

Assessment of Liver Fibrosis by Transient Elastography in Children with Chronic Hepatitis B Virus Infection

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Abstract

Background: This study aimed to investigate the effectiveness of transient elastography (TE) by comparing liver biopsies to assess liver fibrosis in children with chronic hepatitis B (CHB).

Methods: A total of 157 CHB children aged 0 - 6 years in China were enrolled in this single-center prospective study. All patients underwent liver stiffness measurement (LSM) by TE and liver biopsy at an interval of less than a week.

Results: LSM, aspartate aminotransferase (AST)-platelet ratio index (APRI), and fibrosis-4 score (FIB-4) positively correlated with activity grade and fibrosis stage in children with CHB. The area under receiver operating characteristic curves (AUCs) of LSM for identifying significant ($F \geq 2$) and advanced fibrosis ($F \geq 3$) were 0.732 and 0.94, the cut-off values were 5.6 kPa and 6.9 kPa, specificity of 75.7% and 91.5%, and sensitivity of 67.4% and 81.3%, respectively. Compared to LSM, the overall diagnostic performance of APRI and FIB-4 for significant and advanced fibrosis was suboptimal with low AUCs and sensitivity. Since LSM, platelet, and $\text{Log}_{10}\text{HBsAg}$ were independent factors with the fibrosis stages ($F < 2$ and $F \geq 2$) on the liver biopsy, the LPS index was formulated to predict $F \geq 2$ by combining LSM, platelet, and $\text{Log}_{10}\text{HBsAg}$. The AUC of LPS for $F \geq 2$ was increased to 0.792, which was higher than that of LSM (0.732, $p < 0.05$), with an improved sensitivity (76.6% vs 67.4%).

Conclusions: TE represents a promising technology for the diagnosis of advanced fibrosis in CHB children aged 0 - 6 years.

Introduction

Hepatitis B virus (HBV) infection is one of the most common causes of chronic liver disease (CLD) worldwide, especially in China where more than 80 million adults and 37,000 children are affected [1, 2]. Although the natural history of chronic HBV-infected children remains poorly understood, limited studies have shown that 1% - 5% of hepatitis B e-antigen (HBeAg)-positive children developed cirrhosis before adulthood [3-6]. In addition, 25% of adult patients who acquire HBV infection in childhood will develop liver cancer or cirrhosis, which leads to the greatest burden of morbidity and mortality [7]. Thus, there is a critical need to decrease the risk of disease progression to cirrhosis and even achieve a functional cure for children with chronic hepatitis B (CHB) with antiviral treatment. Additionally, one of the most important indicators for antiviral treatment is histological evidence of necro-inflammation and fibrosis according to guidelines of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), as well as the American Association for the Study of Liver Diseases [8]. Therefore, early diagnosis of the extent of liver inflammation and fibrosis is important for the treatment of CHB during childhood [8, 9].

Currently, liver biopsy remains the gold standard for determining the degree of liver inflammation and fibrosis, and is pivotal for guiding antiviral treatment in children with CHB [8, 9]. In addition, follow-up monitoring is required for these patients to evaluate the efficacy of antiviral treatment [10]; however, children may suffer from pain, additional expenses, and risks associated with post-procedure hospitalizations by undergoing a liver biopsy [11]. Moreover, a liver biopsy requires highly skilled physicians and medical devices. Thus, non-invasive diagnostic tests for CHB children to diagnose liver cirrhosis are necessary to avoid the risks and costs associated with liver biopsies.

The aspartate aminotransferase (AST)-platelet ratio index (APRI) and fibrosis-4 score (FIB-4) obtained by calculating laboratory parameters have been used to identify the fibrosis stages in adult patients with CHB. The results showed that APRI and FIB-4 were insufficient due to high rates of misclassification [12], whereas the diagnostic performance of APRI and FIB-4 remained unknown in children with CHB. Additionally, transient elastography (TE) has been widely adopted as a novel noninvasive assessment tool to diagnose the stage of liver fibrosis and monitor the development of chronic liver disease (e.g., CHB and chronic hepatitis C [CHC]) due to its accuracy and reproducibility in adult patients [13]. Several studies have shown that liver stiffness measurement (LSM) by TE is useful to assess liver fibrosis in children with CLD [14–15]. Although LSM was evaluated for hepatitis B/C-related fibrosis in children across three studies, due to small sample sizes, limited patient populations (primarily adolescents and young adults) and multiple causes of liver disease [11, 15, 16], no studies have assessed the performance of TE for liver fibrosis in children with CHB. Thus, in this study, we enrolled 157 CHB children aged 0 – 6 years to evaluate the diagnostic performance of TE in comparison with liver biopsies for liver fibrosis in children with CHB.

Patients And Methods

Patients

This prospective study included 157 CHB subjects aged 0 - 6 years from June 2015 to March 2020 at Fifth Medical Center of Chinese PLA General Hospital. Eligible patients were aged ≤ 6 years, met the criteria for CHB according to the guidelines of prevention and treatment for chronic hepatitis B of China [17], underwent LSM and liver biopsy with an interval of less than a week, and written informed consent was obtained from the parent or legal guardian of the child subjects. The exclusion criteria consisted of: 1) patients with white blood cell (WBC) $< 2.75 \times 10^9/L$, PLT $< 80 \times 10^9/L$, total bilirubin $> 51 \mu\text{mol/L}$, alanine aminotransferase (ALT) $\geq 400 \text{ IU/L}$, serum creatinine $> 133 \mu\text{mol/L}$ or international normalized ratio > 1.5 ; 2) patients with positive hepatitis A/C/delta virus, human immunodeficiency virus, or a chronic liver disease other than CHB (e.g., autoimmune hepatitis, Wilson's disease, hepatolenticular degeneration, and hepatocellular carcinoma); 3) patients with evidence of decompensation (i.e., clinical ascites); or 4) any other serious physical and mental illnesses.

Clinical and Laboratory Parameters

Demographic data, including age, gender, body weight, and height (Body Mass Index [BMI] = body weight in kg/height in meters²) were collected. Routine blood tests, liver function tests, plasma HBV DNA quantification, and serological HBV markers, including HBeAg and hepatitis B surface antigen (HBsAg) quantification, as well as abdominal ultrasound examination were performed. APRI and FIB-4 were calculated as previously reported [12].

Liver Histology and Liver Stiffness Measurements

After the laboratory examinations were performed, ultrasonic-guided liver biopsies were carried out in all subjects using a one-second needle biopsy. Liver specimens were prepared for histological evaluation by a senior pathologist who was blinded to the LSM results according to the meta-analysis of histological data for the viral hepatitis (METAVIR) scoring system [18]. LSM expressed in kilopascals (kPa) was measured using Fibroscan® with an S probe (Echosens, France) by a certified and experienced physician blinded to the liver biopsy results. In this study, only the LSM results were considered reliable when an interquartile range (IQR)/LSM of ≤ 0.3 , up to 10 validated measurements, and a success rate of $\geq 60\%$ were obtained.

Statistical Analysis

For the descriptive analysis, quantitative variables were expressed as the mean \pm SD or medians (IQR), whereas categorical variables were expressed as the number of subjects (percentages). A comparison of quantitative variables was conducted using a Student's t-test/one-way ANOVA for normally distributed variables or Tamhane's T2 for anomalous distributed variables, whereas categorical variables were compared using a Chi-squared test. Correlations were assessed using a Spearman's rank correlation coefficient, and factors associated with the degree of liver fibrosis were identified with a logistic regression analysis. The diagnostic value of LSM was evaluated based on sensitivity, specificity, positive, and negative predictive values (PPV and NPV), positive and negative likelihood ratio (PLR and NLR), and area under receiver operating characteristic (ROC) curves (AUC) using a Hanley-McNeil test. The LSM cut-off values for predicting different stages of liver fibrosis were determined at the highest sensitivity and specificity. All of the above statistical analyses were performed using SPSS 25.0 statistical software, and statistical significance was considered at $p < 0.05$.

Results

Patient demographic and laboratory variables

Among the 157 patients who were enrolled, 92 (58.6%) patients were male, the median age was 3.0 years old (IQR, 1.9, 4.1), and the median BMI was 16.01 (15.00, 17.28) (Table 1). Moreover, the laboratory variables, including the WBC count (8.2 ± 2.1 , $10^9/L$), PLT count [287 (236, 344), $10^9/L$], alanine aminotransferase (ALT) [73 (42, 145), IU/L], AST [79 (55, 136), IU/L], Log_{10} HBV DNA quantification [7.87 (7.00, 8.01), IU/mL], and serological HBV markers are summarized in Table 1.

Noninvasive assessment indices for liver fibrosis and patient histological features

Next, noninvasive assessment indices were analyzed. As shown in Table 1, the LSM was 5.2 (4.4 - 6.1) kPa, ranging from 1.1 kPa to 12.6 kPa, APRI was 0.6778 (0.4573, 1.1296), and FIB-4 was 0.0951 (0.0639, 0.1434). In addition, 59 patients presented with mild or lack of necroinflammatory activity ($A < 2$), 96 patients were A2, and 2 patients were A3. There were 111 patients who exhibited a lack of or mild liver fibrosis (F0-F1), 30 individuals presented as F2, and 16 patients showed advanced fibrosis ($F \geq 3$) (Table 1).

Correlation between LSM, APRI or FIB-4 and histological features in children with CHB

The activity grades in our study were divided into two groups: $A < 2$ and $A \geq 2$, and the liver fibrosis stages were classified into three groups: F0-F1, F2, and F3-F4 in accordance with previous studies [14]. The distribution of LSM, APRI, and FIB-4 according to activity grade and stages of liver fibrosis are displayed in Figure 1. A comparative analysis showed that the $A \geq 2$ group [5.5 (4.6 - 6.5) kPa] had a higher median LSM value than that of the $A < 2$ group [4.8 (4.1 - 5.4) kPa] ($P < 0.001$) (Fig. 1a). Patients classified as F3-F4 stage had a significantly higher LSM compared to F0-F1 stage (8.3 vs 4.9 kPa; $P < 0.001$) and F2 stage (8.3 vs 5.6 kPa; $P < 0.001$) patients, whereas there was no significant difference in LSM values between patients in the F0-F1 stage and F2 stage groups (Fig. 1b). With regards to APRI, the $A \geq 2$ group had higher values compared to the $A < 2$ group (0.9726 vs 0.4664, $p < 0.001$), whereas only the F3-F4 stage had significantly higher values than those of F0-F1 stage (1.4040 vs 0.5662, $p < 0.05$) (Fig. 1c and d). In addition, the FIB-4 levels were higher in the $A \geq 2$ group compared with those in the $A < 2$ group (0.1104 vs 0.0814, $p < 0.01$); however, there was no significant differences in the fibrosis stages among the three groups (F0-F1, 0.0896, F2, 0.1321 and F3-F4, 0.1337, all $p > 0.05$) (Fig. 1e and f). We next estimated the

correlation between LSM, APRI or FIB-4, and activity grades ($A < 2$ and $A \geq 2$) or liver fibrosis stages (F0-F1, F2, and $F \geq 3$). The results revealed that LSM ($r = 0.275$, $P < 0.001$), APRI ($r = 0.478$, $P < 0.001$), and FIB-4 ($r = 0.249$, $P < 0.01$) were positively correlated with the degree of activity. We also found the three parameters were positively correlated with the fibrosis degree (LSM, $r = 0.414$, $P < 0.001$; APRI, $r = 0.357$, $P < 0.001$ and FIB-4, $r = 0.277$, $P < 0.001$). Overall, these data suggest that LSM, APRI and FIB-4 are positively associated with the severity of liver inflammation and fibrosis in CHB children.

Performance of LSM, APRI, and FIB-4 for liver fibrosis stages

To further evaluate the performance of LSM, APRI, and FIB-4 for the liver fibrosis stages, an ROC curve analysis was performed for all patients. The AUCs of LSM identifying fibrosis stages $F \geq 2$ and $F \geq 3$ among children with CHB were 0.732 (95% confidence interval, 0.639 - 0.826) and 0.941 (0.897 - 0.985), respectively (Table 2). The optimal cut-off values were 5.6 kPa and 6.9 kPa, specificity (%) values were 75.7 (66.6 - 83.3) and 91.5 (85.6 - 95.5), and sensitivity (%) values were 67.4 (52.0 - 80.5) and 81.3 (54.4 - 96.0) for $F \geq 2$ and $F \geq 3$, respectively (Table 2 and Fig. 2a and b). Additionally, compared to LSM, although the specificities of APRI predicting $F \geq 2$ and $F \geq 3$ were moderately higher, both the AUCs and sensitivities of APRI and FIB-4 for $F \geq 2$ and $F \geq 3$ were lower, especially for $F \geq 3$ (Table 2 and Fig. 2a and b). Overall, these data suggest that LSM is reliable for assessing advanced liver fibrosis, which is superior to that of APRI and FIB-4, whereas all of these parameters were suboptimal for identifying significant liver fibrosis.

Independent parameters associated with the fibrosis stage $F \geq 2$ according to the liver biopsy

We next performed a univariate analysis of the parameters associated with fibrosis stages of the liver biopsies (Table S1). We observed that ALT, AST, gamma-glutamyl transpeptidase (γ -GT), cholinesterase, PLT, HBeAg, and HBsAg quantification, $\text{Log}_{10}\text{HBsAg}$, $\text{Log}_{10}\text{HBV DNA}$, $A \geq 2$, and LSM were significantly associated with the fibrosis stage ($F \geq 2$) of the liver biopsy (all $p < 0.05$) (Table S3). Based on these results, further multivariate analyses showed that LSM, PLT, and $\text{Log}_{10}\text{HBsAg}$ were independent factors associated with the fibrosis stages of the liver biopsy (all $p < 0.05$) (Table 3).

Combination of LSM, PLT and $\text{Log}_{10}\text{HBsAg}$ to determine liver fibrosis stage $F \geq 2$

Since LSM was associated with a relatively poor diagnostic accuracy for $F \geq 2$ as shown in Table 2 and Fig. 2, LSM, PLT, and $\text{Log}_{10}\text{HBsAg}$ were further combined as independent factors associated with fibrosis stages to create an algorithm that could predict the presence of $F \geq 2$ in our patients. This algorithm was the LPS index ($\text{LSM, PLT and } \text{Log}_{10}\text{HBsAg}$) = $0.511 \times \text{LSM} - 0.006 \times \text{PLT} - 0.682 \times \text{Log}_{10}\text{HBsAg} + 0.769$. The data revealed that the AUC increased to 0.792 (0.720 - 0.852), which was higher than that of LSM (0.792 vs 0.732, $p < 0.05$) (Table 4 and Fig. S1). More importantly, the sensitivity increased by almost 10 percent (76.7% vs 67.4%) (Table 5 and Fig. S1). Taken together, these findings demonstrate that compared to LSM, the combination of LSM, PLT, and $\text{Log}_{10}\text{HBsAg}$ could better predict liver fibrosis of $F \geq 2$ with a higher AUC and greater sensitivity.

Discussion

This study is the first to report that LSM represents a better noninvasive index for predicting HBV-related fibrosis stages from liver biopsies than APRI and FIB-4 in a large sample size of children aged 0 - 6 years. In addition, LSM

could better distinguish the patients with F0-F2 vs F3-F4 (AUC 0.941) compared to the patients with F0-F1 vs F2-F4 (AUC 0.732), suggesting a promising index to diagnose liver fibrosis of $F \geq 3$.

To date, liver biopsies remain the most common test used to assess HBV-related fibrosis in children; however, its invasiveness restricts the ability to perform the repeated assessments required for dynamic monitoring of CHB development and the effects of antiviral treatment [8-9]. Recently, a pediatric nonalcoholic steatohepatitis study presented AUCs of TE for fibrosis of $F \geq 2$ and $F \geq 3$ to be 0.992 and 1, respectively, and the cut-off values were 7 kPa and 9 kPa, respectively for predicting the corresponding fibrosis stages [14]. Another study found that the 8.6 kPa cutoff point could be used to discriminate between stages F0-F2 and F3-F4 for children and young adults with multiple causes of liver disease [11]. In our study, we found that the AUCs were 0.732 and 0.941 and the cut-off values were 5.6 kPa and 6.9 kPa for fibrosis stages $F \geq 2$ and $F \geq 3$, respectively. The discrepancies between the findings of these studies may be due to differences in the age of the participants at the time of enrolment and causes of the disease [19]. Consistent with our findings, the study by Anna et al. reported an LSM of 5.4 (4.0, 7.1) kPa for the F2 stage in children with CHC (20). Moreover, a previous study demonstrated that LSM was able to adequately predict the liver fibrosis stage in adult patients with CHB, and the ROC curves were 0.81 for F0-F1 vs F2-F4 and 0.93 for F0-F2 vs F3-F4 [21], which is consistent with the children with CHB in our study. However, the cut-off values in adult patients with CHB were 7.2 kPa and 8.1 kPa for fibrosis stages $F \geq 2$ and $F \geq 3$, respectively [21]. This difference in the cut-off values was also affected by the age of subjects in two studies [22]. Overall, this is the first study to suggest that TE represents a highly effective methodology for identifying children aged 0 - 6 years with CHB who exhibit advanced fibrosis ($F \geq 3$). Moreover, TE is vital for outpatient monitoring and clinical decision-making for patients with advanced fibrosis, similar to CHB in adults [23].

We additionally found that APRI and FIB-4 provided no advantages over LSM in the discriminated hepatic fibrosis stages of $F \geq 2$ and $F \geq 3$. In agreement with some studies that have focused on adults with CHB [24, 25], we found that APRI and FIB-4 were not suitable for predicting the HBV-related fibrosis stages of $F \geq 2$ and $F \geq 3$ in CHB children. These data also indicate that TE, APRI, and FIB-4 were suboptimal for the diagnosis of the $F \geq 2$ stage. Previous studies have shown that PLT count, \log_{10} HBsAg, alkaline phosphatase, ALT, AST, BMI, and inflammation were correlated with HBV/HCV-related fibrosis [26-28]. Similarly, in our study, we found that LSM, PLT, and \log_{10} HBsAg were independent factors associated with the fibrosis stage $F \geq 2$. Based on these independent factors, this study is the first to apply the LPS index to improve the diagnostic performance of $F \geq 2$ with a higher AUC (0.792) and sensibility (76.6%).

This study had several limitations. First, due to the low incidence of children with HBV-related advanced fibrosis, the sample size in subjects with F3-F4 was small, which also limited our ability to validate the cutoff points for identifying advanced fibrosis. Second, we only evaluated the children aged 0 - 6 years and our study was performed at a single center. To address these drawbacks, future studies are required to enlarge the sample size to validate the cutoff points and evaluate the performance of TE for children aged 7 - 18 years with CHB by conducting a multi-center study.

In conclusion, LSM rather than APRI and FIB-4 offers excellent performance for children aged 0 - 6 years with HBV-related advanced fibrosis in China, whereas TE, APRI and FIB-4 are suboptimal for the diagnosis of stage $F \geq 2$. Thus, the combination of LSM, PLT, and \log_{10} HBsAg could significantly enhance the diagnostic performance for stage $F \geq 2$.

Declarations

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Compliance with Ethical Standards:

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Conflict of Interest: Zhiqiang Xu, Jinfang Zhao, Jiaye Liu, Yi Dong, Fuchuan Wang, Jianguo Yan, Lili Cao, Pu Wang, Aiqin Li, Jing Li, Shishu Zhu, Yanwei Zhong, Min Zhang, and Fu-Sheng Wang have no conflicts of interest to disclose.

Ethical approval: This study was approved by the ethics committees of our hospital (NO. 2015151D) and fully complied with the Declaration of Helsinki and the Guideline for Good Clinical Practice. This article does not contain any studies with animals performed by any of the authors.

Informed consent: informed consent was obtained from all subjects who participated in the study.

Abbreviations

AUC, area under receiver operating characteristics (ROC) curves; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; APRI, aspartate aminotransferase (AST)-platelet ratio index (APRI); HBeAg, hepatitis B e-antigen; BMI, Body Mass Index; HBsAg, hepatitis B surface antigen; CHB, chronic hepatitis B; COI, cut off index; CLD, chronic liver disease; CHC, chronic hepatitis C; FIB-4, fibrosis-4 score (FIB-4); IQR, interquartile range; kPa, kilopascal; LSM, liver stiffness measurement; LPS index, $(\text{LSM}, \text{PLT and } \text{Log}_{10} \text{ HBsAg}) = 0.511 \times \text{LSM} + 0.006 \times \text{PLT} + 0.682 \times \text{Log}_{10} \text{ HBsAg} + 0.769$; METAVIR, meta-analysis of histological data in viral hepatitis; PLT, platelet; PPV and NPV, positive and negative predictive values; PLR and NLR, positive and negative likelihood ratio; γ -GT, gamma-glutamyl transpeptidase; TE, transient elastography; WBC, white blood cell.

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Tables

Table 1. Patient variables

Variable	Patients (n=157)
Male gender, n (%)	92 (58.6)
Age (median, IQR, years)	3.0 (1.9, 4.1)
BMI (median, IQR, kg/m ²)	16.01 (15.00, 17.28)
ALT (median, IQR, IU/L)	73 (42, 145)
AST (median, IQR, IU/L)	79 (55, 136)
Total bilirubin (median, IQR, μmol/L)	6.2 (4.9, 8.3)
ALP (median, IQR, IU/L)	283 (233, 338)
γ-GT (median, IQR, IU/L)	17 (13, 29)
Albumin (median, IQR, g/L)	41 (39, 43)
cholinesterase (median, IQR, IU/L)	7933±1644
WBC count (means±SD, 10 ⁹ /L)	8.2±2.1
PLT count (median, IQR, 10 ⁹ /L)	287 (236, 344)
HBeAg positive, n (%)	143 (91.1)
HBeAg (median, IQR, COI)	1457 (435, 1814)
HBsAg quantification (median, IQR, IU/mL)	18101 (5133, 42793)
Log ₁₀ HBsAg (median, IQR, IU/mL)	4.26 (3.71, 4.63)
Log ₁₀ HBV DNA (median, IQR, IU/mL)	7.87 (7.00, 8.01)
APRI (median, IQR)	0.6778 (0.4573, 1.1296)
FIB-4 (median, IQR)	0.0951 (0.0639, 0.143)
LSM (median, IQR, kPa)	5.2 (4.4-6.1)
Activity grade, n (%)	
A0	2 (1.3)
A1	57 (3.3)
A2	96 (61.1)
A3	2 (1.3)
Fibrosis stage, n (%)	
F0	16 (10.2)
F1	95 (60.5)
F2	30 (19.1)
F3	13 (8.3)
F4	3 (1.9)

Notes: IQR, interquartile range; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyl transpeptidase; WBC, white blood cell; PLT, platelet; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; LSM, liver stiffness

measurement; APRI, aspartate aminotransferase-to-Platelet ratio index; FIB-4, the Fibrosis-4 score; COI, cutoff index.

Table 2. The diagnostic performance of LSM, APRI, and FIB-4 for the identification of fibrosis stages

Fibrosis stage	Cutoff (kPa)	YI	Se (% 95% CI)	Sp (% 95% CI)	PLR (95% CI)	NLR (95% CI)	PPV (% 95% CI)	NPV (% 95% CI)	AUC (95% CI)
LSM									
F ≥ 2	5.6	0.43	67.4 (52.0-80.5)	75.7 (66.6-83.3)	2.3 (1.5-3.6)	0.36 (0.20-0.50)	84.8 (78.5-89.6)	53.4 (43.9-62.8)	0.732 (0.639-0.826)
F ≥ 3	6.9	0.73	81.3 (54.4-96.0)	91.5 (85.6-95.5)	4.9 (1.8-13.5)	0.10 (0.06-0.20)	97.7 (93.9-99.2)	52 (37.5-66.2)	0.941 (0.897-0.985)
APRI									
F ≥ 2	0.7159	0.4222	64.0 (54.3-72.9)	78.3 (63.6-89.1)	2.9 (1.7-5.2)	0.46 (0.30-0.60)	87.7 (80.1-92.6)	47.4 (40.2-54.6)	0.713 (0.636-0.783)
F ≥ 3	0.8156	0.5829	64.5 (56.0-72.4)	93.7 (69.8-99.8)	10.3 (1.5-69.2)	0.38 (0.30-0.50)	98.9 (93.1-99.8)	23.1 (18.8-27.9)	0.790 (0.718-0.851)
FIB-4									
F ≥ 2	0.0928	0.2759	55.8 (46.1-65.3)	71.7 (56.5-84.0)	2.0 (1.2-3.2)	0.62 (0.50-0.80)	82.7 (74.5-88.6)	40.2 (33.8-47.0)	0.655 (0.575-0.729)
F ≥ 3	0.1543	0.3440	84.4 (77.3-90.0)	50.0 (24.7-75.3)	1.7 (1.0-2.8)	0.31 (0.20-0.60)	93.7 (90.1-96.1)	26.7 (16.3-40.4)	0.660 (0.580-0.734)

Note: Se, sensitivity; Sp, specificity; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive values; NPV, negative predictive values and AUC, area under receiver operating characteristics (ROC) curves; LSM, liver stiffness measurement; APRI, aspartate aminotransferase-to-Platelet ratio index; FIB-4, Fibrosis-4 score.

Table 3. Independent factors associated with the fibrosis stages of the liver biopsy

	Estimate ± SE	Odds Ratio (95% CI)	P
LSM (kPa)	0.511 ± 0.131	1.667 [1.289-2.155]	<0.001
PLT (10 ⁹ /L)	-0.006 ± 0.003	0.994 [0.988-0.999]	0.032
Log ₁₀ HBsAg (IU/mL)	-0.682 ± 0.258	0.505 [0.305-0.837]	0.008

Note: SE, standard error and CI, confidence interval; PLT, platelet; LSM, liver stiffness measurement; HBsAg, hepatitis B surface antigen.

Table 4. Improved performance of LPS for the identification of the F ≥ 2 fibrosis stage

Fibrosis stage	Cutoff	YI	Se (% 95% CI)	Sp (% 95% CI)	PLR (95% CI)	NLR (95% CI)	PPV (% 95% CI)	NPV (% 95% CI)	AUC(95% CI)
F ≥ 2	0.30	0.50	76.6 (67.6- 84.1)	73.9 (58.9- 85.7)	2.9 (1.8- 4.8)	0.32 (0.20- 0.50)	87.6 (81.2- 92.1)	56.7 (47.3- 65.6)	0.792 (0.720- 0.852)

Note: LPS, (LSM, PLT and Log_{10} HBsAg) = $0.511 \times \text{LSM} + 0.006 \times \text{PLT} + 0.682 \times \text{Log}_{10} \text{HBsAg} + 0.769$; Se, sensitivity; Youden index; Sp, specificity; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive values and AUC, area under receiver operating characteristics (ROC) curves; CI, confidence interval.

Figures

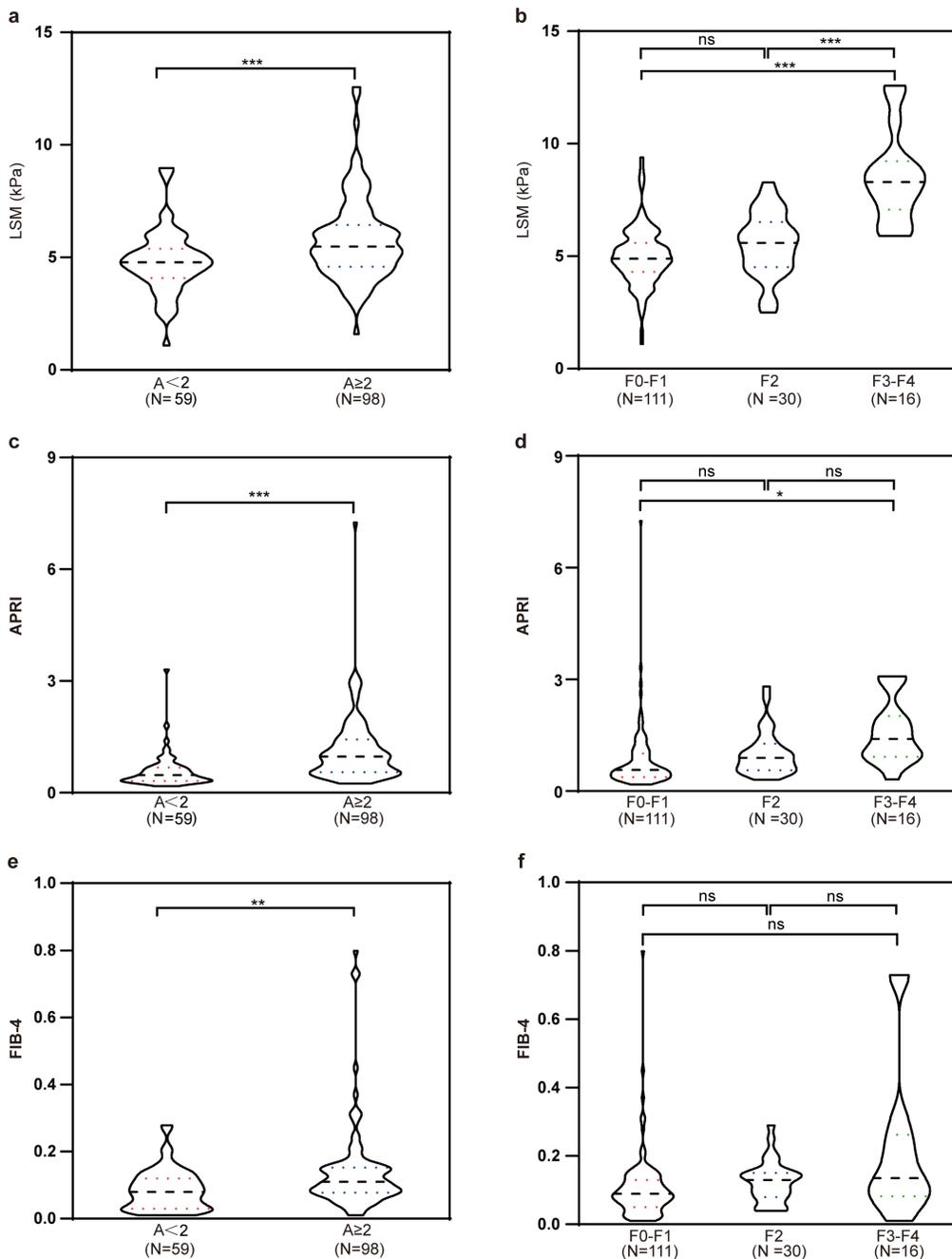


Figure 1

Violin plots of LSM, APRI, and FIB-4 vs activity grade and liver fibrosis stage (a) LSM vs activity grade ($A < 2$ and $A \geq 2$). (b) LSM vs METAVIR liver fibrosis stage (F0-F1, F2, and F3-F4). (c) APRI vs activity grade ($A < 2$ and $A \geq 2$). (d) APRI vs METAVIR liver fibrosis stage (F0-F1, F2, and F3-F4). (e) FIB-4 vs activity grade ($A < 2$ and $A \geq 2$). (f) FIB-4 vs METAVIR liver fibrosis stage (F0-F1, F2, and F3-F4). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; ns = no significant difference. Abbreviations: LSM, liver stiffness measurement; kPa, kilopascal, APRI, aspartate aminotransferase-to-Platelet ratio index; FIB-4, Fibrosis-4 score

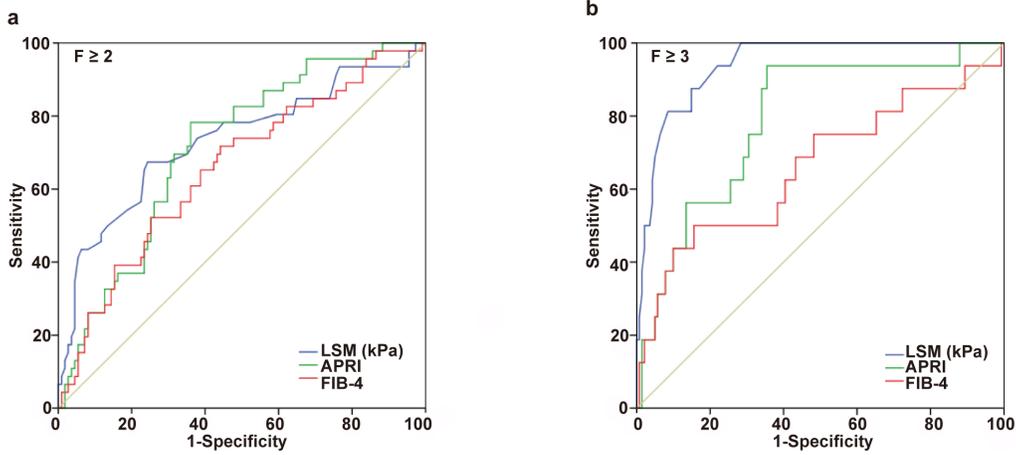


Figure 2

AUCs of LSM, APRI and FIB-4 for the diagnosis of fibrosis stage based on the liver biopsy. The AUC of LSM, APRI, and FIB-4 for the fibrosis of $F \geq 2$ (a) and (b) $F \geq 3$. Abbreviations: AUC, area under receiver operating characteristics (ROC) curves; LSM, liver stiffness measurement; kPa, kilopascal, APRI, aspartate aminotransferase-to-Platelet ratio index; FIB-4, Fibrosis-4 score

Supplementary Files

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- Fig.S1.tif
- Table.S1.doc