | 0.28*| -0.25*|
| Fibrosis stage| 0.54*  | 1              | 0.42*| 0.39* | 0.36*   | 0.32* | 0.35*| -0.26*|
| APRI          | 0.35*  | 0.42*          | 1    | 0.68* | 0.57*   | 0.54* | 0.60*| -0.54*|
| FIB-4         | 0.33*  | 0.39*          | 0.68*| 1     | 0.47*   | 0.83* | 0.69*| -0.39*|
| S-Index       | 0.44*  | 0.36*          | 0.57*| 0.47* | 1       | 0.71* | 0.46*| -0.57*|
| Forns         | 0.34*  | 0.32*          | 0.54*| 0.83* | 0.71*   | 1     | 0.71*| -0.60*|
| PRP           | 0.28*  | 0.35*          | 0.60*| 0.69* | 0.46*   | 0.71* | 1   | -0.73*|
| FIB-5         | -0.25* | -0.26*         | -0.54*| -0.39*| -0.57*  | -0.60*| -0.73*| 1     |

*: Statistically significant, P<0.0001.

Abbreviations: FibroTouch liver stiffness: FT-LSM; Aspartate transaminase-to-platelet ratio index: APRI.
the Forns and FIB-4 strongly correlated ($r = 0.83, P < 0.0001$). The fibrosis stage had the biggest correlation with FT-LSM ($r = 0.54, P < 0.0001$). FIB-5 negative correlated with other serological models, but the remain correlation coefficient was positive.

### 3.3. Performance of serological model and FT-LSM in fibrosis stage assessment

The performance of serological model and FT-LSM in assessing fibrosis stage was shown in Table 3 and Fig 2. The area under the receiver operating characteristic curve (AUROC) of FT-LSM under the diagnosis of $S ≥ 2, S ≥ 3$ and $S = 4$ was 0.75 (95% confidence interval [CI]: 0.72–0.78), 0.83 (95% CI: 0.80–0.86), and 0.85 (95% CI: 0.81–0.89), respectively. The optimal cut-off of FT-LSM for diagnosing $S ≥ 2, S ≥ 3$ and $S = 4$ was 8.7, 10.7, and 12.3, respectively. For fibrosis $S ≥ 2$, the AUROC was 0.72 for APRI (APRI vs LSM, $P = 0.15$), 0.69 for FIB-4 (FIB-4 vs LSM, $P = 0.008$), 0.67 for S-index (S-index vs LSM, $P = 0.0002$), 0.64 for Forns (Forns vs LSM, $P < 0.0001$), 0.66 for PRP (PRP vs LSM, $P = 0.0001$), and 0.63 for FIB-5 (FIB-5 vs LSM, $P < 0.0001$), respectively. For fibrosis $S ≥ 3$, the AUROC was 0.70 for APRI (APRI vs LSM, $P < 0.0001$), 0.72 for FIB-4 (FIB-4 vs LSM, $P < 0.0001$), 0.73 for S-index (S-index vs LSM, $P < 0.0001$), 0.69 for Forns (Forns vs LSM, $P < 0.0001$), 0.71 for PRP (PRP vs LSM, $P < 0.0001$), respectively.

**Table 3. The diagnostic value of FibroTouch and six serological models to fibrosis $S ≥ 2, S ≥ 3$ and $S = 4$.**

| Variable | AUC   | 95% CI     | Cut-off | Specificity | Sensitivity |
|----------|-------|------------|---------|-------------|-------------|
| $S ≥ 2$  |       |            |         |             |             |
| FT-LSM   | 0.75  | 0.72–0.78  | 8.7     | 0.718       | 0.692       |
| APRI$^*$ | 0.72  | 0.68–0.75  | 0.64    | 0.817       | 0.546       |
| FIB-4$^*$| 0.69  | 0.66–0.73  | 0.31    | 0.701       | 0.619       |
| S-index$^*$| 0.67  | 0.63–0.71  | 0.095   | 0.628       | 0.684       |
| Forns$^*$ | 0.64  | 0.61–0.68  | 7.68    | 0.738       | 0.502       |
| PRP$^*$  | 0.66  | 0.62–0.70  | 0.07    | 0.645       | 0.625       |
| FIB-5$^*$| 0.63  | 0.59–0.66  | 39.68   | 0.645       | 0.583       |
| $S ≥ 3$  |       |            |         |             |             |
| FT-LSM   | 0.83  | 0.80–0.86  | 10.7    | 0.788       | 0.742       |
| APRI$^*$ | 0.70  | 0.66–0.74  | 0.64    | 0.705       | 0.627       |
| FIB-4$^*$| 0.72  | 0.68–0.76  | 1.33    | 0.610       | 0.728       |
| S-index$^*$| 0.73  | 0.69–0.76  | 0.10    | 0.594       | 0.811       |
| Forns$^*$ | 0.69  | 0.65–0.73  | 7.3     | 0.583       | 0.696       |
| PRP$^*$  | 0.71  | 0.67–0.75  | 0.073   | 0.618       | 0.724       |
| FIB-5$^*$| 0.64  | 0.60–0.69  | 39.52   | 0.586       | 0.668       |
| $S = 4$  |       |            |         |             |             |
| FT-LSM   | 0.85  | 0.81–0.89  | 12.3    | 0.806       | 0.781       |
| APRI$^*$ | 0.74  | 0.69–0.79  | 0.63    | 0.642       | 0.729       |
| FIB-4$^*$| 0.78  | 0.73–0.83  | 1.4     | 0.609       | 0.812       |
| S-index$^*$| 0.75  | 0.70–0.80  | 0.11    | 0.565       | 0.844       |
| Forns$^*$ | 0.75  | 0.70–0.80  | 8.2     | 0.741       | 0.615       |
| PRP$^*$  | 0.78  | 0.73–0.83  | 0.08    | 0.678       | 0.760       |
| FIB-5$^*$| 0.68  | 0.62–0.75  | 37.95   | 0.710       | 0.615       |

$^*$: comparing with FT-LSM, no statistical significance;
$^*$: comparing with FT-LSM, statistically significant.

Abbreviations: FibroTouch liver stiffness: FT-LSM; Aspartate transaminase-to-platelet ratio index: APRI.

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and 0.64 for FIB-5 (FIB-5 vs LSM, P < 0.0001), respectively. For fibrosis S = 4, the AUROC was 0.74 for APRI (APRI vs LSM, P = 0.0003), 0.78 for FIB-4 (FIB-4 vs LSM, P = 0.02), 0.75 for S-index (S-index vs LSM, P = 0.0001), 0.75 for Forns (Forns vs LSM, P = 0.001), 0.78 for PRP (PRP vs LSM, P = 0.03), and 0.68 for FIB-5 (FIB-5 vs LSM, P < 0.0001), respectively. We did see a rising AUROC trend among FT-LSM, FIB-4, S-index, Forns, PRP, and FIB-5, but the APRI was rising in fibrosis S ≥ 3 and then falling in S = 4 which was different with the other model.

4. Discussion
A total of 850 patients with chronic liver disease enrolled in this single-center retrospective study. The FibroTouch provided better performance with AUROC values of 0.75, 0.83, and 0.85 in diagnosing significant fibrosis, severe fibrosis, and cirrhosis, respectively, which was significantly higher than that with other serological models (except S ≥ 2 group, comparing with APRI, no statistical significance). The good performance in staging the hepatic fibrosis also found in other researchers [3, 4, 12] with small sample sizes (39–432), but our study enrolled 850 CLD patients to explore the accuracy of the FibroTouch, which was more reliable.
to evaluate of the diagnostic value. We also found the AUROC of FibroTouch increased with the severe of liver fibrosis in both CHB patients and the other CLD patients (Fig 3). The cut-off of FibroTouch and five serological models (APRI, FIB-4, S-index, Forns, and PRP) increased with the severe of fibrosis stage, but the FIB-5 decreased with that (Table 3), which was a good sign for grading the fibrosis.

The early diagnosis and accurate evaluation of liver fibrosis is helpful to select clinical treatment, evaluation and prognosis of patients with chronic hepatitis. Liver biopsy is still the gold standard for fibrosis grading, but patients undergoing biopsy often feel discomfort and risk of complications, with a pooled rate of adverse events of 2.3% [13]. At the same time, some tissues biopsied cannot represent the fibrosis of the whole liver. The researchers mainly focused on the noninvasive diagnosis of liver fibrosis in recent years, and they had set up some conventional serological index models. However, these models had different abilities in judging liver fibrosis. Some studies believed that the diagnostic value of FIB-4 [14] (AUC = 0.81, \( P < 0.001 \)) was better than APRI, while others [6] believed that FIB-4 and APRI were consistent in judging liver fibrosis. This study found the AUROCs of APRI in \( S \geq 2 \) (0.72), S-index in \( S \geq 3 \) (0.73), and FIB-4/PRP in \( S = 4 \) (0.77) were higher than the other serological models, which is consistent with the results the serological models may have different diagnostic effects to the
stage of liver fibrosis [15]. Interestingly, the AUROCs of APRI were 0.72 in fibrosis S ≥ 2, 0.70 in S ≥ 3, 0.74 in S = 4, respectively, with a ‘first down and then up’ trend in the general CLD patients (Table 3), which also appeared in the CHB patients (Fig 3). However, the serological model FIB-4, Forns, and FIB-5 were having a ‘first down and then up’ trend (Fig 3) in the other CLD patients. The possible explain for the different serological model trend among CLD patients may attribute to the different progression of disease, such as autoimmune hepatitis [16], Nonalcoholic Fatty Liver Disease [17], and drug-induced liver disease [18].

The hepatic fibrosis of CLD was often accompanied by liver dysfunction and impaired synthesis of coagulation factors. Our study showed the Patients with severe liver fibrosis had significantly higher AST, ALT, GGT, and ALP, and a significantly lower ALB, CHO, and PLT was also seen in the high grade of liver fibrosis. Previous researchers [9, 19] also found the severe liver fibrosis has worse liver dysfunction. Our study found the FIB-5 negative correlated with fibrosis stage, which also found in other researches [10, 20]. Although the positive correlation (except FIB-5 group) among different serological model and fibrosis stage was not that large, we did see a significantly difference among different grade of fibrosis stage (Table 1).

5. Conclusion

Our study showed the FibroTouch has a higher diagnostic value compared with the non-invasive serological models in staging the fibrosis stage. The cut-off of FibroTouch and five serological models (APRI, FIB-4, S-index, Forns, and PRP) increased with the severe of fibrosis stage, but the FIB-5 decreased with the cut-off. We also found the serological models have different diagnostic effects to the stage of liver fibrosis between CHB patients and other CLD patients.

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