GPR, King's Score and S-Index are superior to other non-invasive fibrosis markers in predicting the liver fibrosis in chronic Hepatitis B patients

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Abstract

Background and study aims: **In this study, we investigated the efficacy of nine non-invasive fibrosis markers in the assessment of the degree of fibrosis in patients with chronic Hepatitis B (CHB) in comparison with liver biopsy.**

Patients and methods: **A total of 1454 untreated CHB patients from two different centers who underwent liver biopsy were included in the study. Laboratory results of patients were reviewed retrospectively and the pathology slides were re-evaluated in accordance with the Ishak score. Degree of fibrosis ≥ 3 was accepted as "significant fibrosis", ≥ 4 as "advanced fibrosis", and ≥ 5 as cirrhosis. The diagnostic performance of the markers Aspartate aminotransferase to Platelet Ratio Index (APRI), Fibrosis-4 score (FIB-4), Aspartate aminotransferase to Alanine aminotransferase Ratio (AAR), AAR to Platelet Ratio Index (AAPRI), Gamma-glutamyl transpeptidase to Platelet Ratio (GPR), King's Score, Fibro quotient (Fibro-Q), S Index and Platelet to Lymphocyte Ratio (PLR) were evaluated with ROC analysis.**

Results: **In detecting significant fibrosis, APRI, GPR, King's Score and S Index had AUROC values over 0.70. For advanced fibrosis, all of the models except AAPRI; and for cirrhosis, all of the models had AUROC values over 0.70. In accordance with the chosen staging system, GPR, King's Score and S Index had high diagnostic efficacy whereas APRI, FIB-4, FibroQ and PLR had moderate diagnostic efficacy, AAR and AAPRI had low diagnostic efficacy.**

Conclusions: **GPR, King's Score and S Index had moderate diagnostic performance in detecting significant fibrosis and advanced fibrosis, and high diagnostic performance in detecting cirrhosis.** (Acta gastroenterol. belg., **2022,** 85, **62-68**).

Keywords: Hepatitis B, Liver fibrosis, non-invasive fibrosis markers.

Introduction

Chronic hepatitis B (CHB) is an important global health problem, and leading causes of liver fibrosis, liver cirrhosis and hepatocellular carcinoma. It might be of critical importance to identify patients with significant liver disease and treat them accordingly with antiviral therapy as early as possible in order to lower the disease burden (1). Therefore, accurate assessment of liver fibrosis is an important step in determining the stage of the disease, making the decision to start therapy and estimating disease progression (2). The gold standard method to evaluate fibrosis is liver biopsy (LB). However, LB has disadvantages such as being an invasive procedure, requiring repetition insufficient specimen, being a costly procedure and having differences in the interpretation of the biopsy material (3-5). In addition, requiring repeated biopsies in order to evaluate the dynamic process of liver fibrosis is another disadvantage. Considering the disadvantages of liver biopsy, alternative fibrosis evaluation methods to assess hepatic fibrosis has been evoking interest, such as imaging techniques and non-invasive fibrosis markers. Various non-invasive fibrosis markers were developed using the age of the patient and different combinations of laboratory parameters to estimate the degree of liver fibrosis. Some examples of these tests are Aspartate aminotransferase to Platelet (PLT) Ratio Index (APRI) (6), Fibrosis-4 score (FIB-4) (7), Aspartate aminotransferase to Alanine aminotransferase Ratio (AAR) (8), AAR to Platelet Ratio Index (AAPRI) (9), Gamma-glutamyl transpeptidase to Platelet Ratio (GPR) (10), King's Score (11), Fibro-Q (12), S Index (13) and Platelet to Lymphocyte Ratio (PLR) (14). Most of these fibrosis tests were first studied on chronic hepatitis C (CHC) (6-8). Consequently, research has been conducted on the application of these tests also on Chronic Hepatitis B patients. Although, there is not a consensus on the application of these tests. APRI is the recommended method to determine liver cirrhosis in the World Health Organization (WHO) CHB guidelines (15) and Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis (16).

The aim of this study is to determine and compare the efficacy of non-invasive fibrosis markers such as APRI, FIB-4, AAR, AAPRI, GPR, King's Score, Fibro-Q, S Index and PLR in predicting the degree of liver fibrosis in patients with chronic HBV infection.

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Method

Patient recruitment

Treatment-naive patients with chronic HBV infection who underwent LB from January 2011 to September 2019 in the Health Sciences University Gazi Yasargil Training and Research Hospital and Dicle University Medical Faculty Hospital were included in this study. Chronic HBV infection was defined as hepatitis B surface antigen-positive lasting at least six months.

Inclusion criteria

Patients with chronic HBV infection who had liver biopsy were included in the present study.

Exclusion criteria

Other causes of chronic liver disease except for chronic HBV infection (other viral hepatitis, autoimmune liver disease and drug-induced hepatitis), decompensated hepatic cirrhosis, patients with a history of alcohol and/or drug abuse, and patients with ALT levels above 5 times the upper limit were excluded from the study.

Laboratory investigations

Laboratory tests that were studied within 24 hours prior to liver biopsy were recorded. Alanine aminotransferase (ALT) (IU/L), aspartate aminotransferase (AST) (IU/L), alkaline phosphatase (ALP) (IU/L), gamma-glutamyl transpeptidase (GGT) (IU/L), total protein (g/L), albumin (g/L), total bilirubin (mg/dL), and direct bilirubin (mg/dL) were studied with Abbott architect c1600, INR with IL ACL TOP 500 and complete blood count parameters with Mindray BC 6800. For both genders, the upper limit of normal (ULN) of ALT was accepted as 41 U / L and of AST as 40 IU / L.

Liver biopsy

Patients with liver biopsy indications underwent the biopsy with a 16-gauge tru-cut needle in accompaniment of ultrasonography. All specimens were stained with hematoxylin and eosin stain (H&E) and at least 11 portal areas were examined. Modified Ishak histological activity index was used in order to stage the liver fibrosis (F0-F6) (17). Patients were divided into 4 groups according to the biopsy results as "no significant fibrosis" (F0, F1, F2), "significant fibrosis" (F3-F6), "advanced fibrosis" (F4-F6) and "cirrhosis" (F5, F6).

Fibrosis indices

Non-invasive markers used to determine hepatic fibrosis (AAR, AAPRI, APRI, GPR, S index, King's score, FIB-4 model, Fibro-Q model, PLR) were calculated in accordance with the formulas in Table 1.

Table1. — **Formulas of non-invasive hepatic fibrosis markers**

Fibrosis Markers	Formula
APRI	[(AST/ upper limit of normal for AST) / PLT (10^9 /L)]x100
FIB-4	(Age (year) x AST) / (PLT (10^9/L) x √ALT)
AAR	AST / ALT
AAPRI	AAR / PLT (10^9/L)
GPR	(GGT/ upper limit of normal for GGT) / PLT (10^9/L) x 100
King's Score	(Age (years) x AST x INR) / PLT (10^9/L)
Fıbro-Q	[10 x age (year) x AST x INR] / [PLT (10^9/L) x ALT]
S Index	(1000 x GGT) / (PLT (10^9/L) x Albumine^2)
PLR	PLT count (10^9/L) / Lymphocyte (10^9/L)

APRI, AST to Platelet ratio index; FIB-4, fibrosis-4 index; AAR, AST to ALT ratio; AAPRI, AAR/Platelet ratio index; GPRI, GGT to PLT ratio index; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transferase; Fibro-Q, Fibro quotient; PT, prothrombin time; PLT, platelet; INR, international normalized ratio.

Statistical analysis

In this study, statistical analysis was conducted with SPSS 16.0 (IBM Analytics, New York, USA) and MedCalc® Statistical Software version 20.011 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) softwares. In addition to using descriptive statistical methods (mean, standard deviation) in data analysis, distribution of the variables were examined with Shapiro-Wilk normality test, one-way variance analysis for between-group variance comparisons for variables with normal distribution, Tukey multiple comparison test for subgroup comparisons, independent t test for comparing groups of two, Kruskal Wallis test for between-group variance comparisons for variables with non-normal distribution, Mann Whitney U test for comparing groups of two and chi-square test for qualitative data comparisons were performed. Diagnostic performance of each test, 95% confidence intervals (95% CIs), diagnostic accuracy and area under the ROC curve were defined to assess significant fibrosis, advanced fibrosis and cirrhosis. The cut-off values for each parameter were determined according to the Youden index. The results were evaluated with a significance level of $p<0.05$.

Results

Characteristics of the Patients

A total of 1454 treatment-naive patients were included in the study in accordance with the inclusion criteria. The mean age of the patients was 33 and 957 (65,8%) of the patients were males. Additionally, 1053 (72,4%) patients were HBeAg negative. The patients were divided into 7 fibrosis groups as F0, F1, F2, F3, F4, F5, F6 in accordance with the Ishak score, and the number of patients in these fibrosis degree groups were 147 (10.1%), 472 (32.5%), 600 (41.3%), 163 (11.2%), 36 (2.5%), 31 (2.1%), 5 (0.3%) respectively. Demographical and laboratory

Table 2. — **Demographic and laboratory characteristics of patients according to their fibrosis groups**

Variables	F0 (n:147)	F1 (n:472)	F2 (n:600)	F3 (n:163)	F4 (n:36)	F5 (n:31)	F6 (n:5)	p
HBeAg(-)/(+),n	110/32	316/142	425/162	121/42	27/8	25/6	5/0	0.230†
Gender (female/male)	57/90	195/277	184/416	44/119	10/26	7/24	0/5	<0.001†
Age, y	30.44±9.792	31.83±11.022	32.41±11.069	34.55±12.356	37.25±14.042	42.81±11.496	42.80±17.297	<0.001‡
AST (IU/L)	30.31±14.673	31.88±15.712	36.48±18.453	44.41±20.454	47.22±19.695	47.81±30.654	36.4±3.507	<0.001‡
ALT (IU/L)	41.84±28.559	48.28±31.533	58.69±37.906	73.02±42.616	71.44±38.995	57.42±33.204	47.20±18.580	<0.001‡
Albumin (g/L)	4.46±0.507	4.28±0.432	4.30±0.448	4.24±0.457	4.28±0.451	4.12±0.269	3.68±0.601	<0.001‡
INR	1.15±0.111	1.15±0.113	1.154±0.107	1.16±0.107	1.14±0.127	1.15±0.104	1.09±0.057	0.726‡
Lymphcyte ($x10^3$)	2.27±0.732	2.27±0.693	2.29±0.698	2.40±0.721	2.65±0.837	2.30±0.882	2.64±0.342	0.030‡
Platelet ($x10^3$)	238.49±59.043	240.12±58.566	234.13±50.691	212.60±48.554	222.37±69.528	171.22±51.55	140.60±31.910	<0.001‡

† Chi-squared test, ‡Data are presented as means±standard deviations and analyzed by analysis of variance (ANOVA). HBeAg, *Hepatitis B e antigen;* AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltranspeptidase; INR, international normalized ratio.

Table 3. — **Median values of the studied markers for fibrosis stages**

	No significant fibrosis			**Significant Fibrosis**			**Advanced Fibrosis**			**Cirrhosis**		
	median	**min**	**max**	**median**	**min**	**max**	**median**	**min**	**max**	**median**	**min**	**max**
APRI	0,32	0,05	1,79	0,5†	0,04	2,33	0,55†	0,09	2,33	0,66†	0,20	2,33
FIB-4	0,61	0,13	4,57	0,86†	0,04	5,86	1,2†	0,38	5,86	1,56†	0,43	5,86
AAR	0,70	0,17	5,24	0,68	0,03	1,93	0,75	0,40	1,93	0,8‡	0,40	1,93
AAPRI	0,45	0,13	3,48	0,5†	0,02	2,09	0,58†	0,23	2,01	0,74†	0,26	2,01
GPR	0,13	0,02	2,06	0,25†	0,03	1,91	0,32†	0,05	1,91	0,37†	0,09	1,91
KingScore	4,43	0,79	59,44	8,05†	0,50	58,98	10,26†	1,76	58,98	11,92†	1,96	58,98
FibroQ	1,07	0,22	10,89	1,27†	0,05	9,51	1,82†	0,48	9,51	2,77†	0,59	9,51
Sindex	4,47	0,57	124,79	8,16†	1,10	102,20	11,7†	1,65	56,66	15,07†	3,81	56,66
PLR	106	39	1748	86†	28	805	77†	28	210	71†	28	210

†: p<0. 001 against no significant fibrosis group, ‡: p=0. 011 against no significant fibrosis group. Data are presented as medians, min-max and analyzed by analysis of Mann-Whitney U test against no significant fibrosis group separately. APRI, AST/Platelet ratio index; FIB-4, fibrosis-4 score; AAR, AST/ALT ratio; AAPRI, AAR to Platelet Ratio Index; GPR, GGT to platelet ratio; Fibro-Q, Fibro quotient; PLR, Platelet to Lymphocyte Ratio.

Table 4. — **The comparison of the AUROCs of studied indices in predicting significant fibrosis, advanced fibrosis and cirrhosis**

	Significant fibrosis (Fib3-6)				Advanced fibrosis (Fib4-6)				Cirrhosis (Fib5-6)			
	AUROC	SE	95%Cl	p	AUROC	SE	95%Cl	p	AUROC	SE	95%Cl	p
APRI	0.719	0.18	0.684-0.754	<0.001	0.754	0.29	0.697-0.810	<0.001	0.781	0.039	0.705-0.857	<0.001
FIB-4	0.682	0.20	0.643-0.722	<0.001	0.772	0.31	0.710-0.834	<0.001	0.860	0.34	0.794-0.927	<0.001
AAR	NS	NS	NS	NS	NS	NS	NS	NS	0.624	0.41	0.544-0.704	<0.011
AAPRI	0.566	0.20	0.526-0.606	0.001	0.672	0.32	0.609-0.734	<0.001	0.792	0.036	0.721-0.863	<0.001
GPR	0.721	0.22	0.679-0.764	<0.001	0.796	0.34	0.729-0.863	<0.001	0.851	0.40	0.774-0.929	<0.001
King's Score	0.725	0.19	0.688-0.762	<0.001	0.787	0.31	0.727-0.847	<0.001	0.844	0.035	0.776-0.913	<0.001
Fibro Q	0.594	0.22	0.552-0.636	<0.001	0.717	0.33	0.652-0.782	<0.001	0.843	0.035	0.775-0.911	<0.001
S Index	0.715	0.22	0.671-0.759	<0.001	0.783	0.36	0.712-0.853	<0.001	0.859	0.36	0.788-0.929	<0.001
PLR	0.663	0.20	0.297-0.376	<0.001	0.738	0.33	0.197-0.327	<0.001	0.790	0.41	0.129-0.291	<0.001

ROC Curve Analysis. APRI, AST/Platelet ratio index; FIB-4, fibrosis-4 score; AAR, AST/ALT ratio; AAPRI, AAR to Platelet Ratio Index; GPR, GGT to platelet ratio; Fibro-Q, Fibro quotient; PLR, Platelet to Lymphocyte Ratio; NS, Non-significant.

features of the patients according to their fibrosis degree are presented in Table 2. The number of patients with significant (F3-F6) and advanced fibrosis (F4-F6) and cirrhosis (F5-F6) were 235, 72 and 36 respectively. A statically significant difference was determined between the fibrosis degree groups in terms of age (p<0.001), AST (p<0.001), ALT (p<0.001), albumin (p<0.001), lymphocyte (p=0.030), thrombocyte (p<0.001) and gender (p<0.001).

The median HBV DNA level of the study group was 5.10 log10 IU/mL (min; 3.30, max; 9.81). Considering the HBV DNA levels according to stages, the median HBV DNA levels of no significant fibrosis, significant fibrosis, advanced fibrosis, and cirrhosis were 4.91 (min; 3.30, max; 9.81), 5.95 (min; 3.32, max; 9.66), 5.51 (min; 3.47, max; 8.59), 5.47 (min; 3.31, max; 8.23) log10 IU/mL respectively.

The relationship between non-invasive fibrosis markers and fibrosis stages

The statistical relationship between the median values of non-invasive fibrosis markers and fibrosis stages is presented in Table 3. Median values of non-invasive fibrosis markers differed significantly between fibrosis stages (Table 3).

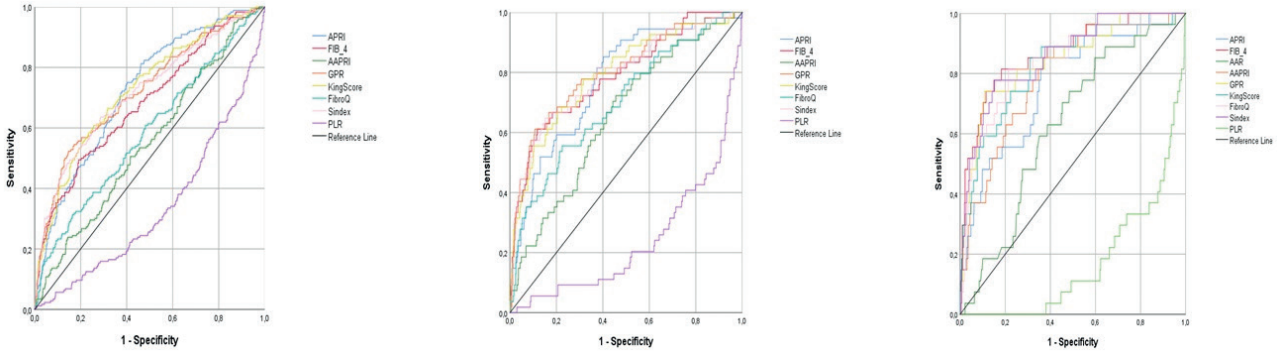

Figure 1. — Receiver operating characteristic (ROC) curves for noninvasive models in the diagnosis of significant fibrosis (1a), advanced fibrosis (1b), and cirrhosis (1c).

Diagnostic performance of non-invasive fibrosis markers for fibrosis groups

ROC analysis was performed to evaluate the diagnostic performance of the studied non-invasive fibrosis markers. The results are presented in Table 4 and Figure 1. The diagnostic performance of the non-invasive markers was defined as the AUROC value of ≥0.9 as excellent, 0.9> AUROC ≥0.8 as good, 0.8> AUROC ≥0.7 as moderate and AUROC < 0.7 as poor (18). In the significant fibrosis group (F3-F6), AUROC values for APRI, GPR, King's score and S Index were higher than 0.70. For advanced fibrosis, all models except AAPRI; and for cirrhosis, all models had AUROC values better than 0.70 (Table 4).

The optimal cut-off values for evaluated non-invasive fibrosis markers

Sensitivity, specificity, PPV and NPV values are presented in Table 5 with optimal cut-off values of these tests that determine fibrosis degrees.

Extensive evaluation of non-invasive markers

It is hard to separate one or more models as superior ones considering that non-invasive fibrosis markers with better diagnostic performance differ in determining different fibrosis degrees (19). In prior similar studies, a simple scoring system was used to determine which of these non-invasive fibrosis markers had better performance (19, 20). In our study, we used a simple scoring system to evaluate the diagnostic performances of non-invasive markers in a similar manner (**Table** 6). According to this scoring system, GPR, King's Score and S Index were included in high diagnostic efficacy group A; APRI, FIB-4, FibroQ and PLR were in moderate diagnostic efficacy group B; and AAR and AAPRI were in low diagnostic efficacy group C.

Discussion

In this study, we evaluated the diagnostic performances of nine non-invasive fibrosis models in determining the degree of fibrosis in treatment-naive patients with chronic HBV infection in comparison with liver biopsy results. Four out of nine models (APRI, GPR, King's Score and S Index) had AUROC values over 0.70 for significant fibrosis, advanced fibrosis and cirrhosis. King's score in determining significant fibrosis (0.725), GPR in determining advanced fibrosis (0.796) and FIB-4 in determining cirrhosis (0.860) had higher AUROC values compared to other non-invasive markers. With our scoring system, we found GPR, King's score and S index to be the markers with the best diagnostic performance.

It was demonstrated for the first time by Wai *et al.* (6) that APRI may determine significant fibrosis and cirrhosis in CHC patients with high accuracy. In the another study, Wai *et al.* (21) used APRI model in CHB patients to evaluate significant fibrosis and cirrhosis. They found 0.63 and 0.73 AUROC values respectively and stated that this model was not appropriate for CHB. Kim *et al.* (22) presented in their study on 575 patients with CHB that APRI had AUROC values of 0.69 and 0.65 respectively for the diagnosis of advanced fibrosis and cirrhosis, and stated that APRI was not an appropriate model to use for the evaluation of hepatic fibrosis after CHB treatment. In contrast, in a meta-analysis by Xiao *et al*. (23), they found AUROC values for APRI in determining significant fibrosis, advanced fibrosis and cirrhosis as 0.740, 0.734 and 0.726 respectively, and stated that APRI can determine hepatitis B related fibrosis with moderate sensitivity and accuracy. The cut off values for significant fibrosis, advanced fibrosis and cirrhosis were 0.5 (sensitivity 70.0%, specificity 60.0%), 0.52-0.8 (sensitivity 55.6%, specificity 74.2%) and 0.53-0.77 (sensitivity 74.8%, specificity 72.8%) respectively. In our study, we determined that APRI had moderate diagnostic performance in predicting significant fibrosis, advanced fibrosis and cirrhosis (AUROC values 0.719, 0.754, 0.781 respectively). As a result of this study, we found out that APRI had lower performance in comparison with GPR, King's Score and S Index.

GPR is a non-invasive fibrosis marker developed in France and West Africa to evaluate fibrosis in patients with HBV. Researchers compared GPR with APRI and FIB-4 and found that the AUROC of GPR was superior to APRI and FIB-4 in determining significant fibrosis

Table 5. — **Optimal cut off values of studied indices in predicting significant fibrosis, advanced fibrosis and cirrhosis, and corresponding parameters of diagnosis**

Fibrosis stage		Cut-off values	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR-	Accuracy, %
Significant fibrosis (Fib3-6)	APRI	>0.341	79	55	25.14	93.23	1.74	0.38	58.45
	FIB-4	>0.765	57.4	70	26.37	89.38	1.86	0.62	67.19
	AAR	NS	NS	NS	NS	NS	NS	NS	NS
	AAPRI	>0.489	53.2	57	19.23	86.23	1.23	0.82	56.18
	GPR	>0.239	52.1	85.5	40.16	90.53	3.59	0.56	80.23
	King's Score	>6.88	60	75.3	31.72	90.76	2.43	0.53	72.82
	Fibro Q	>1.077	63	50.4	19.57	87.68	1.27	0.73	52.41
	S Index	>6.28	63.3	71.7	29.08	91.41	2.23	0.51	70.34
	PLR	≤90.53	60	67	26.07	89.64	1.83	0.6	66.16
Advanced fibrosis (Fib4-6)	APRI	>0.39	73.6	62.3	10.54	97.52	1.96	0.42	63.07
	FIB-4	>0.935	63.9	82.2	17.49	97.47	3.59	0.44	81.18
	AAR	NA	NA	NA	NA	NA	NA	NA	NA
	AAPRI	>0.534	62.5	64	9.3	96.64	1.73	0.59	63.82
	GPR	>0.227	66.7	83.4	18.36	97.79	3.98	0.4	82.35
	King's Score	>8.43	60	84.9	18.75	97.33	3.96	0.47	83.48
	Fibro Q	>1.69	57.1	77.5	12.86	96.87	2.53	0.55	76.3
	S Index	>8.07	65.5	82.1	16.9	97.69	3.63	0.42	81.08
	PLR	≤90.49	71	67.4	11.38	97.51	2.17	0.43	67.62
Cirrhosis (Fib5-6)	APRI	>0.395	80.6	63.8	6.16	99.1	2.22	0.31	64.14
	FIB-4	>1.02	75	85.6	13.3	99.14	5.19	0.29	85.24
	AAR	0.66	80.6	43.7	4.04	98.65	1.41	0.46	43.82
	AAPRI	>0.519	83.3	61.7	6.01	99.2	2.16	0.27	62
	GPR	>0.284	75	89.3	16.28	99.23	6.98	0.28	88.87
	King's Score	>6.137	85.7	69.9	7.65	99.41	2.85	0.2	70.33
	Fibro Q	>1.735	80	78.7	9.86	99.26	3.75	0.25	78.72
	S Index	>8.65	77.8	84.9	12.43	99.28	5.16	0.26	84.72
	PLR	≤82.5	69.5	77.4	8.33	98.85	3.08	0.39	77.19

ROC Curve Analysis. APRI, AST/Platelet ratio index; FIB-4, fibrosis-4 score; AAR, AST/ALT ratio; AAPRI, AAR to Platelet Ratio Index; GPR, GGT to platelet ratio; Fibro-Q, Fibro quotient; PLR, Platelet to Lymphocyte Ratio. NS, Non-significant; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Table 6. — **Non-invasive models scoring system according to AUROCs**

Fibrosis Stages		Points		
	0	1	2	3
F3-6	<0,700	0.700-0.750	0.750-0.800	≥0.800
F4-6	<0,700	0.700-0.750	0.750-0.800	≥0.800
F5,6	<0,700	0.700-0.750	0.750-0.800	≥0.800

Grade A, 6-9 points; Grade B, 3-5 points; Grade C, 0-2 points.

and advanced fibrosis in training and validation cohorts in Africa (10). Similarly, a study by Liu *et al.* (24) was found GPR superior to APRI and FIB-4 in determining different degrees of hepatic fibrosis related to CHB. In a meta-analysis by Lian *et al.* (25), the AUROC values of GPR in predicting significant fibrosis, advanced fibrosis and cirrhosis were 0.733, 0.777 and 0.796 respectively, and the cut off values were determined as 0.32-0.35 (sensitivity 49.0%, specificity 70.0%), 0.32-0.91 (sensitivity 69.0%, specificity 69.0%) and 0.48-0.72 (sensitivity 67%, specificity 74%) respectively. Lian *et al.* (25) stated that GPR had moderate diagnostic accuracy in predicting CHB related fibrosis and cirrhosis in their meta-analysis. In our study, we determined that GPR had moderate diagnostic accuracy in determining significant fibrosis and advanced fibrosis, and high diagnostic accuracy in determining cirrhosis.

S Index is the non-invasive fibrosis marker developed by Zhou *et al.* (13) to determine hepatic fibrosis in patients with CHB. In their study, the AUROC values of S Index in predicting significant fibrosis and cirrhosis was 0.812 and 0.890 respectively. In a study conducted on 40 patients with CHB and CHC, by Tarigan *et al.* (26) showed that AUROC values of S index in predicting significant fibrosis and cirrhosis were 0.938 and 0.917 respectively. Tag-Adeen *et al.* (27) performed a study on 200 Egyptian patients with CHB, and determined that S Index was superior to other studied non-invasive fibrosis models in predicting all degrees of fibrosis (AUROC values for significant fibrosis, advanced fibrosis and cirrhosis were 0.816, 0.905 and 0.961 respectively) and calculated cut off values as 0.3 (sensitivity 41%, specificity 94%), 0.5 (sensitivity 30%, specificity 97%) and 0.9 (sensitivity 27%, specificity 99%) respectively.

In our study, S index had moderate diagnostic accuracy in determining significant fibrosis and advanced fibrosis, and high diagnostic accuracy in determining cirrhosis.

Wang *et al.* (28) determined AUROC values of King's score in CHB patients with ALT≤40 to predict significant fibrosis, advanced fibrosis and cirrhosis as 0.75, 0.773 and 0.831 respectively. In a study conducted by Dong *et al*. (19), AUROC values of King's score to predict significant fibrosis, advanced fibrosis and cirrhosis were determined as 0.756, 0741 and 0.779 respectively. In another study, the AUROC values of King's score in predicting significant fibrosis and cirrhosis were 0.657 and 0.881 and the cut off values were 7.1 (sensitivity 49.5%, specificity 80%) and 7.76 (sensitivity 64.9%, specificity 84.7%) respectively (29). Similar to GPR and S Index, King's score had moderate diagnostic accuracy in determining significant fibrosis and advanced fibrosis, and high diagnostic accuracy in determining cirrhosis in our study.

Although APRI, GPR, King's Score and S Index were found to be superior to other noninvasive models in determining the level of liver fibrosis in chronic hepatitis B, the fibrosis values were overestimated due to the low sensitivity and specificity values of these tests in determining the optimal cut-off values. It would be more appropriate to use the combination of two or more of APRI, GPR, King's Score ve S Index models to enhance the accuracy of the evaluation of liver fibrosis.

One of the limiting factors of this study is that it was conducted retrospectively, and secondly, there were limited number of patients with F4, F5 and F6 degree fibrosis. The reason for this second factor is that, in the reimbursement system of our country, a biopsy is not obligatory for patients with laboratory and imaging findings consistent with compensated cirrhosis to start the treatment.

Conclusion

In this study, we determined that the diagnostic performances of all non-invasive fibrosis markers except AAR increase as the degree of liver fibrosis increases in patients with CHB. To the best of our knowledge, this is the first large scaled study from southeastern Anatolian region of Turkey, a prevalent area for chronic HBV infection, to examine the diagnostic accuracy of noninvasive markers of hepatic fibrosis in patients underwent to LB. The non-invasive markers with the best diagnostic performance in predicting the degree of hepatic fibrosis among the studied non-invasive markers were GPR, King's score and S Index. GPR, King's score and S Index had moderate diagnostic performance in determining significant fibrosis and advanced fibrosis, and high diagnostic performance in determining cirrhosis. One of these non-invasive markers or their combinations might be cost-effective, simple and practical strategies for determining the degree of hepatic fibrosis and for patient follow-up after treatment. Besides, it might help identify patients to undergo liver biopsy and prevent unnecessary biopsies in countries such as our country where LB is obligatory to start the treatment.

Conflict of interest statement

All authors certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received or pending), are the following: None.

The Authors contributions

Study concept and design: NE, FU and BE; Methodology: NE, ETT and HK; Data analysis and interpretation: NE, MA and AEA; Drafting of the manuscript: NE, BE and AEA; Critical revision of the manuscript: NE, AEA, FU and BE; Statistical analysis: NE, MA and BE. All authors read and approved the final version of the manuscript.

Ethical Approval

This study was approved by the ethics committee of Dicle University Medical Faculty with the decision numbered 179 and dated May 07, 2020. Written informed consent was obtained from all participants at each stage of the study. All patients gave their consent to participate to the study.

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Consent to publish

The Authors have obtained consent to publish from the participant (or legal parent or guardian for children) to report individual patient data.

Data availability statement

The Authors declare that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality. Moreover, the Authors ensure that their datasets are presented in the main manuscript.

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