A Simple Noninvasive Model to Predict Significant Fibrosis in Children With Chronic Hepatitis B

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Abstract

Objectives: to develope a noninvasive model for significant fibrosis in children with chronic hepatitis B (CHB).

Methods: A total 116 CHB pediatric patients who had undergone liver biopsy were included in the study. Blood routine examination, coagulation function, liver biochemistry, viral serology and viral load were analyzed. Receiver operating characteristic (ROC) curve analysis was used to analyze sensitivity and specificity of all possible cut-off values.

Results: Based on the correlation and difference analysis, 7 available clinical parameters [Total bile acid (TBA), Gamma-glutamyl transpeptidase(GGT), Aspartate transaminase(AST), Direct bilirubin to total bilirubin ratio (D/T), Alanine aminotransferase(ALT), Prealbumin (PA),and Cholinesterase（CHE）] were included for modeling analysis. A model to predict significant liver fibrosis (Ishak fibrosis score ≥2) was derived using the two best parameters (PA and GGT) The original model was . After mathematical calculation, the G index 600×GGT/PA2 predicts significant fibrosis with an area under the receiving operating characteristics (AUROC) curve of 0.733（95% IC (0.643-0.811). The area under the receiver operating characteristic curve (AUROC) of G index (0.733,) was higher than that of APRI (0.680) and FIB-4(0.601) to predict significant fibrosis in children with CHB. If the G index's values outside 0.28-1.16, 52% of children with CHB could avoid liver biopsy with an overall accuracy of 75%.

Conclusions: The G index can predict and exclude significant fibrosis in children with HBV, which may reduce the liver biopsy need for children with CHB.

Background

The widespread infection of Hepatitis B Virus (HBV) is a global public health problem. HBV infection is the most common cause of cirrhosis and hepatocellular carcinoma in China[1]. Among them, misdiagnosis or untreated of children with CHB are important factors that leading to the development of end-stage liver disease in adulthood[2]. Therefore, it’s important to grasp the opportunity of antiviral treatment timely and accurately which can prevent children with CHB development to end-stage liver disease[3, 4].

Children with CHB lack of typical clinical signs and symptoms, most of them are found during healthy check-up. There may be severe histopathological changes in the liver in pediatric patients due to their immune toleranc, although the alanine aminotransferase (ALT) is normal[5]. For those children with normal liver biochemistry, the indications for antiviral therapy need to rely on the liver biopsy (S≥2 or G≥2). But children have higher risk and lower success rate in liver biopsy compared to adults. It’s difficult to assess dynamically the fibrosis 134 by liver biopsy.

Although many noninvasive models have been established, the model data were from adults with CHB or chronic hepatitis C(CHC). The classical models in adult such as APRI[6] and FIB-4[7] haven't been verified

in Children. And there were few reports about no noninvasive model for children with CHB. The aim of this study is to develop a noninvasive simple model to predict the fibrosis in pediatric patients.

Methods

Patients

A retrospective study included 116 patients with CHB (age<15 years old) who underwent liver biopsy from the First Affiliated Hospital of Guangxi Medical University from October 2009 to June 2019 were divided into two cohorts: no significant fibrosis group (n=65) and significant fibrosis group (n=51). The included criteria: base on the diagnostic criteria of the 2015 WHO CHB Guidelines[1]: all patients with hepatitis B surface antigen (HBsAg) positive for more than 6 months, HBsAg and/or HBV DNA are still positive. Exclusion criteria: (1) Patients with other viral infection or autoimmune liver disease (ALD), inherited metabolic liver disease decompensated cirrhosis and systemic disease such as rheumatism, systemic lupus erythematosus and diabetes. (2) patients received antiviral therapy within 6 months before the liver biopsy. The study was approved by the Human Ethics Committee of the First Affiliated Hospital of Guangxi Medical University.

Patients baseline situation and laboratory parameters were collected at the time of liver biopsy. Which included age, gender, ALT, AST, alkaline phosphatase (ALP), GGT, albumin, prealbumin, bilirubin, globulin, Cholinesterase, Total bilirubin,Indirect bilirubin,Direct bilirubin,APTT, INR, Fibrinogen, White blood cell, Thrombocytocrit,platelet count HBeAg status and HBV DNA levels,. .

Liver biopsy

After the informed consent was signed by parents, Liver biopsy was performed under ultrasound guidance using an automated biopsy ejection 18G/16G cutting needle (BARD Max-Core Disposable Biopsy Instrument, USA). The standard of liver tissue confession requires that the length ≥ 1cm and the number of portal areas ≥6. Specimens were fixed in 10% formaldehyde solution to make conventional paraffin sections, which were stained with Hematoxylin-eosin or Masson. According to the Scheuer system standard significant fibrosis was defined as S2 or more[8]. The specimens were evaluated by tow independently pathologists.

Statistical analysis

IBM SPSS 22.0 and MedCalc 19.07 were used for data analysis. Normality analysis of variables was completed by Kolmogorov-Smirnov test. The data were represented by the median (25th percentile,75th percentile). Spearman correlation coefficient was used to analyze the relationship between variables parameters and live fibrosis stages. Independent sample T-test (normal distribution data) and Mann-Whitney U test (non-normal distribution data) were used to compare the Variables' difference between the two groups (no significant fibrosis group and significant fibrosis group). logarithm of variables that were statistically significant in difference analysis and correlation analysis were used logistic regression

analysis to establish noninvasive model. ROC curve analysis was used to evaluate diagnostic accuracy of models and select the optimal cut-off values. Finally, the AUROC of new models was compared to the two pre-existing non-invasive indexes(APRI =[AST(IU/L)/ULN]×100/PLT(×10^9/L)and FIB-4= [Age(Y)×AST(IU/L)]/[PLT(×10^9/L)× ALT (IU/L)$^{1/2}$] by Delong test. P<0.05 was considered statistically significant.

Results

General information

There were 151 pediatric patients underwent liver biopsy. and 35 cases were excluded. 116 patients (80 males and 36 females) were included in the study. The median age was 6 years old. there were 65 (56.03%) cases in the no significant fibrosis group and 51(43.97%) cases in the significant fibrosis group (Table 1).

Table 1
Characteristics of the Patients in training Set

Variable	Training Set (n = 116)
Age(y)	6(3–10)
Male gender (n, %)	80(68.96)
Liver fibrosis stage† (n, %)	
S0	34(29.31)
S1	31(26.72)
S2	32(27.59)
S3	11(9.48)
S4	8(6.90)
† Liver fibrosis stage: Take the fibrosis score of liver biopsy as the gold standard	

Correlation analysis between variables and liver fibrosis stages

The spearman correlation analysis was used to test the correlation between variables and liver fibrosis stages (Table 2). The results showed that TBA, GGT, AST, Ratio of Direct bilirubin to Total bilirubin (D/T) and ALT were positively correlated with fibrosis stages, PA, CHE were negatively correlated with fibrosis stages. All the correlation coefficients of these variables were less than 0.5., so it was difficult to assess the fibrosis stages by s single indicator in children with CHB.

Table 2
Spearman's correlation between Variables and Liver fibrosis stage

Variable †	Training Set(n = 116)	R Value	P Value
Age(year)	6.00(3.00–10.00)	-0.129	0.167
D/T	0.30(0.30–0.40)	0.203	0.029*
ALT (U/L)	55.00(33.00-150.00)	0.187	0.045*
AST(U/L)	57.50(35.50–127.00)	0.286	0.002**
AST/ALT	1.00(0.70–1.30)	0.095	0.312
GGT(U/L)	19.00(15.00-39.65)	0.329	0.000**
ALP (U/L)	249.00(220.00-296.00)	-0.002	0.980
Globulin (g/L)	25.30(22.70–28.70)	0.045	0.635
Albumin (g/L)	43.40(41.50–45.30)	0.061	0.514
Prealbumin (mg/L)	163.90(141.85-190.45)	-0.285	0.002**
Cholinesterase (U/L)	8194.00(7348.50–9567.00)	-0.191	0.004**
Total protein (g/L)	68.55(64.65–71.90)	0.034	0.713
Total bile acid (μmol/L)	10.30(5.85–20.80)	0.292	0.001**
Total bilirubin (μmol/L)	6.30(4.80–10.30)	0.041	0.663
Indirect bilirubin (μmol/L)	4.00(3.05–6.65)	-0.040	0.669
Direct bilirubin (μmol/L)	2.20(1.50–3.20)	0.138	0.139
APTT(s)	35.00(32.55–37.45)	0.156	0.094
INR(s)	0.95(0.91-1.00)	-0.039	0.678
Thrombin time (s)	11.60(10.90–12.40)	-0.051	0.584
Fibrinogen (g/L)	2.83(2.59–3.28)	-0.165	0.077
Prothrombin time (s)	11.20(10.60–11.80)	0.007	0.942
MPV(fl)	8.19(7.64–9.21)	0.055	0.555
Platelet count (10^9/L)	287.90(245.00-336.10)	-0.113	0.227

†variables are presented as median(interquartile range (IQR))

Abbreviation: D/T, direct bilirubin to total bilirubin ratio; ALT, Alanine transaminase; AST, Aspartate transaminase; AST/ALT, aspartate transaminase to ratio; GGT, gamma-glutamyl transpeptidase; ALP, Alkaline phosphatase; APTT, activated partial thromboplastin time; INR, international normalized ratio; MPV, mean platelet volume; Lg, logarithm base 10;R Value, correlation coefficient.

Variable †	Training Set(n = 116)	R Value	P Value
White blood cell (10^9/L)	7.67(6.10–9.66)	-0.040	0.669
Thrombocytocrit (ml/L)	0.24(0.20–0.28)	-0.078	0.405
Lg[HBVDNA(copies/ml)]	7.36(6.72–8.01)	-0.054	0.567
†variables are presented as median(interquartile range (IQR))			
Abbreviation: D/T, direct bilirubin to total bilirubin ratio; ALT, Alanine transaminase; AST, Aspartate transaminase; AST/ALT, aspartate transaminase to ratio; GGT, gamma-glutamyl transpeptidase; ALP, Alkaline phosphatase; APTT, activated partial thromboplastin time; INR, international normalized ratio; MPV, mean platelet volume; Lg, logarithm base 10;R Value, correlation coefficient.			

Difference analysis between the no significant fibrosis group and significant fibrosis group.

According to the liver biopsy, the patients were divided into two groups: no significant fibrosis group (S < 2 n = 65) and significant fibrosis group (S ≥ 2 n = 51). Difference analysis between the two groups had been shown in Table 3. The results suggested that PA(P = 0.002), ALT(P = 0.045), AST(P = 0.002), CHE(P = 0.004), GGT(P = 0.000) and TBA(P = 0.001) were independent predictors of significant fibrosis.

Table 3
The difference analysis between the two groups in training set

Variable †	No Significant Fibrosis n = 65	Significant Fibrosis n = 51	Statistics Value	P Value
Age(year)	3.00(6.00–10.00)	2.00(6.00-9.50)	Z=-0.648§	0.517
D/T	0.30(0.30–0.40)	0.40(0.30–0.40)	Z=-1.639§	0.101
ALT (U/L)	45.00(28.00-119.00)	72.00(39.50–203.00)	Z=-2.128§	0.033*
AST(U/L)	45.00(30.00–79.00)	76.00(42.50–173.00)	Z=-3.010§	0.003**
AST/ALT	1.00(0.70–1.30)	1.00(0.75–1.44)	Z=-0.773§	0.440
GGT(U/L)	17.00(14.00–21.00)	29.00(17.00-47.50)	Z=-3.873§	0.000**
ALP (U/L)	243.00(223.00-295.00)	252(208–295)	Z=-0.117§	0.907
Globulin (g/L)	24.90(22.40–28.70)	26.00(23.30–28.70)	T=-1.172‡	0.244
Albumin (g/L)	43.40(41.50–45.30)	43.40(41.60-45.35)	T=-0.031‡	0.975
Prealbumin (mg/L)	175.00(146.60-202.10)	152.60(126.95–178.70)	T = 3.338‡	0.001**
Cholinesterase (U/L)	8691.00(7519.00-9845.00)	7981.00(7044.00-8632.50)	Z=-2.172§	0.030*
Total protein (g/L)	68.30(64.80–71.90)	69.10(64.70–71.70)	T=-0.611‡	0.542
Total bile acid (μmol/L)	8.40(5.10-15.73)	15.50(6.65-26.00)	Z=-2.535§	0.012*
Total bilirubin (μmol/L)	6.50(5.00-8.70)	5.70(4.80–8.70)	Z=-0.320§	0.749
Indirect bilirubin (μmol/L)	4.50(3.30-6.00)	3.80(2.90–7.30)	Z=-0.281§	0.779
Direct bilirubin(μmol/L)	2.20(1.40–2.90)	2.20(1.60–3.65)	Z=-1.303§	0.193
APTT(s)	34.70(32.50–37.30)	35.20(32.90–37.50)	T=-0.092‡	0.926
INR(s)	0.95(0.91–1.02)	0.94(0.90–0.99)	Z=-0.914§	0.361
Thrombin time (s)	11.60(10.90–12.50)	11.60(10.95–12.20)	T=-0.090‡	0.929

†Variables are presented as median(interquartile range (IQR)).‡Normal distribution data: Independent sample T-test. §Non-normal distribution data: Mann-Whitney U test.

Abbreviation: D/T, direct bilirubin to total bilirubin ratio; ALT, Alanine transaminase; AST, Aspartate transaminase; AST/ALT, aspartate transaminase to ratio; GGT, gamma-glutamyl transpeptidase; ALP, Alkaline phosphatase; APTT, activated partial thromboplastin time; INR, international normalized ratio; MPV, mean platelet volume; Lg, logarithm base 10.

Variable †	No Significant Fibrosis n = 65	Significant Fibrosis n = 51	Statistics Value	P Value
Fibrinogen (g/L)	2.89(2.62–3.28)	2.68(2.51–3.27)	Z=-1.196§	0.232
Prothrombin time (s)	11.20(10.70–12.00)	11.10(10.60–11.70)	Z=-0.818§	0.413
MPV(fl)	8.13(7.50–8.97)	8.21(7.92–9.34)	Z=-1.179§	0.238
Platelet count (10^9/L)	288.70(250.80-343.20)	282.60(240.70–330.00)	T = 0.763‡	0.447
White blood cell (10^9/L)	7.64(6.25–10.13)	8.05(5.80–9.35)	Z=-1.093§	0.274
Thrombocytocrit (ml/L)	0.25(0.20–0.29)	0.24(0.21–0.28)	T=-0.001‡	0.900
Lg[HBVDNA(copies/ml)]	7.39(6.73–8.28)	7.32(6.77–7.81)	Z=-1.046§	0.296
†Variables are presented as median(interquartile range (IQR)).‡Normal distribution data: Independent sample T-test. §Non-normal distribution data: Mann-Whitney U test.				
Abbreviation: D/T, direct bilirubin to total bilirubin ratio; ALT, Alanine transaminase; AST, Aspartate transaminase; AST/ALT, aspartate transaminase to ratio; GGT, gamma-glutamyl transpeptidase; ALP, Alkaline phosphatase; APTT, activated partial thromboplastin time; INR, international normalized ratio; MPV, mean platelet volume; Lg, logarithm base 10.				

The formula Establishment of noninvasive model and selection of cut-off values

After taking logarithm change of variables that with statistical significance in difference analysis and Spearman correlation analysis. Fitting multiple model was calculated by logistic regression analysis. And determine the final model by backward stepwise procedures: Y=-1.803LN (PA (mg/L)) + 0.769LN(GGT(U/L)) + 6.436 (AUROC 0.732, 95%CI 0.642–0.810). Because the formula was difficult to calculate in application, we used the mathematical relations to simplify it and got the G index (AUROC 0.733, 95%CI 0.643–0.811):

$$G\ Index = 600 \times GGT(U/L)/(PA(mg/L))^2$$

When the G index value ≤ 0.28, it could be consideredwithout no significant liver fibrosis (the sensitivity was 86.27% and the specificity was 38.46%). in all the 51 patients in significant fibrosis group, there were only 7 cases (13.73% six cases in S2, one in S3) with G index value ≤ 0.28. In all the 116 patients, the negative predictive value (NPV) was 78.13%, and diagnostic accuracy (DA) was 59.48% (69/116) (Table 4).

Table 4
Accuracy of G index and APRI in Predicting Significant Fibrosis

Model	Patients n = 116 n(%)	S0-1 n = 65 n(%)	S2-4 n = 51 n(%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
G index								
≤ 0.28	32(28)	25(38)	7(14)	86.27	38.46	52.38	78.13	59.48
> 0.28	84(72)	40(62)	44(86)					
≤ 1.16	88(76)	57(88)	31(61)					
> 1.16	28(24)	8(12)	20(39)	39.22	87.69	71.43	64.77	66.38
APRI								
≤ 0.26	28(24)	21(32)	7(14)	86.27	32.31	50.00	75.00	56.03
> 0.26	88(76)	44(68)	44(86)					
≤ 0.9	90(78)	57(88)	33(65)					
> 0.9	26(22)	8(12)	18(35)	35.29	87.69	69.23	63.33	64.66
FIB-4								
≤ 0.05	14(12)	9(14)	5(10)	88.24	12.31	45.10	64.29	47.41
> 0.05	102(88)	56(86)	46(90)					
≤ 0.4	104(90)	60(92)	44(86)	17.65	95.38	58.33	57.69	57.76
> 0.4	12(10)	5(8)	7(14)					

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; DA, diagnose accuracy.

When the G index value > 1.16, it could be considered that children have significant liver fibrosis, the specificity was 87.69% and the specificity was 39.22%. This specificity suggested that the majority of children without significant liver fibrosis had a G index value ≤ 1.16. Of the 65 children with CHB without significant liver fibrosis, only 8 (12.31%) had a G index > 1.16. And the positive predictive value was 71.43%. Of the 116 children with CHB who were enrolled, 20 of 28 children with G index > 1.16 had significant liver fibrosis. The DA was 66.38 (77/116), as shown in Table 4. When the values of G index outside 0.28 and 1.16, pediatric patients could reduce liver biopsy need in up to 52% of individuals, with an overall accuracy of 75%.

Comparison of the G index **model to the two** pre-existing non-invasive indexes **model**

Using MedCale19.07 to analyze AUROCs of models that including APRI, FIB-4 and G Index (Fig. 1). The AUROCs of G Index, APRI and FIB-4 were 0.733 (95% CI 0.643–0.811), 0.680 (95% CI 0.587–0.764) and 0.601 (95% CI 0.506–0.691) respectively. According to Delong test, there was a statistical difference between the G index and FIB-4 in children with CHB (P = 0.0365) (Table 5). Although there was no significant difference between the G Index and APRI (P > 0.05). The cut-off values of APRI (Table 4) in children were 0.26 and 0.9 which were different from adults (0.5 and 1.5) [6]. As for FIB-4, its AUROC was significantly less than that of G index(P < 0.05). And the optimal cut-off values (0.05 and 0.4) in children (Table 4) were also different from adults (1.45 and 3.25) [7].

Table 5
Pairwise comparison of ROC curves

Model comparison	Difference Between Areas	Standard Error	P Value	95% Confidence Interval
G Index and APRI	0.733 − 0.680 = 0.053	0.0329	0.1061	-0.0113 to 0.118
G Index and FIB-4	0.733 − 0.601 = 0.132	0.0633	0.0365*	0.00830 to 0.256
APRI and FIB-4	0.680 − 0.601 = 0.079	0.0626	0.2068	-0.0437 to 0.202

Abbreviations: APRI, aminotransferase-to-platelet ratio index; FIB-4, fibrosis index based on 4 factors.

Discussion

In recent years, ikenaga et al[9] shown that cirrhosis was reversible. Early intervention could delay the occurrence of cirrhosis, and even reduce the incidence of cirrhosis and liver cancer. It was reported that children with CHB who received antiviral treatment for 5 years old could achieve higher HBsAg clearance rate[10]. At present, many studies shown that WFA (+)-M2BP[11], GP73[12] and other new molecular biological indicators were independent predictors of significant fibrosis in CHB. However, new molecular indicators are difficult to carry out widely in clinical due to the limitation of detection cost, detection technology and lack of big data validation. Many researches on noninvasive models of CHB have shown that some information of liver fibrosis can be obtained from routine laboratory results. Our study tried to build a simple noninvasive diagnosis model for pediatric patients, and to reduce liver biopsy needed by pediatric patients.

In this study, the spearman correlation analysis showed that D/T, TBA, GGT, AST and ALT were positively correlated with fibrosis stages. CHE and PA were negatively correlated with fibrosis stages But the P value of D/T, AST, ALT and CHE (likelihood ratio test) in logistic correlation analysis were more than 0.05. Our study didn't analyze the further relationship between these variables and fibrosis stages. The new model G index showed that using the cut-off values (0.28 and 1.16) could reduce 52% of the patients who needed liver biopsy

GGT, the variable in G index model, mainly exists in the cytoplasm of hepatocytes and the epithelium of intrahepatic bile duct, which can regulate the metabolism of extracellular glutathione. With development of liver fibrosis, the destruction of hepatocytes increased, GGT in cells is released into the blood which leads to the concentration of GGT in the blood increasing significantly. GGT has been proved to be an independent predictor of liver fibrosis in noninvasive models of adult[13, 14]. It’s consistent with the results of our study. PA is an acute reactive protein secreted by hepatocytes, which is involved in the transport of vitamin A in vivo. It has a short half-life and can sensitively and accurately reflects the synthetic and metabolic functions of the liver and the nutritional status[15]. When the fibrosis progressed, the synthesis and release of prealbumin was decreased. However, the mechanism of GGT and PA in the progression of liver fibrosis needs more studies to confirm in the further.

This study verified the diagnostic value of classical adult models (ARPI and FIB-4) for children with CHB was low. Among them, the cut-off values of APRI in children were 0.26 and 0.90, which were different from adults (0.5 and 1.5)[6]. When using our cut-off values, APRI could reduce 47% of the patients needed liver biopsy. The AUROC of FIB-4 was significantly lower than the G index ($P < 0.05$). Moreover, FIB-4 formula contains “Age”, we speculated that the cut-off values of children was different from adults, which was also confirmed in the study. In our research, the cut-off values of FIB4 in children were 0.05 and 0.4. Which was significantly different from its in adults (1.45 and 3.25)[7]. So APRI and FIB4 weren't fully suitable for children with CHB.

There were some limitations in the study: it was a retrospective analysis. the G index model should need more cases to confirm. At present, the ROC Curve analysis is generally used to evaluate the diagnostic efficacy. This analysis method is easily affected by the uneven distribution of disease degree. Although

some scholars have proposed to use the DANA formula[19] to correct the impact of the incidence of fibrosis stages. It's only the public formula obtained from the analysis of patients CHC, and it's unsure whether the DANA formula is also applicable to patients with CHB.

In conclusion, the classical adult noninvasive models (FIB-4 and APRI) aren't fully applicable to children with CHB. G index constructed by GGT and PA is a simple model in clinical practice. The G index can predict and exclude significant fibrosis in children with HBV, which may reduce the liver biopsy need for children with CHB.

Abbreviations

CHB：chronic hepatitis B；

HBV：Hepatitis B Virus,

ROC：Receiver operating characteristic ,

AUROC：receiver operating characteristic curve,

TBA：Total bile acid ,

GGT： Gamma-glutamyl transpeptidase；

AST： Aspartate transaminase；

D/T：Direct bilirubin to total bilirubin ratio；

ALT： Alanine aminotransferase；

PA：Prealbumin；

CHE：Cholinesterase

Declarations

- Ethics approval and consent to participate

The study has been approved by the Human Ethic Committees of the First Affiliated Hospital of Guangxi Medical University.

- Consent to publish

Not applicable

- Availability of data and materials

Not applicable

- Competing interests

The authors declare that they have no competing interests

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- Authors' Contributions

Kang-Ling Zhang and Xiu-qi Chen contributed to the study design and drafting of the paper, they contributed equally to this manuscript and consider as co-first authors. Xiang Yun; Mei-Xiong Yang; Lian-Cheng Lan and Li Huang contributed to the data collection and analysis. Zi-Li Lv contributed to the data analysis made critical revision of the paper for important intellectual content. Qing Tang and Qing-wen Shan contributed the conception and design of study and revised the final paper and consider as co-correspondence authors.

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- Authors' Information

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Figures

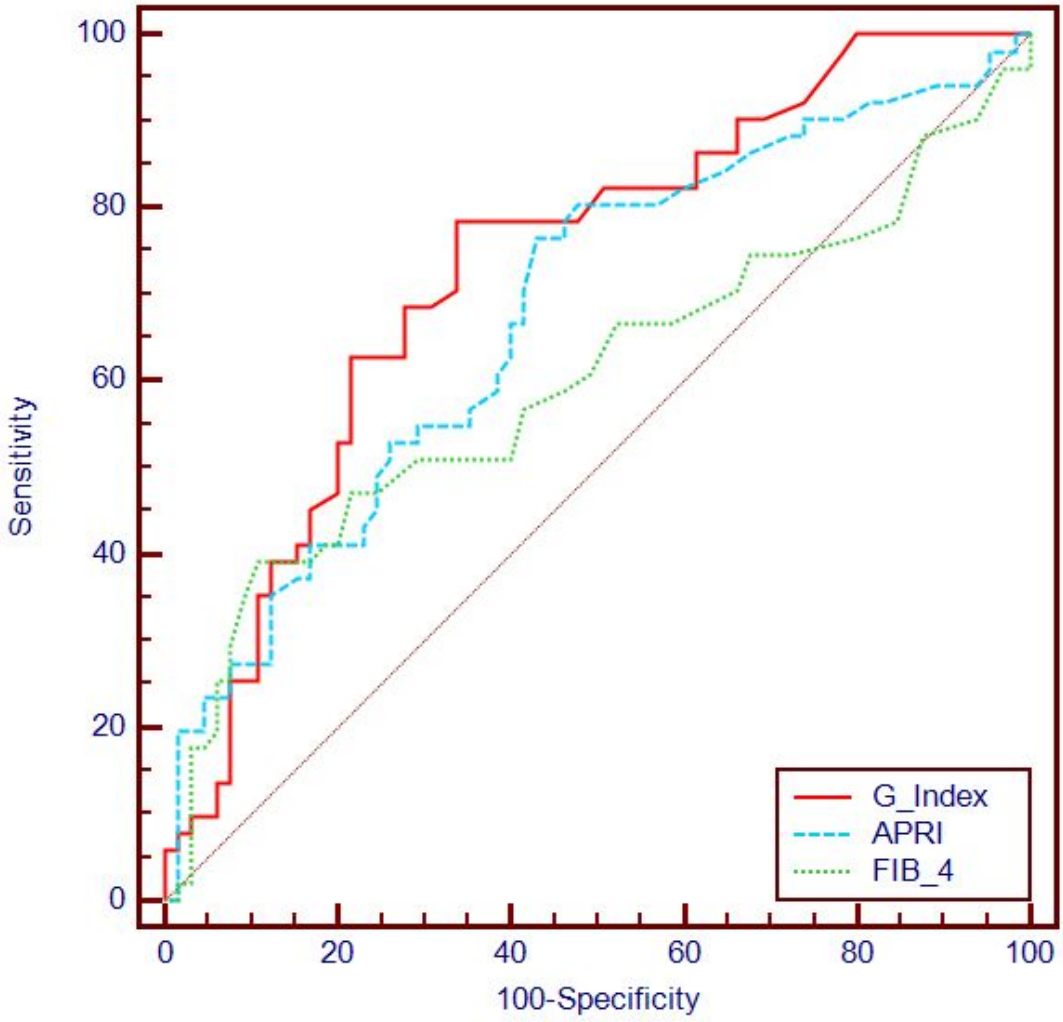

Figure 1

Comparison of ROC curves of different predictive models in predicting significant fibrosis