Comparison and Validation of APRI and FIB-4 for Evaluating Liver Fibrosis in Chinese Hepatitis B Virus-infected Patients with Persistently Normal ALT, Mildly and Significantly Elevated ALT

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Abstract

Background: Many noninvasive models based on serum markers composition are used for the assessment of liver fibrosis, reducing the need for liver biopsy. However, most of the models have rarely been validated in Chinese hepatitis B patients. We aim to evaluate and validate chronic hepatitis B(CHB) patients with normal ALT, mildly and significantly elevated ALT levels.

Methods: This single-center retrospective study enrolled 285 patients with CHB who underwent liver biopsy. There were 156 patients in normal ALT group, 85 patients in mildly elevated ALT group, and 44 patients in significantly elevated ALT group. The diagnostic accuracy of APRI and FIB-4 was evaluated by areas under the characteristic curves (AUROC) using the histological assessment of the fibrosis stages of the biopsy specimens as the standards.

Results: Among 285 patients with CHB, 156 patients had normal ALT level, of which 65 (41.7%) had significant fibrosis(S2-4). The evaluation of significant fibrosis, AUROC in APRI and FIB-4 were 0.608, 0.634, 0.708 and 0.638, 0.679, 0.734 in normal ALT, mildly and significantly elevated ALT, respectively. The assessment of advanced fibrosis, AUROC in APRI and FIB-4 were 0.636, 0.751, 0.708 and 0.652, 0.763, 0.734 in normal ALT, mildly and significantly elevated ALT groups, respectively.

Conclusions: APRI and FIB-4 may not be ideal noninvasive markers for evaluating liver fibrosis in Chinese HBV-infected patients with normal ALT levels. Compared with HBV-infected patients with normal ALT, APRI and FIB-4 had high accuracies in diagnosing liver fibrosis in patients with mildly and significantly elevated ALT.

Background

Hepatitis B virus (HBV) infection remains a major public health problem worldwide, and 350-400 million people are known to be chronic HBV surface antigen (HBsAg) carriers. HBV-infected is a dynamic process, it's subsequent development inevitably to persistent inflammation and liver fibrosis. This increases the risk of cirrhosis, hepatocellular carcinoma (HCC) and end-stage liver disease [1, 2]. Therefore, early and accurate assessment of liver fibrosis for subsequent treatment and prognosis is vitally important.

Serum alanine aminotransferase (ALT) levels reflect the severity of liver damage [3], but ALT levels are not consistently elevated in all patients with chronic HBV-infected. Liver biopsy of CHB patients with normal or mild elevation of ALT had been reported to indicate moderate to severe inflammation and/or significant fibrosis, requiring antiviral therapy [4–6]. Currently, liver biopsy is still considered as the "gold standard" for the assessment of liver fibrosis [7]. However, because liver puncture is an invasive procedure, poor patient compliance and specimen limitations have limited it's clinical application [8]. Therefore, many noninvasive methods have been developed for the assessment of liver fibrosis based on serum markers, such as the APRI and FIB-4 index [9, 10]. However, studies have shown that APRI and FIB-4 have high diagnostic value in the evaluation of patients with chronic hepatitis C or CHB with elevated

liver enzyme [11, 12]. The diagnostic accuracy of these models for CHB patients with normal ALT level is unclear.

In this study, we conducted a retrospective analysis of patients with CHB to evaluate and validate the diagnostic value of APRI and FIB-4 index in predicting liver fibrosis in patients with HBV-infected.

Methods

Patients

A total of 285 CHB patients who had undergone liver biopsy were retrospectively enrolled in the Department of Infectious Disease Zhejiang Provincial People's Hospital from October 2018 to December 2020. Chronic HBV-infected was defined as hepatitis B surface antigen seropositive for at least 6 months [13]. According to ALT levels, among 285 patients with CHB were divided into normal ALT levels group (ALT≤ULN), mildly elevated level group (1-2ULN), and significantly elevated ALT level group (>2ULN). The exclusion criteria were as follows: co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) infection, hepatitis D virus (HDV) infection, autoimmune liver disease, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), decompensated cirrhosis, HCC, and another cause of chronic liver disease. The retrospective study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital.

Liver biopsy and histopathological

All patients received ultrasound-guided percutaneous liver biopsy using an 18 G needle. Specimens were fixed, paraffin-embedded and stained with hematoxylin and eosin (H&E). All specimens were independently evaluations by two experienced pathologists who blinded to patients' clinical and laboratory details. Histological grading was considered as necro-inflammation (G0–4) and stage of liver fibrosis (S0-4), according to the Scheuer classification system [14]. In this study, significant fibrosis was defined as S≥2 and advanced significant was defined as S≥3[15].

Noninvasive models calculations and clinical examination

Two noninvasive markers were calculated according to the original article [9, 10]. APRI: AST(ULN) * 100 / PLT;FIB-4：age * AST / PLT * $ALT^{1/2}$; Clinical examination were obtained within 1 days before liver biopsy. Clinical examination including white blood cell count (WBC), platelet count (PLT), prothrombin time (PT), the international standardization ratio (INT), albumin (ALB), globulin (GLB), serum total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP). The serum load of HBV-DNA was assessed via real-time polymerase chain reaction (ABI 7300 platform, Applied Biosystems, Foster City, CA, USA). Core antibody (anti-HBC) were detected using the CLIA system. The normal upper limit of ALT is 40U/L. ALT levels were stratified as follows: normal ALT levels group (ALT≤ULN), mildly elevated level group (1-2ULN), and significantly elevated ALT level group (>2ULN).

Statistical analyses

All date analyses were processed using SPSS software version 21.0 (SPSS Inc./IBM, Chicago, IL, USA). Continuous variables were conducted using the non-parametric Mann-Whitney test, and categorical variables were compared using the Chi-square test. The diagnostic performance of APRI and FIB-4 index for discriminating significant fibrosis (S≥2) and advanced significant (S≥3) were analyzed and evaluated by using receiver operate characteristic curves (ROCs) and the areas under ROC curves (AUROCs), with 95% confidential interval (CI), related sensitivities and specificities calculated. P-value < 0.05 were considered statistically significant.

Results

Demographic data and baseline characteristics

Baseline characteristics for all patients are shown in Table 1. Among 285 patients with CHB, 156 patients in normal ALT levels group (ALT≤ULN), 85 patients in mildly elevated level group (1-2ULN), and 44 patients in significantly elevated ALT level group (2ULN). Significant fibrosis (S2-4) was observed 65 (41.7%) of patients with ALT≤ULN, 35 (41.2%) of patients with ALT between 1 and 2 ULN, compared with 28 (63.6%) patients with ALT2ULN. Patients with elevated ALT level were more likely to have significant fibrosis than those with normal ALT level.

Table 1
Demographic, laboratorial and clinical characteristics of different groups of patients

Variable	ALT≤1ULN (n=156)	ALT 1-2ULN (n=85)	ALT 2ULN (n=44)	P value
Age (yr)	40.0(32.0-47.0)	39.0(31.5-47.0)	35.0(27.3-48.8)	0.387
Male(n, %)	85(54.5%)	61(71.8%)	39(88.6%)	0.001
PT (s)	11.6(11.1-12.1)	11.7(11.1-12.1)	12.0(11.4-12.3)	0.040
INR	1.02(0.97-1.06)	1.02(0.97-1.06)	1.05(1.01-1.11)	0.009
WBC (*10^9/L)	5.62(4.65-6.42)	5.41(4.56-6.46)	5.44(4.47-6.79)	0.897
PLT (*10^9/L)	192.0(157.3-228.0)	190.0(152.0-212.5)	189.5(144.8-221.3)	0.568
TBIL (umol/L)	14.5(11.4-18.6)	14.6(12.4-19.4)	17.2(12.8-22.6)	0.084
ALB (g/L)	44.0(41.3-45.6)	44.1(41.6-46.5)	42.2(37.5-45.1)	0.003
GLB (g/L)	29.5(26.9-31.9)	30.0(27.3-32.1)	30.0(27.2-32.7)	0.592
GGT (U/L)	17.0(13.0-27.0)	29.0(20.0-52.5)	48.0(30.1-93.8)	0.000
ALP (U/L)	80.0(65.3-96.0)	91.0(74.0-101.0)	94.0(82.3-114.8)	0.000
ALT (U/L)	25.0(20.0-32.8)	52.0(47.0-62.5)	151.0(88.8-480.8)	0.000
AST (U/L)	24.5(21.0-29.0)	37.0(32.0-43.0)	79.0(50.3-204.3)	0.000
Log_{10}(HBV-DNA) (CO/ml)	3.57(2.88-6.86)	5.28(3.41-7.08)	6.25(5.06-7.37)	0.000
Fibrosis stages (n, %)				0.001
S0	2(1.3%)	1(1.2%)	1(2.3%)	
S1	89(57.0%)	49(57.6%)	15(34.1%)	
S2	47(30.1%)	22(25.9%)	18(40.9%)	
S3	9(5.8%)	5(5.9%)	6(13.6%)	
S4	9(5.8%)	8(9.4%)	4(9.1%)	

PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell; PLT, platelet; TBIL, total bilirubin; ALB, albumin; GLB, globulin; GGT, glutamyl transpeptidase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Anti-HBC, anti-hepatitis B virus core antibody;

Compared with the diagnostic performance of APRI and FIB-4 in Significant liver fibrosis

We determined the accuracy of APRI and FIB-4 index in normal ALT group, mildly elevated, significantly elevated ALT and all patients group by AUROC (Table 2 and Figure 1). The AUROC of APRI was 0.608 in normal ALT group (95%CI,0.517-0.699; sensitivity,73.8%; specificity,46.2%; P=0.022); the AUROC of FIB-4 was 0.638 (95%CI,0.550-0.726; sensitivity,56.9%; specificity,65.9%; P=0.003), (Figure 1A). The AUROC of APRI was 0.634 in mildly elevated ALT group (95%CI,0.514-0.753; sensitivity,85.7%; specificity,40.0%; P=0.037); the AUROC of FIB-4 was 0.679 (95%CI,0.565-0.794; sensitivity,68.6%; specificity,60.0%; P=0.005), (Figure 1B). The AUROC of APRI was 0.708 in significantly elevated ALT group (95%CI,0.528-0.887; sensitivity,82.1%; specificity,75.0%; P=0.023); the AUROC of FIB-4 was 0.734 (95%CI,0.567-0.902; sensitivity,82.1%; specificity,75.0%; P=0.01), (Figure 1C). Compared with normal ALT group, APRI and FIB-4 were more accurate in diagnosing liver fibrosis in significantly elevated ALT group. In three groups of patients, FIB-4 was better than APRI in the diagnostic of liver fibrosis.

Table 2
AUROC of APRI and FIB-4 for diagnosing significant fibrosis in patients with persistently normal ALT, mildly and significantly elevated ALT

	AUROC	95%CI	P value	Sensitivity	Specificity
ALT≤1ULN					
FIB-4	0.638	0.550-0.726	0.003	56.9%	65.9%
APRI	0.608	0.517-0.699	0.022	73.8%	46.2%
ALT1-2ULN					
FIB-4	0.679	0.565-0.794	0.005	68.6%	60.0%
APRI	0.634	0.514-0.753	0.037	85.7%	40.0%
ALT2ULN					
FIB-4	0.734	0.567-0.902	0.01	82.1%	75.0%
APRI	0.708	0.528-0.887	0.023	82.1%	75.0%

ALT, alanine aminotransferase; APRI, Aspartate aminotransferase-to-platelet ratio index; ULN, upper limit of normal; AUROC, areas under by receiver operating characteristic; CI, confidence interval;

Compared with the diagnostic performance of APRI and FIB-4 in advanced liver fibrosis

Advanced fibrosis was assessed by AUROC. The accuracy of APRI and FIB-4 index in the assessment of advanced fibrosis in patients with normal ALT, mildly and significantly elevated ALT, and all patients were defected (Table 3 and Figure 2). The AUROC of APRI was 0.636 in normal ALT group (95%CI,0.509-0.763; sensitivity,100.0%; specificity,32.6%; P=0.061); the AUROC of FIB-4 was 0.652 (95%CI,0.541-0.763; sensitivity,61.1%; specificity,68.1%; P=0.037), (Figure 2A). The AUROC of APRI was 0.751 in mildly elevated ALT group (95%CI,0.607-0.896; sensitivity,69.2%; specificity,77.8%; P=0.004); the AUROC of FIB-4

was 0.763 (95%CI,0.618-0.907; sensitivity,84.6%; specificity,56.9%; P=0.003), (Figure 2B). The AUROC of APRI was 0.708 in significantly elevated ALT group (95%CI,0.528-0.887; sensitivity,82.1%; specificity,75.0%; P=0.023); the AUROC of FIB-4 was 0.734 (95%CI,0.567-0.902; sensitivity,82.1%; specificity,75.0%; P=0.01), (Figure 2C). Compared with normal ALT group, APRI and FIB-4 were more accurate in diagnosing liver fibrosis in the group with significantly elevated ALT. In the three groups of patients, FIB-4 better than APRI in the diagnostic of liver fibrosis in normal ALT group, mildly and significantly elevated ALT groups.

Table 3
AUROC of APRI and FIB-4 for diagnosing advanced fibrosis in patients with persistently normal ALT, mildly and significantly elevated ALT

	AUROC	95%CI	P value	Sensitivity	Specificity
ALT≤1ULN					
FIB-4	0.652	0.541-0.763	0.037	61.1%	68.1%
APRI	0.636	0.509-0.763	0.061	100.0%	32.6%
ALT1-2ULN					
FIB-4	0.763	0.618-0.907	0.003	84.6%	56.9%
APRI	0.751	0.607-0.896	0.004	69.2%	77.8%
ALT2ULN					
FIB-4	0.734	0.567-0.902	0.01	82.1%	75.0%
APRI	0.708	0.528-0.887	0.023	82.1%	75.0%

ALT, alanine aminotransferase; APRI, Aspartate aminotransferase-to-platelet ratio index; ULN, upper limit of normal; AUROC, areas under by receiver operating characteristic; CI, confidence interval;

Table 3
AUROC of APRI and FIB-4 for diagnosing advanced fibrosis in in patients with persistently normal ALT, mildly and significantly elevated ALT

	AUROC	95%CI	P value	Sensitivity	Specificity
ALT≤1ULN					
FIB-4	0.652	0.541-0.763	0.037	61.1%	68.1%
APRI	0.636	0.509-0.763	0.061	100.0%	32.6%
ALT1-2ULN					
FIB-4	0.763	0.618-0.907	0.003	84.6%	56.9%
APRI	0.751	0.607-0.896	0.004	69.2%	77.8%
ALT2ULN					
FIB-4	0.734	0.567-0.902	0.01	82.1%	75.0%
APRI	0.708	0.528-0.887	0.023	82.1%	75.0%

ALT, alanine aminotransferase; APRI, Aspartate aminotransferase-to-platelet ratio index; ULN, upper limit of normal; AUROC, areas under by receiver operating characteristic; CI, confidence interval;

Evaluation of APRI and FIB-4 in the diagnostic performance of significant and advanced fibrosis

Clinically, significant and advanced fibrosis are the indications of antiviral therapy. Therefore, it's all crucial to determine the stage of liver fibrosis for treatment and prognosis of the disease. Based on the AUROC, we found that APRI and FIB-4 had high accuracy in differentiating significant fibrosis from advanced fibrosis, especially FIB-4 index. The sensitivity and specificity of the two models at optimal cut-off values were further compared, and both models distinguished significant fibrosis from advanced fibrosis with different accuracy and significance. In the diagnostic of advanced fibrosis, the accuracy of mildly elevated ALT group was the highest, the best cut-off value was 0.416, the sensitivity and specificity of FIB-4 were 84.6% and 56.9%, respectively. When the diagnostic of significance fibrosis, the accuracy was the highest in significantly elevated ALT group, with best cut-off value was 0.571, the sensitivity and specificity of FIB-4 were 82.1% and 75.0%, respectively.

Discussion

Chronic HBV infection can progress to persistent or intermittent liver inflammation, and further to cirrhosis, HCC and end-stage liver disease [1, 2], which is the leading cause of most viral hepatitis related mortality. Therefore, early and reasonable antiviral therapy can significantly reduce the necro-inflammatory activity, and reduce the occurrence of HCC and other related complications [16, 17]).

In recent years, serum ALT levels reflect the severity of liver damage [3], but ALT levels are not consistently elevated in all patients with chronic HBV-infected. Studies have shown sever liver damage in some patients with CHB with normal ALT levels [18, 19]. Liver biopsy in 28–37% of CHB patients with normal ALT or mildly elevated ALT levels suggests moderate or severe inflammation or significant fibrosis, requiring antiviral therapy [4–6]. In addition, several large cohort studies have reported that patients with CHB with normal ALT levels are risk for developing cirrhosis and HCC [20, 21]. Other studies have shown that 18% of CHB patients with normal ALT levels have significant liver fibrosis [4, 5]. Therefore, normal ALT levels do not rule out the absence of liver damage. Given the fact that early and long-time antiviral therapy can reverse liver fibrosis and cirrhosis, accurate assessment of disease progression is critical.

Although liver biopsy remains the gold standard for evaluating liver fibrosis. However, due to the occurrence of related complications and risk associated with liver biopsy, it's not appropriate for all patients [22]. Considering the shortcoming of liver biopsy, most noninvasive methods had been developed for the evaluation of liver fibrosis, such as transient elastography (TE), serum markers and LSM. Among these noninvasive methods, APRI and FIB-4 had received high scores in several major guidelines for the management of CHB. However, their diagnostic accuracy remains unclear [1, 23–25].

Both APRI and FIB-4 used routine laboratory tests to predict the severity of liver fibrosis, and were validated in patients with HBV-infected with mild elevated ALT. In this study, we compared the diagnostic performance of two models to predict significant and advanced fibrosis in patients with CHB with normal ALT, mildly and significantly elevated ALT. Based on our data, 65(41.7%) of patients with normal ALT had significant fibrosis. Among patients with mildly elevated ALT, 35(41.2%) had significant fibrosis. Of the patients with significantly elevated ALT, 28(63.6%) had significant fibrosis.

In a retrospective study, the AUROC of APRI in patients with F2, F3 and F4 fibrosis in CHB was 0.72, 0.812 and 0.707, respectively [26]. Another study found that the AUROC of APRI was 0.65, 0.659 and 0.735 in CHB patients with normal ALT, mildly and significantly elevated ALT [27]. Based on our data, the AUROC of APRI in CHB patients with normal ALT, mildly and significantly elevated ALT was 0.608, 0.634, 0.708 and 0.636, 0.751, 0.708 in significant and advanced fibrosis, respectively. Therefore, we believe that APRI is more accurate in the diagnostic of advanced fibrosis than significant fibrosis, especially in the patients with CHB with mildly elevated ALT.

Based on this study, FIB-4 is better than APRI in the diagnostic of both significant and advanced fibrosis. A previous study showed that FIB-4 had a high diagnostic accuracy for CHB, with AUROC in differentiating between significant and advanced fibrosis was 0.730 and 0.748 in all patients [28]. In our study, the AUROC of FIB-4 in CHB patients with normal ALT, mildly and significantly elevated ALT was 0.638, 0.679, 0.734 and 0.652, 0.763, 0.734 in significant and advanced fibrosis, respectively. Surprisingly, FIB-4 was superior to APRI in the diagnostic both significant and advanced fibrosis.

Our study also has some limitations. First of all, the patients included in this study were all from the same medical institution, the absence and deviation of clinical data may have a certain impact on the accuracy of models. Secondly, we defined normal ALT levels based on our own laboratory values. The AST levels

of most patients have a great influence for liver fibrosis, so we can conduct stratified study on the AST level in the further study. Finally, we should analyze and verify many noninvasive models to better evaluate liver fibrosis.

Conclusions

In conclusion, we evaluated the performance of two noninvasive models in different levels of ALT. The results showed that FIB-4 index and APRI have high diagnostic value for advanced fibrosis with mildly elevated ALT. Both two models have the same diagnostic value in excluding liver fibrosis with significantly elevated ALT. In the case of significant fibrosis, APRI and FIB-4 has a better diagnostic performance in CHB patients with mildly elevated ALT. These noninvasive models are highly applicable to patients with CHB and can reduce the need for clinical liver biopsy.

Abbreviations

CHB: Chronic hepatitis B; HBV: Hepatitis B virus; HCC, Hepatocellular carcinoma WBC: White blood cell; PLT: Platelet; TBIL: Total bilirubin; ALB: Albumin; GLB: Globulin; GGT: Glutamyl transpeptidase; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Anti-HBC: Anti-hepatitis B virus core antibody; HBeAg: Hepatitis B e antigen; ULN: Upper limit of normal; AUROC: Areas under the characteristic curves; CI: Confidence interval;

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate. According to the guidelines of Helsinki declaration in 1975 and the approval of the local research. All patients were given written informed consent for analysis. The study received approval from the Institutional Review Board of Zhejiang Province People's Hospital (IRB NO. 2020QT322).

Consent for publication

Not applicable.

Availability of data and material

The datasets analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests with respect to this manuscript.

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No other financial interests were involved in the design, data collection, analysis, or interpretation of this manuscript.

Authors' contributions

SSC: collect, analysis data and perform manuscript drafting; YHG, JL, XD, YYZ, HL: search literature; HJH: design study and revised the manuscript;

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Figures

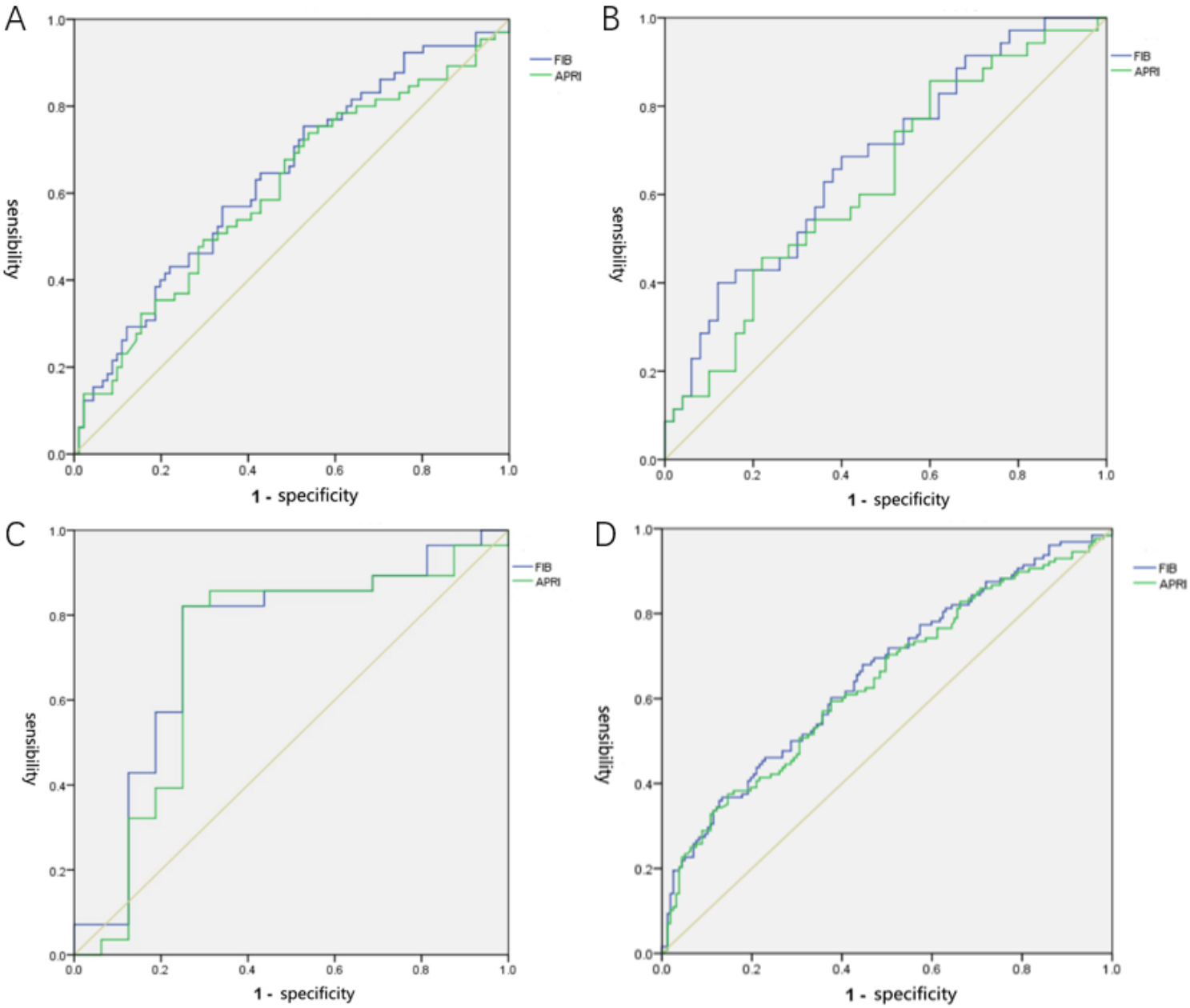

Figure 1

Receiver operating characteristic (ROC) curves for APRI and FIB-4 index in normal ALT group, mildly elevated, significantly elevated ALT group and all patients group. (A) The AUROC of APRI was 0.608 and FIB-4 was 0.638 in normal ALT group. (B) The AUROC of APRI was 0.634 and FIB-4 was 0.679 in mildly elevated ALT group. (C) The AUROC of APRI was 0.708 and FIB-4 was 0.734 in significantly elevated ALT group. (D) The AUROC of APRI was 0.640 and FIB-4 was 0.657 in all patients.

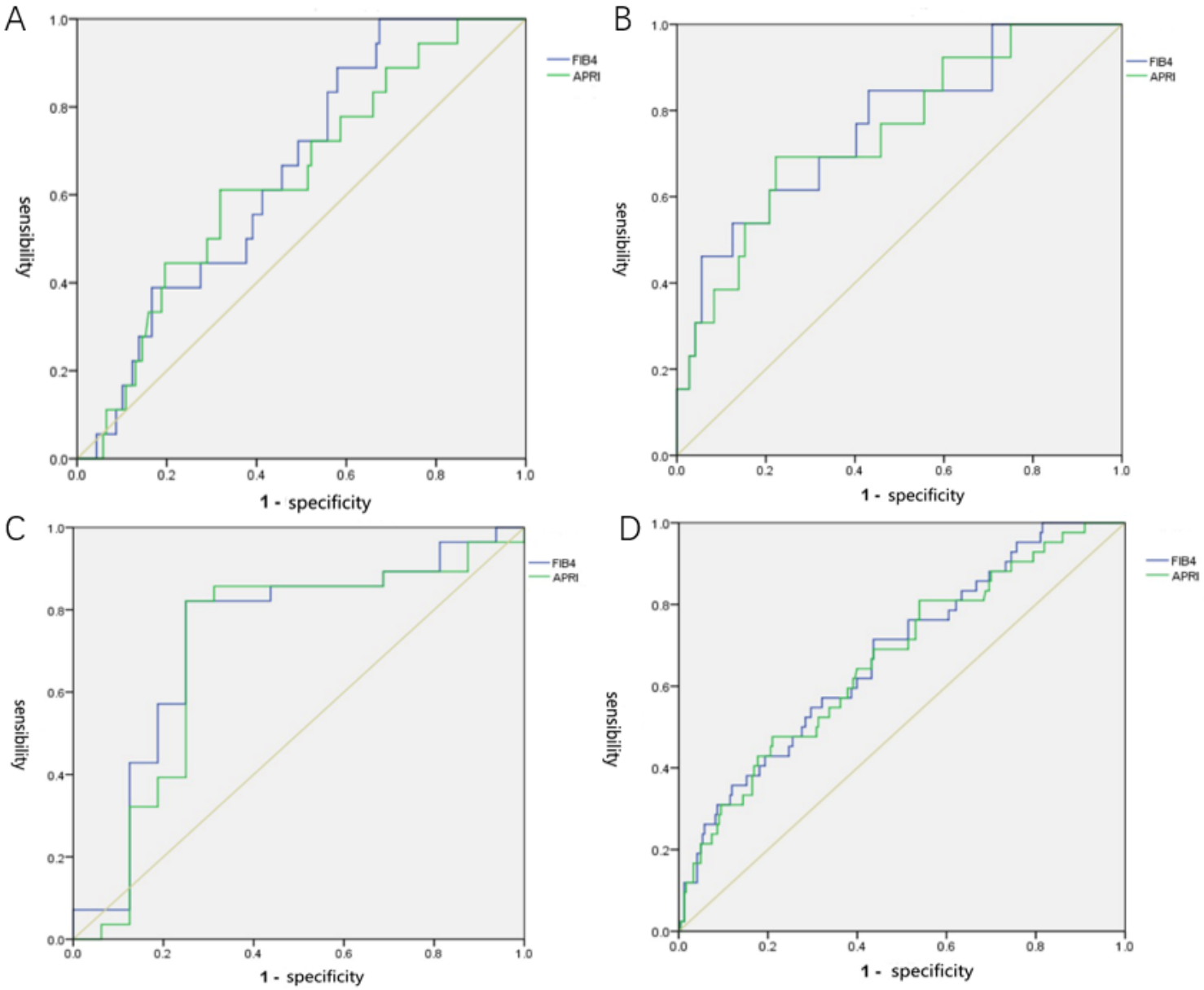

Figure 2

Receiver operating characteristic (ROC) curves for APRI and FIB-4 index in normal ALT group, mildly elevated, significantly elevated ALT group and all patients group. (A) The AUROC of APRI was 0.636 and FIB-4 was 0.652 in normal ALT group. (B) The AUROC of APRI was 0.751 and FIB-4 was 0.763 in mildly elevated ALT group. (C) The AUROC of APRI was 0.708 and FIB-4 was 0.734 in significantly elevated ALT group. (D) The AUROC of APRI was 0.666 and FIB-4 was 0.667 in all patients.