Development of a Simple Noninvasive Model to Predict Significant Fibrosis in Patients with Chronic Hepatitis B: Combination of Ultrasound Elastography, Serum Biomarkers, and Individual Characteristics

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OBJECTIVES: The accurate assessment of liver fibrosis is clinically important in patients with chronic hepatitis B (CHB). Blood tests and elastography are now widely used for the noninvasive diagnosis of liver fibrosis in CHB patients. The aim of this study was to develop a new and more accurate predictive model, which combines elastography data, serum biomarkers, and individual characteristics, to discriminate between CHB patients with and without significant liver fibrosis.
METHODS: Two noninvasive methods, specifically, an ultrasound elastography technique termed acoustic radiation force impulse imaging (ARFI) and a blood test, were used to assess a cohort of 345 patients (estimation group, 218 patients; validation group, 127 patients) with CHB. Multivariate logistic regression analysis revealed that ARFI, the aspartate aminotransferase (AST) to platelet ratio, and age were significantly associated with fibrosis. Based on these results, we constructed and validated a model for the diagnosis of significant hepatic fibrosis.
RESULTS: The area under the receiver operating characteristic (ROC) curve was 0.921 for the estimation group and 0.929 for the validation group, significantly higher than those for ARFI (0.887, 0.893) and for the AST-to-platelet ratio index (APRI; 0.811, 0.859). Using an optimal cutoff of 3.05 in the validation group, all the indices of the proposed model, including accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic odds ratio, were better than those for ARFI or APRI.
CONCLUSIONS: We developed a simple noninvasive model that used ultrasound elastography, routine serum biomarkers, and individual characteristics to accurately differentiate significant fibrosis in patients with CHB. Compared with elastography or the biomarker index alone, this model was significantly more accurate and robust.

INTRODUCTION

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. Its prevalence is highest in sub-Saharan Africa and East Asia, where 5–10% of the adult population is chronically infected.[1,2] Liver fibrosis is a common feature that develops over the course of chronic hepatitis B (CHB). Accurate assessment of liver fibrosis in patients with CHB is necessary not only to predict the prognosis but also to determine an appropriate antiviral therapy scheme.[3,4] For many years, liver biopsy has been considered to be the gold standard for CHB staging and is still recommended for the clinical management of patients. However, liver biopsy is a costly and invasive procedure hampered by sample bias and poor interobserver reproducibility and has a risk of rare but potentially life-threatening complications.[5,6] These limitations have stimulated the development of noninvasive approaches.

Recently, many noninvasive methods have been proposed as alternatives to liver biopsy.[7] Most of these methods can be categorized as either blood or elastographic tests.[8] The blood tests measure biomarkers in serum samples, which can directly or indirectly evaluate functional liver alterations due to liver fibrosis. As no single serum biomarker can achieve a satisfactory diagnostic performance, several indices or models that combine serum biomarkers have been developed to predict hepatic fibrosis in both hepatitis C and hepatitis B.[7–9] Elastography, the other main approach for assessing liver fibrosis, measures liver stiffness, which may change significantly as fibrosis develops. Two ultrasound-based elastography techniques, transient elastography and acoustic radiation force impulse imaging (ARFI), have been extensively validated in large cohorts of patients with liver fibrosis and are widely used in routine clinical practice.[10–12]

Liver fibrosis is a complex process in which the different stages have a variety of characteristics. Therefore, combining various noninvasive methods may be better than a single method because they supply complementary information about the liver status. Various researchers have proposed methods to combine blood tests,[13,14] elastography methods,[15,16] and fusions of these two methods.[17–21]

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Because elastography and blood test methods are based on different rationales, combining these two methods tends to be more effective than combining two blood tests.[9] Most of the studies that have used this type of combination adopted similar strategies based on a decision flowchart that combines elastography with serum biomarker methods.[18,20] However, this strategy has some inherent limitations. First, these algorithms have difficulty incorporating more than two methods. Second, they use currently available serum biomarker indices and, therefore, cannot fully utilize the complementary information provided by elastography and biomarker data. Most importantly, when the noninvasive methods show unexplained discordance, a liver biopsy should still be performed.[9]

In this study, we proposed a new algorithm that combines a patient's personal information, routine serum biomarkers, and ultrasound elastography for assessing liver fibrosis in patients with CHB. By using multivariate logistic regression analysis, we constructed and validated a specific model aimed at distinguishing CHB patients with and without significant liver fibrosis. The innovation is that the liver stiffness assessed by elastography is incorporated into this predictive model. To the best of our knowledge, this is the first study to combine individual characteristics, serum biomarkers, and elastography in one specific formula for evaluating liver fibrosis in patients with CHB.

MATERIALS AND METHODS

Patients. This study was conducted with the approval of the Ethics Committee Board of the Shenzhen Third People's Hospital in accordance with the 1975 Declaration of Helsinki, and written informed consents were obtained.

This cohort study enrolled 358 consecutive patients with CHB who had undergone percutaneous liver biopsy in the Shenzhen Third People's Hospital from 2013 to 2015. The inclusion criterion for the patients was being HBsAg-positive for more than 6 months without having received antiviral treatment before this study. Exclusion criteria for the patients were as follows: anti-HCV antibody positive, with human immune deficiency virus or hepatitis D virus (HDV), hepatitis A virus, hepatitis E virus super-infection or co-infection, autoimmune liver diseases, alcoholic steatosis, HCC (hepatocellular carcinoma), pregnancy, and ascites as well as clinically obvious jaundice. Patients with biopsy samples shorter than 15 mm or containing less than 10 portal tracts were also excluded.

Histological examination. Liver biopsy tissue specimens were obtained by a needle puncture under the ultrasonography guidance. Liver specimens were conventionally stained and evaluated semiquantitatively according to the METAVIR scoring system. The liver fibrosis stage was determined using a 0–4 scale: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with a few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis.

Laboratory tests. The following blood parameters were examined on the day of biopsy using the Siemens ADVIA 2400 chemistry system (Siemens Healthcare, Malvern, PA): alanine aminotransaminase level (ALT), aspartate aminotransaminase level (AST), γ-glutamyl transpeptidase level, cholesterol, alkaline phosphatase, total bilirubin, total protein, serum albumin, and γ globulins. Enzymatic activity was evaluated at 37 °C according to International Federation of Clinical Chemistry standards. An automatic blood-counter system (Sysmex XE-5000, Kobe, Japan) was used for the peripheral platelet count (PLT).

Elastography tests. The ARFI measurement was conducted one day before or on the day of biopsy using a commercial ultrasound scanner (Acuson S2000, Siemens Medical Solutions, Malvern, PA) with a convex array probe (4C1, Siemens Medical Solutions). The measurement was taken in the right liver, avoiding large vessels and bile ducts. The speed of the shear wave in the liver tissue was recorded at 12 different locations, 3 locations for each segment (s5, s6, s7, and s8). For the measurement of segments s5 and s8, the examined subject lays in a dorsal decubitus position, while for the measurement of segments s6 and s7, the subject lays in a left lateral decubitus position. The mean value of all the acquisitions was calculated as the ARFI result. ARFI failure was defined as a success rate of less than 60% or an interquartile range of more than 30%.

Statistical analysis. Data from a randomly generated split sample of 218 patients were used to estimate the model, and data from the remaining 127 patients were used to validate the model. All of the data were expressed as median and interquartile ranges unless otherwise stated. The statistical analysis was performed with SPSS software (SPSS, Chicago, IL, USA). The following variables were considered potential predictors of significant fibrosis ($\geq$ F2): individual characteristics (age, sex, and body mass index), the results of serum biochemical parameters (PLT, AST, ALT, γ-glutamyl transpeptidase, cholesterol, albumin, bilirubin, AST/ALT, AST/PLT), and the results of elastography (ARFI). All continuous variables were analyzed after logarithmic transformation for normality of distribution. Categorical variables were compared by χ^2- or Fisher exact tests, whereas continuous variables were compared with the Student's *t*-test. A two-sided *P* value of less than 0.05 was considered statistically significant.

To formulate the predictive models, a univariate analysis was performed on the variables mentioned above using the data from the estimation group. Significant variables from the univariate analysis ($P < 0.05$) were then subjected to multivariate analysis by forward logistic regression. A predictive model was constructed by modeling the values of the independent variables and their coefficient of regression. To simplify the model, a scale was constructed, ranging from 0 (absence of fibrosis) to 10 (cirrhosis).

The model derived from the estimation group was then applied to the validation and combined groups to test its generalizability. The diagnostic value of this model for evaluating significant fibrosis was assessed in the estimation and validation group by the receiver operating characteristic (ROC) curve. The area under the ROC (AUROC) values were calculated and compared with those of the ARFI test and the

aspartate aminotransferase-to-platelet ratio index (APRI) using the method developed by Hanley and McNeil.[22] The optimal cutoff value was chosen in the estimation group by maximizing the Youden index for the corresponding curve.[23] This cutoff value was then applied to evaluate the diagnostic performance of the model for the validation group using accuracy, sensitivity, specificity, positive and negative predictive values, and likelihood ratios. To estimate the performance improvement, the metrics of net reclassification improvement and integrated discrimination improvement were calculated by comparing the proposed model to the ARFI test and the APRI.[24]

RESULTS

Patients' characteristics. As stated above, we recruited 358 patients for this study. A total of 13 patients were excluded because of insufficient liver tissues for staging of fibrosis, alcoholic steatosis, auto-immune liver diseases, or ARFI failure. The final study cohort included 345 patients (218 patients in estimation group and 127 patients in validation group). The model was constructed with data from the estimation group and was validated in the estimation, validation, and combined groups. The patient characteristics at the time of the liver biopsy are shown in Table 1. There were no significant differences between the estimation and the validation groups in any of the assessed variables or in the data from the liver biopsy.

Development of the predictive model. In the estimation group, three variables, i.e., ARFI, AST/PLT, and age, were identified as independent predictors of significant fibrosis by univariate analysis (Table 2). These variables in decreasing rank were: ARFI ($P<0.001$), AST/PLT ($p<0.001$), and age ($P=0.007$). The three-dimensional space spanned by the

three variables and the data points of the estimation group in this space are shown in Figure 1. A logistic model combining the three independent variables was constructed into the following formula:

$$SF = -2.091 + 5.760\ln(ARFI) + 1.563\ln(age) + 0.981\ln(AST/PLT) \tag{1}$$

The diagnostic value of this model was assessed in the estimation, validation, and combined groups by a ROC curve. As shown in Table 3 and Figure 2, the proposed model had the largest AUROC values, significantly higher than those of APRI and ARFI in the estimation, validation, and combined groups (P values ranging from <0.001 to 0.024). The optimal cutoff value for the presence and absence of significant fibrosis using the data from the estimation group was 3.05 with a 95% confidence interval (2.37, 4.04). By setting the formula of Equation 1 equal to the cutoff value, we can obtain a plane in three-dimensional space. As shown in Figure 3, the plane separates the estimation or the validation group into two sets: the points below the plane were classified as F0–F1 by the model, while the points above the plane were classified as F2–F4.

The performances of APRI, ARFI, and the proposed model are listed in Table 4. The proposed model provided a higher diagnostic accuracy (87.40%) than that of ARFI (84.25%) or APRI (66.14%). The sensitivity, specificity, positive predictive value, and negative predictive value of the proposed model were also better than those of ARFI or APRI. For the comparison between the proposed model and the ARFI test, the net reclassification improvement value was 0.091 ($P=0.007$) and the integrated discrimination improvement value was 0.059 ($P<0.001$). For the comparison between the proposed model and the APRI, the net reclassification improvement value was 0.288 ($P<0.001$) and the integrated discrimination improvement value was 0.106 ($P<0.001$).

Table 1 Baseline characteristics of the 345 patients with CHB at the time of liver biopsy

Variable	Estimation group (*n* = 218)	Validation group (*n* = 127)	All patients (*n* = 345)
Age (y)	38 (32–45)	38 (32–46)	38 (32–45)
Male gender, *n* (%)	190 (87.16%)	108 (85.04%)	298 (86.38%)
BMI (kg/m^2)	22.9 (20.4–25.0)	21.6 (19.9–24.0)	22.4 (20.2–24.6)
PLT (10^9/L)	178.0 (135.8–216.8)	172.0 (133.5–210.0)	176.0 (135.0–216.0)
AST (U/L)	27.0 (20.0–34.8)	25.0 (18.0–33.0)	26.0 (20.0–34.0)
ALT (U/L)	29.0 (19.0–46.8)	26.0 (16.0–41.0)	28.0 (18.0–44.0)
GGT (U/L)	22.0 (16.0–38.0)	22.0 (16.0–36.5)	22.0 (16.0–38.0)
Cholesterol (mg/dL)	167.1 (150.8–184.5)	163.2 (150.8–185.6)	165.6 (150.8–184.4)
Albumin (g/L)	44.6 (43.4–46.6)	44.7 (42.9–47.3)	44.7 (43.3–46.8)
Bilirubin (μmol/L)	14.4 (10.6–18.1)	15.1 (11.8–21.5)	14.5 (10.8–18.8)
ARFI (m/s)	1.36 (1.19–1.66)	1.36 (1.20–1.63)	1.36 (1.19–1.65)
APRI	0.36 (0.23–0.65)	0.34 (0.25–0.55)	0.35 (0.24–0.64)
Stage of fibrosis, n *(%)*			
0	40 (18.4%)	24 (19.0%)	64 (18.6%)
1	35 (16.1%)	21 (16.5%)	56 (16.2%)
2	48 (22.0%)	27 (21.3%)	75 (21.7%)
3	42 (19.3%)	25 (19.7%)	67 (19.4%)
4	53 (24.3%)	30 (23.6%)	83 (24.1%)

ALT, alanine aminotransaminase level; APRI, aspartate aminotransferase-to-platelet ratio index; ARFI, acoustic radiation force impulse imaging; AST, aspartate aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; GGT, γ-glutamyl transpeptidase; PLT, peripheral platelet count.
NOTE. Quantitative variables are expressed as medians (centile 25; centile 75); categorical variables are expressed as *n* (%); there were no significant differences between the estimation and the validation groups in any of the variables.
Comparison between the estimation and the validation groups is shown.

Table 2 Variables associated with the presence of significant fibrosis (stages 2–4) in the estimation group (218 patients) by univariate and multivariate analyses

Variable	No significant fibrosis ($n = 75$)	Significant fibrosis ($n = 143$)	*P* value (univariate)	Odds ratio (95% CI; multivariate)
Age (y)	34 (29–39)	40 (34–46)	0.007[a]	10.90 (1.90–62.26)
Male gender, *n* (%)	64 (85.33%)	126 (88.11%)	0.973	
BMI (kg/m^2)	22.8 (20.4–24.4)	22.9 (20.4–25.1)	0.301	
PLT (10^9/L)	217.0 (188.0–246.0)	159.0 (111.0–195.0)	0.282	
AST (U/L)	22.0 (16.0–29.0)	30.0 (23.0–41.0)	0.282	
ALT (U/L)	23.0 (16.5–34.5)	34.0 (24.0–51.5)	0.267	
GGT (U/L)	17.0 (11.0–24.5)	26.0 (18.0–51.5)	0.315	
AST/ALT	0.86 (0.65–1.22)	0.90 (0.70–1.12)	0.478	
AST/PLT	0.10 (0.07–0.14)	0.20 (0.14–0.35)	<0.001[a]	4.47 (1.98–10.08)
Cholesterol (mg/dL)	169.5 (150.3–190.1)	165.9 (152.4–182.2)	0.195	
Albumin (g/L)	45.5 (43.6–46.7)	44.3 (43.2–46.6)	0.297	
Bilirubin (µmol/L)	11.6 (10.0–16.2)	16.2 (11.0–19.3)	0.103	
ARFI (m/s)	1.18 (1.09–1.27)	1.54 (1.34–1.82)	<0.001[a]	6,625.41 (283.86–154,639.23)

ALT, alanine aminotransaminase level; ARFI, acoustic radiation force impulse imaging; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; GGT, γ-glutamyl transpeptidase; PLT, peripheral platelet count.
NOTE. Quantitative variables are expressed as medians (centile 25; centile 75); categorical variables are expressed as *n* (%).
[a]There was a significant difference between F0/1 and F ≥2 fibrosis stages (*P* <0.05).
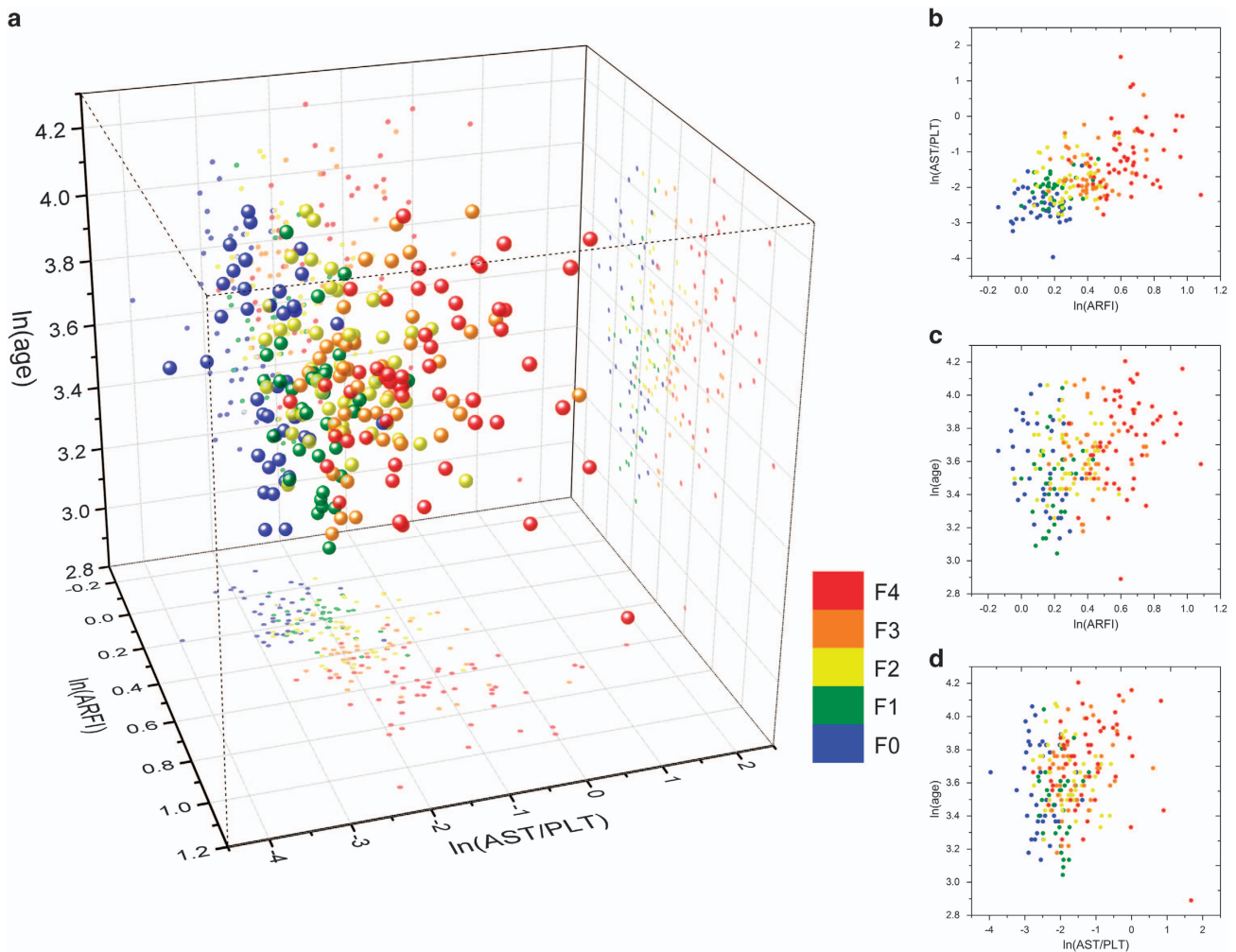
Figure 1 The data points of the estimation group in three-dimensional and two-dimensional spaces spanned by the following three variables: ARFI, AST/PLT, and age. (**a**) The data points in the three-dimensional space; (**b**) the data points in the two-dimensional space spanned by ARFI and AST/PLT; (**c**) the data points in the two-dimensional space spanned by ARFI and age; and (**d**) the data points in the two-dimensional space spanned by AST/PLT and age. ARFI, acoustic radiation force impulse imaging; AST, aspartate aminotransferase; PLT, peripheral platelet count.

Table 3 AUROC values (AUROC ± s.e.) of the APRI, ARFI, and the proposed model

Fibrosis test	Group		
	Estimation	**Validation**	**Combined**
APRI	0.811 ± 0.030	0.859 ± 0.035	0.869 ± 0.022
ARFI	0.887 ± 0.023	0.893 ± 0.028	0.878 ± 0.019
Proposed	0.921 ± 0.020	0.929 ± 0.022	0.919 ± 0.015
Comparison (P value)			
Proposed vs. APRI	<0.001	0.013	<0.001
Proposed vs. ARFI	0.004	0.024	<0.001

APRI, aspartate aminotransferase-to-platelet ratio index; ARFI, acoustic radiation force impulse imaging; AUROC, area under the receiver operating characteristic curve.
Comparisons of AUROCs between the proposed model and APRI or ARFI revealed significant differences in the estimation, validation, and combined groups ($P < 0.05$) are shown.

DISCUSSION

Because of its fundamental role in guiding patient management, accurate staging of hepatic fibrosis in chronic viral hepatitis is clinically important. Recently, several noninvasive methods to evaluate fibrosis have been proposed as alternatives for liver biopsy, which has traditionally been considered as the gold standard for staging fibrosis. Most of the noninvasive methods rely on either blood tests, which quantify levels of serum biomarkers, or elastographic techniques, which measure liver stiffness. In this study, we developed a predictive model that combines serum biomarkers and ultrasound elastography to discriminate CHB patients with and without significant fibrosis. This new model had a significantly better performance than any of the single fibrosis test methods.

Currently, transient elastography and ARFI are the most widely used elastography methods for the assessment of liver fibrosis. These two techniques involve a similar measurement principle: the mechanical excitation of the tissue to induce a shear wave and detection of the shear wave propagation using ultrasound. However, the methods have some essential differences that may significantly affect their performance in clinical applications. ARFI excites the liver by short-duration acoustic radiation force and detects the shear wave propagation using the same ultrasound probe. Transient elastography, on the other hand, uses an external actuator to transmit a low-frequency vibration into the liver; in addition, a single-element transducer, mounted with the actuator, is applied to track the shear wave propagation. A recent meta-analysis of 13 studies summarized the values of transient elastography and ARFI for liver fibrosis evaluation and compared their diagnostic performances.[12] It is concluded that both methods show comparable performance for detecting significant fibrosis and cirrhosis.[9,12] Our study built the model based on the ARFI technique implemented on a Siemens system. However, the ARFI technique from other manufacturers (such as Philips and GE) may perform slightly differently. Therefore, if other particular systems are applied, the coefficient corresponding to the ARFI value in the model should be adjusted according to the correlation between the ARFI values measured by the two systems.
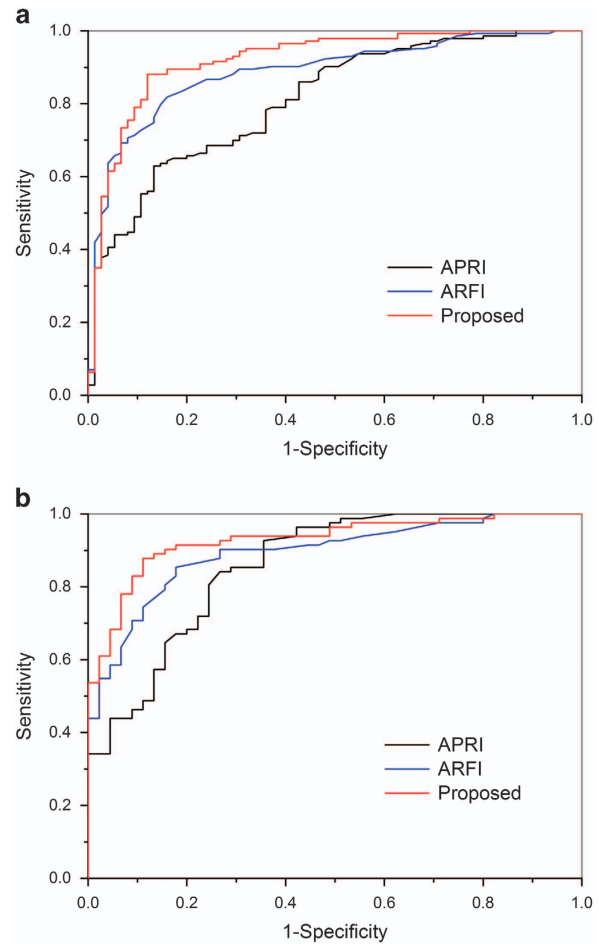
Figure 2 AUROCs of APRI, ARFI, and the proposed model for the diagnosis of significant fibrosis. (**a**) AUROCs in the estimation group and (**b**) AUROCs in the validation group. APRI, aspartate aminotransferase-to-platelet ratio index; ARFI, acoustic radiation force impulse imaging; AUROC, area under the receiver operating characteristic curve; PLT, peripheral platelet count.

As ARFI elastography is a point shear wave elastography technique, its measurement result is affected by measurement procedure, such as depth, liver segment, and probe position.[25] For example, D'Onofrio *et al.*[25] showed that a significant difference was found between the mean shear wave velocity values obtained deep in the right lobe of the liver and the values obtained on the surface of the right lobe (1.56 vs. 1.90 m/s). In this study, we measured ARFI values from four segments (s5, s6, s7, and s8) within the right lobe and used the mean value for statistical analysis. This set-up was adopted by some other studies,[26,27] and it allowed for sampling from many different areas of the liver to reduce the effect of the heterogeneity of liver fibrosis. Therefore, the final mean ARFI value was more representative.

Liver fibrosis is a complex process that involves alterations in functionality and physical properties. Therefore, combining noninvasive methods, especially those from different modalities, can provide complementary information and help to increase the diagnostic accuracy. An algorithm based on
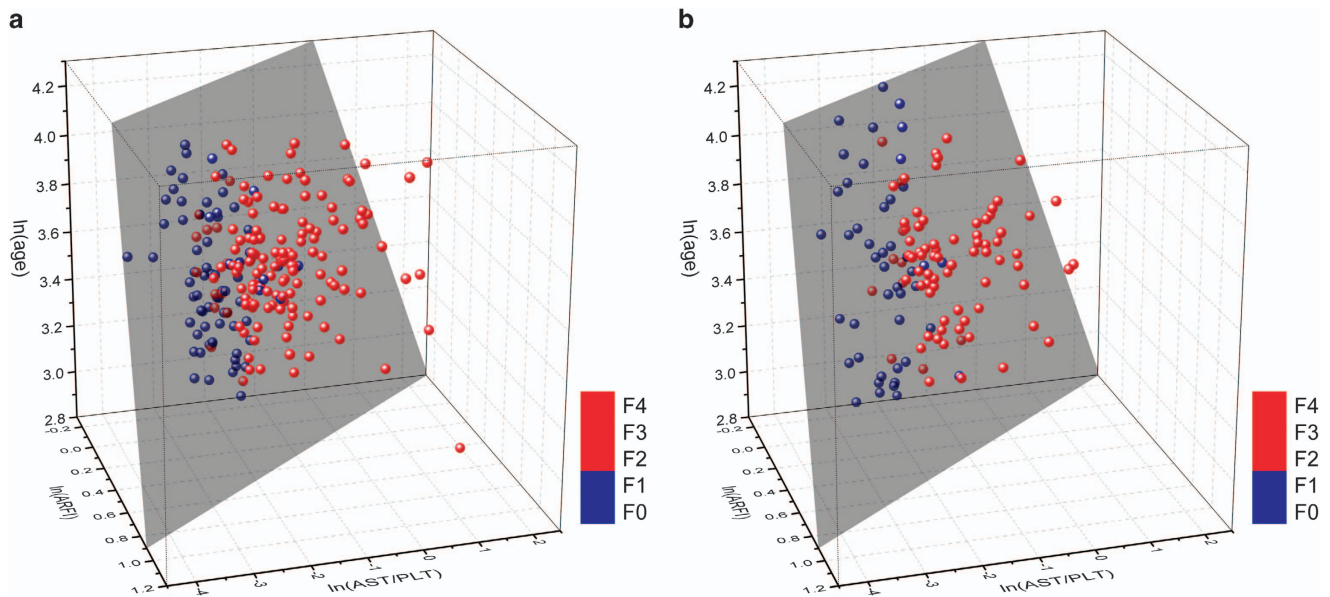
Figure 3 Three-dimensional scatter points and the plane determined by the model for the estimation and validation groups. The blue and red points correspond to the F0–F1 and F2–F4 groups, respectively, according to biopsy. The points below the plane (with shadow) are classified as F0–F1 by the model, while the points above the plane (without shadow) are classified as F2–F4. The points and plane for the (**a**) estimation group and (**b**) validation group.

Table 4 Diagnostic performance of APRI, ARFI, and the proposed model in the validation group ($n = 127$)

	Cutoff	Accuracy (%)	Se (%)	Sp (%)	PPV (%)	NPV (%)	DOR
APRI	0.4	66.14	54.88 (43.49–65.90)	86.67 (73.21–94.95)	88.24 (76.13–95.56)	51.32 (39.57–62.96)	7.92
ARFI	1.3 (m/s)	84.25	85.36 (77.72–93.01)	82.22 (71.05–93.39)	89.74 (83.01–96.47)	75.51 (63.47–87.55)	26.67
Proposed	3.05	87.40	87.91 (80.72–94.89)	86.67 (76.74–96.60)	92.31 (86.39–98.22)	79.59 (68.31–90.88)	47.79

APRI, aspartate aminotransferase-to-platelet ratio index; ARFI, acoustic radiation force impulse imaging; CI, confidence interval; DOR, diagnostic odds ratio; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.
Variables are expressed as estimated value (95% CI).

multivariate logistic regression has been widely used to combine single serum biomarkers into an index or test, such as Forns,[28] FPI,[29] and FibroIndex.[30] The advantage of logistic regression is that it can construct a predictive model with a specific formula. Some recent studies have proposed decision flowchart methods to combine a serum biomarker index with elastography.[18–20] However, this method depends on the cutoff values for each individual method and a liver biopsy is still needed when the noninvasive tests show unexplained discordance. Insofar as we know, no study has previously attempted to assess fibrosis in patients with CHB by combing an elastography test with serum biomarkers using logistic regression.

This study found that ARFI, AST/PLT, and age were independent predictors of significant fibrosis. The value of age as a marker of fibrosis seems reasonable, as fibrosis progression is time-dependent. It is evident that duration of HBV/HCV infection would be a more precise indicator of fibrosis than age.[28] However, the exact duration of HBV/HCV infection is difficult to establish in many cases. Therefore, many currently available serum biomarker indices, such as Forns Index, ELF score, and Zeng score, adopted age instead of years of infection.[9] Regardless of whether a univariate or a

multivariate analysis was used in this study, none of the clinical features that had been included in our analysis, except for age, had a significant relationship with disease progression. The value of the AST/PLT ratio has already been used in the APRI. In 2003, the APRI was proposed as a way to identify significant fibrosis and cirrhosis in patients with chronic hepatitis C.[31] This index has the advantage of including only two routine laboratory parameters and has shown great value in predicting hepatitis C-related fibrosis.[32] Recently, it was also applied to predict the fibrosis stage of HBV patients.[33] The latest guidelines for CHB infection published by the World Health Organization (WHO) recommended the APRI as the preferred noninvasive test for indicating the presence of cirrhosis in resource-limited settings.[34]

The results of this current study clearly show several advantages of the proposed model. First, the model includes personal information, routine serum biomarkers, and ultrasound elastography, which when considered together can provide complementary information about the liver status. Compared with combinations of different serum biomarkers, this combination of different modalities seemed to be more effective. Second, the model is relatively simple and has a straightforward interpretation. As shown in Figure 3, the three

variables form a three-dimensional feature space and the model is represented by a plane in the space. The points below the plane are classified as F0–F1 by the model, while the points above the plane are classified as F2–F4. Third, the model increased the diagnostic accuracy for identifying significant fibrosis compared with a single test. Table 3 lists the AUROC values of the proposed method, ARFI, and APRI. The pairwise comparisons showed that the proposed method had significantly higher AUROCs compared to the other two methods, indicating an improvement in the diagnostic performance. The performance improvements are shown in Table 4. The diagnostic accuracy of the proposed method was 87.40%, higher than that of ARFI (84.25%) or APRI (66.14%). Moreover, the metrics of net reclassification improvement and integrated discrimination improvement also indicate the performance improvement of the proposed model. Finally, the model provided more robust fibrosis staging. As shown in Table 4, the proposed model also improved other indices, including sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic odds ratio.

This study has several limitations. First, the proposed model is a linear combination that cannot theoretically solve a nonlinear classification problem. As shown in Figure 1, there are overlaps in data points between adjacent stages of fibrosis, indicating that the data sets (F0–F1 vs. F2–F4) may not be linearly separable. Therefore, its improvements to diagnostic performance are limited. Second, some characteristics of the patients, such as age and sex, are not evenly distributed in the cohort, indicating a relatively homogenous population. For example, although the range of age was 21–70 years, the interquartile range shown in Table 1 was relatively narrow. Finally, although an external validation is helpful to confirm the performance of the proposed model, it is not included in the current study. We are planning to collect data from HBV patients in other regions or populations to further validate the model.

In conclusion, this study developed a simple noninvasive model that combined elastography data, routine serum biomarkers, and individual characteristics to accurately differentiate significant fibrosis in patients with CHB. Compared with single tests, this model was significantly more accurate and robust. Future directions include applying this model in patients in other regions/populations and comparing this model to other noninvasive tests.

CONFLICT OF INTEREST

Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ Accurate assessment of liver fibrosis is important in patients with chronic hepatitis B.

✓ Liver biopsy is considered the gold standard for fibrosis staging.

✓ Elastography and blood tests are two noninvasive approaches for assessing liver fibrosis.

WHAT IS NEW HERE

✓ A new predictive model combining elastography, serum biomarkers, and individual characteristics is developed to differentiate significant fibrosis.

✓ This new model provides a simple formula with three variables.

✓ This new model has a significantly higher diagnostic accuracy than single elastography test (ARFI) or biomarker test (AST to platelet ratio index, APRI).

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