



Original article

A novel non-invasive score for the prediction of advanced fibrosis in patients with chronic hepatitis B

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ABSTRACT

Introduction and objectives: Evaluation of liver fibrosis is important for treatment decisions, complications and to predict prognosis in patients with chronic hepatitis B (CHB). Our aim was to develop a new non-invasive fibrosis scoring method and prove its accuracy in the differentiation of no/low grade and advanced fibrosis in patients with CHB.

Patients and methods: Our study included 273 chronic hepatitis B patients who underwent liver biopsy from February, 2007 to February, 2019 with medical records retrospectively reviewed. Preparations of these patients were divided into two groups as ≤ 3 no-low grade fibrosis (n=236) and ≥ 4 advanced fibrosis (n=37) according to histological ISHAK fibrosis scoring system.

Results: The newly developed AGAP score and other non-invasive fibrosis scores; Fibrosis-4 index, Aspartate aminotransferase to platelets ratio, Gamma glutamyl transpeptidase to platelet ratio, Goteborg University Cirrhosis Index, King's score, Albumin-bilirubin index, Fibrosis cirrhosis index, Fibrosis index, Fibrosis quotient, Lok score and mean and/or median values of Fibroindex were significantly higher in the advanced fibrosis group compared to the no/low grade fibrosis group (p<0.001). However, there was no significant difference in AAR score among the groups (p=0.265). With cut-off value of 4.038, AUROC value of 0.803, sensitivity of 75.7%, specificity of 73.7% and accuracy of 0.740, AGAP score showed the best performance in advanced fibrosis differentiation compared to 12 other non-invasive fibrosis scoring methods.

Conclusions: The newly developed AGAP score showed better performance in patients with CHB compared to 12 other non-invasive fibrosis scores in differentiation of no/low grade fibrosis and advanced fibrosis.

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1. Introduction

Hepatitis B virus (HBV) infection is a serious health problem occurring in different geographical regions in the world with different frequencies despite effective vaccine and antiviral drugs. The global estimated prevalence of HBV infection is 3.9% and affects 291 million individuals, and is more commonly seen in Africa and the Western Pacific [1]. Chronic HBV infection can cause complications ranging from no/low grade fibrosis in the liver to decompensated

liver cirrhosis and hepatocellular cancer. Approximately 30–40% of all deaths due to complications from cirrhosis and hepatocellular carcinoma develop as a result of chronic HBV infection. These developing complications are the cause of higher costs in health systems [2]. Evaluation of liver fibrosis is very important for both prognosis and treatment because many complications such as advanced fibrosis cirrhosis and hepatocellular carcinoma are quite common [3]. Invasive or non-invasive methods are used in order to evaluate liver fibrosis, and liver biopsy is the gold standard for evaluating fibrosis. However, as liver biopsy is performed invasively with percutaneous, transjugular or endoscopic ultrasound, it can increase the cost and may cause many complications such as pain, bleeding, infection, perforation, and even death. In addition, sampling error, inconsistency in histological evaluation, and limited and contraindicated cases in dynamic liver fibrosis follow-up are major disadvantages for biopsy [4]. Of the non-invasive methods, transient elastography performed radiologically is the most widely used. However, this is a costly method used in limited centers, and this method has a limited diagnostic defined as patients with chronic hepatitis B infection. Serum markers,

Abbreviations: HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBVDNA, hepatitis B virus DNA; HDV, hepatitis D virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; PT, prothrombin time; INR, international normalized ratio; HIV, human immunodeficiency virus; Fib-4, fibrosis-4 index; APRI, aspartate aminotransferase to platelets ratio; GPR, gamma glutamyl peptidase platelet ratio; GUCI, Goteborg University Cirrhosis Index; ALBI, albumin-bilirubin index; FCI, fibrosis cirrhosis index; FI, fibrosis index; FibroQ, fibrosis quotient

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another common method among non-invasive methods, are simple, useful and inexpensive. Serum markers, which have been used especially in recent years, were initially limited to hepatitis C, and then they began to be used extensively to evaluate fibrosis in other liver diseases such as HBV and non-alcoholic fatty liver disease [5]. In recent years, an increasing number of non-invasive fibrosis scores have been used and new scores have been developed to evaluate inflammation, fibrosis and treatment response in patients with CHB. There are many studies regarding liver fibrosis evaluation, treatment and follow-up and aspartate aminotransferase-to-platelet ratio index (APRI) and Fibrosis-4 index (Fib-4) in the literature [6–8]. In a study conducted by Teshale et al. it was shown that APRI and Fib-4 markers distinguished F2–F4 from F0 with higher sensitivity and specificity compared to F1 and are beneficial in following the progression of fibrosis [8]. Gamma-glutamyl transpeptidase to platelet ratio (GPR), a recently used non-invasive fibrosis score, was found to be more accurate in evaluating liver fibrosis in chronic HBV infection compared to APRI and FIB-4 [9]. In a study conducted by Dong et al. GPR and King's scores were found to be the most successful scores in distinguishing significant fibrosis in patients with chronic HBV infection [10]. Although there are many studies regarding non-invasive fibrosis scores used in the evaluation of fibrosis in chronic HBV infection, various discussions still continue [11]. New non-invasive scores are needed in order to evaluate advanced fibrosis, since the diagnostic performances of APRI, Fib-4, GPR and others, which are among the non-invasive fibrosis scoring methods, are not completely satisfactory. In this study, our aim was to evaluate the clinical importance of non-invasive scoring methods used in the diagnosis of liver fibrosis and to determine the new non-invasive fibrosis scoring method with high accuracy.

2. Materials and methods

2.1. Study design and patients

The patients who had positive hepatitis B surface antigen (HBsAg) and underwent liver biopsy from February, 2007 to February, 2019 were determined retrospectively from the medical records of our hospital. Of these patients, those who had at least 6 months of HBsAg positivity and whose HBV-DNA was higher than 2000 IU/ml were defined as patients with chronic hepatitis B infection. Patients who had received hepatitis B treatment, patients who had acute viral infection, other chronic viral infections other than hepatitis B [hepatitis C virus (HCV), hepatitis D virus (HDV), human immunodeficiency virus (HIV)], hepatocellular cancer, chronic liver disease (autoimmune, genetic, drug-induced, and nonalcoholic fatty) and patients with a history of alcohol use (20 grams of alcohol each day) were excluded from this study. A total of 273 patients who complied with these criteria were included in the study. The study was conducted in accordance with the 1975 Helsinki Declaration guidelines and was approved by Ethics Committee of Cumhuriyet University Faculty of Medicine, Turkey (dated: 07/04/2019, issue no: 2019-07/49).

2.2. Liver biopsy and histological evaluation

Liver biopsy was performed using a 16-gauge needle under ultrasound. These specimens were fixed with 10% formalin, embedded in paraffin and then stained with hematoxylin-eosin. These biopsy materials were stained with histochemical Masson's trichrome and reticular fiber dyes. These preparations were evaluated by two liver pathologists and concluded by a joint decision. Histological necroinflammatory activity and fibrosis staging were performed in biopsy samples according to ISHAK scoring system. ISHAK staging according to fibrosis severity is as follows: F0, absence of fibrosis; F1, Fibrous expansion of some portal areas, with or without short fibrous septa; F2, Fibrous expansion of most portal areas, with or without short

fibrous septa; F3, Fibrous expansion of most portal areas with occasional portal to portal bridging; F4, Fibrous expansion of portal areas with marked bridging as well as portal to central; F5, marked bridging with occasional nodules (incomplete cirrhosis); F6, cirrhosis, probable or definite [12]. According to ISHAK fibrosis scoring, fibrosis was evaluated in two groups as F0-3 no/low grade fibrosis (=METAVIR F0-2) and F4-6 advanced fibrosis (=METAVIR F3-4) [13].

2.3. Serum markers, new non-invasive fibrosis scoring method AGAP and others

When biopsy was performed, age, sex, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TB), albumin, gamma globulin, platelet count (PLT), prothrombin time (PT), and international normalized ratio (INR) values of the patients were recorded. In addition, hepatitis B serological markers and serum HBV DNA were measured using COBAS AmpliPrep/COBAS TaqMan (CAP-CTM; Roche, Branchburg, NJ, USA) and the lower limit value was considered to be 20 IU/mL. In many studies, especially AST, GGT and PLT were widely used in non-invasive fibrosis scoring formulas. The formula of AGAP = $[AST (IU/L) \times GGT(IU/L)] \times [Age (years) / PLT^2]$ was developed by using these parameters. In this formula, a non-invasive scoring method, and compare it with other non-invasive fibrosis scores in patients with no/low grade and advanced fibrosis (Table 1).

2.4. Statistical analysis

The data obtained in our study was loaded to the SPSS 22.0 statistical program (SPSS Inc. Chicago, IL, USA) for the statistical analysis, and Kolmogorov-Smirnov Z test was used in order to select the correct test regarding the numerical data in the evaluation. The comparison of the two categories in the variables suitable for normal distribution found as a result of the test was carried out with Independent Sample t Test, and the comparison of the two categories in variables that were not suitable for normal distribution as a result of the test was performed with the Mann-Whitney U Test. The cutoff values of non-invasive fibrosis markers in the determined groups were calculated by ROC Analysis. The superiority of non-invasive fibrosis markers over each other was demonstrated by calculating Accuracy, LR +, LR-, PPV and NPV statistics with the values obtained as a result of the analysis. The examination of the differences of

Table 1
Non invasive scores (14-17).

Fibrosis tests	Calculations
Fib-4 index	$[10 \times Age (years) \times AST(IU/L)] / [PLT(10^9/L) \times ALT(IU/L)]$
AGAP	$[AST (IU/L) \times GGT(IU/L)] \times [Age (years) / PLT^2]$
APRI	$[AST (IU/L) / AST (ULN) / PLT (10^9/L)] \times 100$
GPR	$GGT (IU/L) / [GGT (IU/L) ULN] \times PLT (10^9/L)$
AAR	$AST (IU/L) / ALT(IU/L)$
GUCI	$[AST(IU/L) / AST (IU/L) ULN \times INR \times 100] / PLT (10^9/L)$
King's	$[Years \times AST (IU/L) \times INR] / PLT (10^9/L)$
ALBI	$[\log bilirubin (\mu mol/L) \times 0.66] + [Albumin (g/L) \times -0.085]$
FI	$8 - 0.01 \times PLT (10^3 / \mu l) - Albumin (g/dL)$
FCI	$[ALP(U/L) \times bilirubin (\mu mol/L)] / [Albumin (g/L) \times PLT(10^9/L)]$
FibroQ	$[10 \times age(years) \times AST (IU/L) \times INR] / [PLT (10^9/L) \times ALT (IU/L)]$
Fibro index	$[1.738 - 0.064 \times PLT + 0.005 \times AST(IU/L) + 0.463 \times gamma globulin (g/dL)]$
Lok index	$[-5.56 - 0.0089 \times PLT(10^9/L) + 1.26 \times AST/ALT (IU/L) + 5.27 \times INR]$

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma glutamyl transpeptidase; ALP: Alkaline phosphatase; PLT: Platelet; INR: International normalized ratio; Fib-4: Fibrosis-4 index; APRI: AST/PLT ratio index; GPR: Gamma-glutamyl transpeptidase to platelet ratio; AAR: aspartate alanine aminotransferase ratio; AST/PLT ratio; GUCI:Goteborg University Cirrhosis Index; ALBI: Albumin-bilirubin score; FI: Fibrosis index; FCI: Fibrosis cirrhosis index; FibroQ: Fibroquotient; ULN; upper limit of normal.

categorical variables was performed with the help of Chi-Square test. All analyzes were interpreted at p<0.05 significance level.

3. Results

3.1. Patients characteristic

A total number of 273 patients who underwent liver biopsy from February, 2007 to February, 2019 were included in our study. Histologically, liver biopsies of these patients were divided into two groups as no/low grade and advanced fibrosis. Of the patients, 134 (49.1%) were female and 139 (50.9%) were male and there was no difference between the fibrosis groups in terms of sex (p=0.680). In addition, the mean age of the patients was 48.7±15.2. It was 47.2±15.5 and 52.1±13.3 in no/low grade and advanced fibrosis group, respectively. The mean age was no difference between the fibrosis groups in terms of age (p=0.07) (Table 2).

3.2. Laboratory values and non-invasive fibrosis variables of no/low grade and advanced fibrosis groups

Among the laboratory values, ALT, AST, GGT, ALP, TB, PLT, INR, gamma globulin and albumin were significantly higher in the advanced fibrosis group compared to no/low grade fibrosis group (p<0.05) (Table 2). Non-invasive fibrosis scores; Fib-4, APRI, GPR, GUCI, King's, ALBI, FCI, FI, FibroQ, Lok and Fibroindex values that are evaluated in many studies in the literature were found to be significantly higher in the advanced fibrosis group compared to the no/low grade fibrosis group (p<0.001), however, there was no significant difference between the groups in terms of AAR values (p=0.265) The AGAP score that we developed was significantly higher in the

advanced fibrosis group compared to no/low grade fibrosis group (p<0.001) (Table 2).

3.3. Comparison of AUROC values between no/low grade and advanced Fibrosis groups

AGAP, a non-invasive fibrosis score, that we developed was found to have the highest AUROC value in ROC analysis compared to other scores [AUROC=0.803 (95% CI: 0.728-0.878); P<0.001]. After the AGAP score, GPR, Fib-4 and King's (0.791, 0.774 and 0.773, respectively; P <0.001) scores were detected to have the best AUROC values. Other non-invasive scores; APRI, GUCI, ALBI, FI, FCI, FibroQ, Lok and Fibroindex were statistically significant to predict advanced fibrosis (p<0.001). However, there was no significant difference between AAR score in no/low grade fibrosis and advanced fibrosis groups (p=0.265) (Table 3). Comparison of ROC curves has been shown for the diagnostic precision of Fib-4, APRI, GPR, AGAP, AAR, GUCI, King's, ALBI, FI, FCI, FibroQ, Lok and Fibroindex between no/low grade fibrosis and advanced fibrosis groups in chronic hepatitis B patients (Figure 1).

3.4. Threshold values of non-invasive fibrosis scores

Threshold values for non-invasive fibrosis scores are presented in Table 4. Cut-off values for Fib-4, APRI, GPR, AGAP, AAR, GUCI, King's, ALBI, FI, FCI, FibroQ, Lok and Fibroindex scoring methods were found to be 1.995, 1.002, 0.627, 4.038, 0.898, 1.030, 16.700, -2.650, 2.215, 0.171, 3.226, 0.385 and 0.984, respectively. In our study, AGAP, which is a new scoring method, had the highest sensitivity and specificity (75.7% and 73.7%), whereas, the AAR score was the lowest (59.5% and 55.1%). The sensitivity and specificity of the other non-invasive fibrosis scoring methods such as Fib-4, APRI, GPR, GUCI, King's, ALBI, FI, FCI, FibroQ, Lok and Fibroindex were found to be (67.6% and 73.7%), (70.3% and 72.5%), (73.4% and 71.6%), (70.3% and 72.9%), (70.3% and 73.3%), (67.6% and 59.7%), (73.4% and 65.7%), (70.3% and 72.9%), (67.6% and 72%), (73% and 68.6%) and (70.3% and 69.1%), respectively. After this new AGAP score, the GPR, King's and Fib-4 scores were observed to perform well. When the positive and negative predictive values of non-invasive fibrosis scores were examined, the AGAP score had the highest (95.1% and 31.1%, respectively), while the AAR score had the lowest value (89.6% and 17.1%, respectively). In addition, among these scoring methods, the AGAP score had the highest diagnostic accuracy rate with a value of 0.740. This accuracy rate was

Table 2
Demographic and clinical data and fibrosis score values between no/low grade and advanced fibrosis groups.

Parameters	No/Low grade fibrosis (n: 236)	Advanced fibrosis (n: 37)	P
Age. (years)*	47.21 ± 15.5	52.11 ± 13.34	0.070
Sex (male/female). n	115/121	24/13	0.680
ALT (IU/L)**	42 (24.5-73.5)	71 (25-100)	0.001
AST (IU/L)**	34 (24-61.5)	53 (36-93)	0.004
GGT(IU/L)**	27.5 (16-50)	73 (39-117)	<0.001
ALP (IU/L)**	75 (61.5-97.5)	92 (81-121)	0.001
TB (mg/dL)**	0.66 (0.5-0.93)	0.94 (0.7-1.2)	0.001
Gamma globulin g/dL*	2.79 ± 0.58	3.08 ± 0.86	0.055
Albumin g/dL*	4.06 ± 0.52	3.80 ± 0.58	0.004
PLT(x10 ⁹ /L)*	207.8 ± 64.1	154.7 ± 65.3	<0.001
INR*	1.04 ± 0.09	1.13 ± 0.13	<0.001
Fib-4**	1.22 (0.77-2.14)	3.03 (1.57-4.3)	<0.001
APRI**	0.56 (0.34-1.05)	1.24 (0.64-1.94)	<0.001
GPR**	0.31 (0.18-0.71)	1.1 (0.64-2.6)	<0.001
AGAP**	1.14 (0.36-4.39)	12.47 (4.06-28.84)	<0.001
AAR**	0.87 (0.65-1.14)	0.92 (0.66-1.43)	0.265
GUCI**	0.59 (0.34-1.1)	1.39 (0.74-2.12)	<0.001
King's**	7.66 (4.67-18.28)	26.03 (11.72-33.43)	<0.001
ALBI*	-2.74 ± 0.47	-2.44 ± 0.52	<0.001
FI**	1.86 (-0.67-4.79)	2.80 (0.06-4.45)	<0.001
FCI**	0.11 (0.07-0.18)	0.21 (0.15-0.43)	<0.001
FibroQ**	1.89 (1.11-3.39)	4.69 (1.79-5.98)	<0.001
Lok**	0.29 (0.18-0.43)	0.63 (0.34-0.79)	<0.001
Fibroindex*	0.74 ± 0.55	1.40 ± 1.19	<0.001

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. GGT: Gamma-glutamyl transpeptidase. ALP: Alkaline phosphatase. TB: total bilirubin. PLT: platelet. INR: International normalised ratio. Fib-4: Fibrosis-4 index. APRI: Aspartate aminotransferase to platelets ratio. GPR: Gamma-glutamyl transpeptidase to platelet ratio; AAR: Aspartate alanine aminotransferase ratio. GUCI: Goteborg University Cirrhosis Index. ALBI: Albumin, bilirubin index. FibroQ: Fibrosis quotient. FI: Fibrosis index. FCI: Fibrosis cirrhosis index.

* Mean ± SD.
** Median.

Table 3
Areas under the curve of noninvasive scoring.

Scores	AUROC	(95% CI)	P
Fib-4	0.774	0.697-0.851	<0.001
APRI	0.743	0.659-0.827	<0.001
GPR	0.791	0.715-0.868	<0.001
AGAP	0.803	0.728-0.878	<0.001
AAR	0.557	0.449-0.665	0.265
GUCI	0.751	0.669-0.834	<0.001
King's	0.773	0.697-0.848	<0.001
ALBI	0.668	0.571-0.765	0.001
FI	0.731	0.633-0.829	<0.001
FCI	0.751	0.668-0.835	<0.001
FibroQ	0.718	0.623-0.812	<0.001
Lok index	0.765	0.678-0.851	<0.001
Fibroindex	0.744	0.650-0.837	<0.001

Fib-4: Fibrosis-4 index. APRI: Aspartate aminotransferase to platelets ratio. GPR: Gamma-glutamyl transpeptidase to platelet ratio; AAR: Aspartate aminotransferase. GUCI: Goteborg University Cirrhosis Index. ALBI: Albumin, bilirubin index. FibroQ: Fibrosis quotient. FI: Fibrosis index. FCI: Fibrosis cirrhosis index.

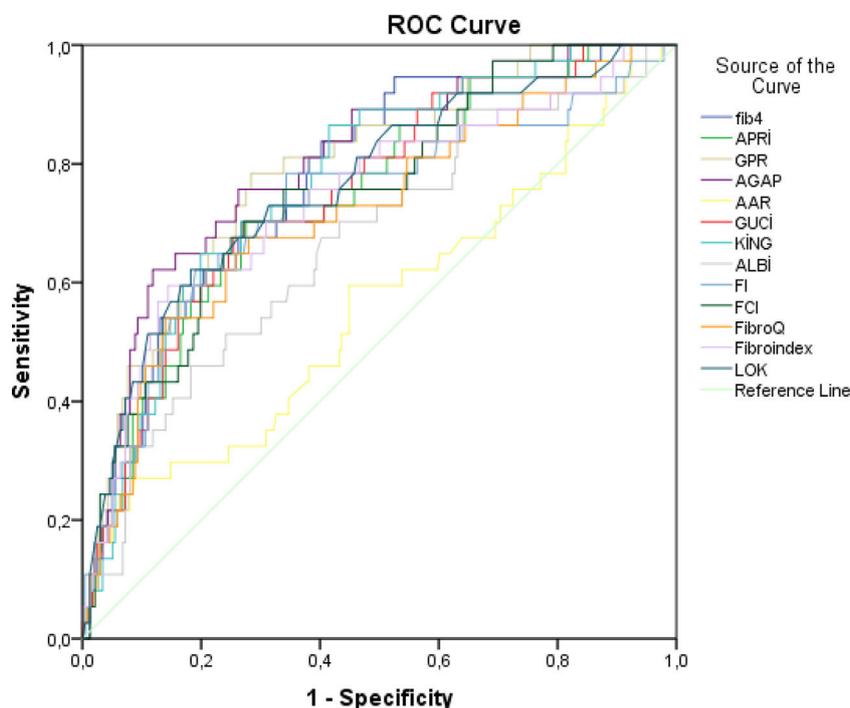


Fig. 1. ROC curve of non-invasive fibrosis scores between no/low grade and advanced fibrosis groups.

followed by Fib-4, FCI and APRI scores (0.729, 0.729 and 0.722, respectively).

The comparison of the AUROC, cut-off, sensitivity, specificity, PPV and NPV values of the noninvasive fibrosis scores evaluated in our study with the current studies in the literature are presented in Table 5.

4. Discussion

Liver fibrosis is extremely important in treatment and in terms of complications in patients with CHB. Although liver biopsy is the gold standard for evaluating liver fibrosis, invasive intervention that may cause serious complications, high cost and limitations such as the heterogeneous distribution of histopathological changes within the parenchyma have led to the search for alternative methods. Therefore, non-invasive, simple and inexpensive scoring methods have been developed to evaluate fibrosis in patients with CHB. The 2015 WHO guideline recommends some non-invasive fibrosis markers

such as APRI and Fib-4 in the evaluation of fibrosis in patients with CHB, however, their diagnostic values are still controversial [14]. In our study, we divided 273 patients with CHB who underwent liver biopsy into no/low grade and advanced fibrosis groups in order to determine a new scoring method for advanced fibrosis detection. For this purpose, we planned a retrospective study comparing 12 non-invasive serum markers used practically in the evaluation of liver fibrosis in patients with CHB and the new AGAP score that we developed.

According to the results of ROC analysis in our study, while non-invasive fibrosis scoring methods; Fib-4, APRI, GPR, AGAP, GUCI, King's, ALBI, FI, FCI, FibroQ, Lok and Fibroindex were successful in the differentiation of advanced and no/low grade fibrosis, the AAR score was unsuccessful. In our study, the highest AUROC value was observed in the AGAP score (0.803, $P < 0.001$) and then in GPR, Fib-4 and APRI scores (0.791, 0.774, and 0.743 respectively $P < 0.001$) and the lowest value was observed in AAR score (0.557, $P = 0.265$). In the study carried out by Wang et al., the AUROC values of GPR, Fib4 and

Table 4 Performances of non-invasive fibrosis scores according to threshold values.

Scores	Cut-off	Sen(%)	Spe(%)	PPV(%)	NPV(%)	+LR	-LR	Accuracy
Fib-4	1.995	0.676	0.737	0.935	0.287	2.570	0.440	0.729
APRI	1.002	0.703	0.725	0.940	0.286	2.556	0.410	0.722
GPR	0.627	0.734	0.716	0.934	0.296	2.761	0.302	0.718
AGAP	4.038	0.757	0.737	0.951	0.311	2.878	0.330	0.740
AAR	0.898	0.595	0.551	0.896	0.171	1.325	0.735	0.553
GUCI	1.030	0.703	0.729	0.935	0.281	2.594	0.407	0.722
King's	16.70	0.703	0.733	0.940	0.292	2.633	0.405	0.729
ALBI	-2.650	0.676	0.597	0.917	0.184	1.677	0.543	0.538
FI	2.215	0.734	0.657	0.951	0.264	2.286	0.329	0.674
FCI	0.171	0.703	0.729	0.935	0.287	2.594	0.407	0.729
FibroQ	3.226	0.676	0.72	0.934	0.275	2.414	0.450	0.714
Lok	0.385	0.73	0.686	0.942	0.267	2.325	0.394	0.692
Fibroindex	0.984	0.703	0.691	0.937	0.263	2.275	0.430	0.692

Fib-4: Fibrosis-4 index. APRI: Aspartate aminotransferase to platelets ratio. GPR: Gamma-glutamyl transpeptidase to platelet ratio; AAR: Aspartate aminotransferase. GUCI: Goteborg University Cirrhosis Index. ALBI: Albumin. bilirubin index. FibroQ: Fibrosis quotient. FI: Fibrosis index. FCI: Fibrosis cirrhosis index. Sen: sensitivity. Spe: specificity. PPV: positive predictive value. NPV: negative predictive value. +LR: positive likelihood ratio. -LR: negative likelihood ratio.

Table 5
Comparison of the noninvasive fibrosis scores in detecting advanced fibrosis.

Index	Author	Cut-off	AUROC	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)
AGAP	*	4.038	0.803	75.7	73.7	95.1	29.6
GPR	*	0.627	0.791	73.4	71.6	95.4	29.6
	Wang RQ	0.53	0.836	76	81	61	89
	Huang	0.413	0.801	84.6	70.3	NA	NA
	Hu	0.548	0.826	74	91	NA	NA
	Lu	0.58	0.686	79	58	67	72
Fib-4	*	1.995	0.774	67.6	73.7	93.5	28.6
	Wang RQ	1.19	0.803	69	77	56	85
	Huang	1.095	0.781	75.6	73.4	NA	NA
	Wu	1.48	0.790	62.86	85.53	44.9	92.4
	Kayadibi	1.45	0.863	78.3	81.1	46.2	94.7
APRI	*	1.002	0.743	70.3	72.5	94	28.6
	Wang RQ	0.43	0.758	85	58	46	90
	Huang	0.751	0.672	74.3	70.3	NA	NA
	Wu	0.22	0.730	65.71	73.37	31.9	91.8
	Kayadibi	1.0	0.795	55.3	91.2	46.2	94.7
AAR	*	0.898	0.557	59.5	55.1	89.6	17.1
	Sha	0.411	0.542	63	45	NA	NA
	Karacaer	0.600	0.493	52.5	47	17.6	82.1
GUCI	*	1.030	0.751	70.3	72.9	94	29
	Sebastiani	1.0	0.560	21.4	91.2	82.4	81.4
King's	*	16.7	0.773	70.3	73.3	94	29.2
	Celik	7.76	0.881	64.9	84.7	NA	97
	Karacaer	5.76	0.807	73	73	36.3	92
ALBI	*	-2.650	0.668	67.6	59.7	91.7	18.4
	Alsabaey	-2.70	0.698	42.6	91	73.6	66.2
FI	*	2.215	0.731	73.4	65.7	95.1	26.4
	Sayar	10.34	0.620	62	65.3	11.8	95.8
FibroQ	*	3.226	0.718	67.6	72	93.4	27.5
	Celik	2.69	0.682	59.5	61.4	NA	95.4
	Wang HW	3.3	0.855	74.7	79.3	54.7	90.3
Lok	*	3.226	0.765	67.6	72	93.4	27.5
	Wang HW	0.46	0.833	79.9	73.3	50.1	91.6
Fibroindex	*	0.984	0.744	70.3	69.1	93.7	26.3
	Wu	3.25	0.722	80.00	57.61	26.4	93.8

* Results of the present study. Fib-4: Fibrosis-4 index. APRI: Aspartate aminotransferase to platelets ratio. GPR: Gamma-glutamyl transpeptidase to platelet ratio; AAR: Aspartate alanine aminotransferase ratio. GUCI: Goteborg University Cirrhosis Index. ALBI: Albumin bilirubin index. FibroQ: Fibrosis quotient. FI: Fibrosis index. Se: sensitivity. Sp: specificity. PPV: positive predictive value. NPV: negative predictive value. +LR: positive likelihood ratio. -LR: negative likelihood ratio. NA: not available.

APRI scores between the groups of METAVIR F0-2 and F3-4 were 0.836, 0.803 and 0.758, respectively ($P < 0.001$) [15]. The AUROC values of GPR, Fib-4 and APRI scores in previous studies are similar to those of our study, and the highest AUROC value among these is that of GPR [15-18]. There was no significant difference in AUROC value compared to the AAR score, advanced fibrosis, no / low grade fibrosis group as in our study [19,20]. According to our study, GUCI and King's scores could be used in the differentiation of advanced fibrosis and mild fibrosis in chronic hepatitis B patients and were found to be significant (AUROC values were 0.751 and 0.773 respectively). In the studies conducted, there was a significant difference in GUCI and King's scores in terms of AUROC value compared to advanced fibrosis and no / low grade fibrosis group [20-22]. In our study, the AUROC values of ALBI, FI, FibroQ and Lok scores were found 0.668, 0.731, 0.718 and 0.765, respectively. In studies published, ALBI, FI, FibroQ and Lok scores were found to be significant and to have AUROC values similar to our study compared to advanced fibrosis, no / low grade fibrosis group [22-26]. In our study, the AUROC values of Fibro index was found to be 0.7644, and the AUROC value was 0.722 ($p < 0.001$) in the study by Wu et al [16].

According to our study, the AGAP score with cut-off value of 4.038, and sensitivity, specificity and accuracy values of 75.7%, 73.7% and 0.740, respectively, was the scoring method with the highest sensitivity among the non-invasive fibrosis scores. Cut-off values for non-invasive fibrosis scores; Fib-4, APRI and GPR were 1.995, 1.002 and 0.627, respectively and their sensitivity, specificity and accuracy values were (67.6%, 73.7%, 72.9%), (70.3%, 72.5%, 72.2%) and (73.4%,

71.6%, 71.8%), respectively. In the studies published, cut-off values for Fib-4, APRI ve GPR were similar to the values that we found in our study, with alternating rates of 1.48 - 1.45, 0.75-1.0 and 0.41-0.53 respectively. In addition, the values of sensitivity and specificity are similar to our study [15-17,27]. In our study, the cut-off values for GUCI, ALBI and FibroQ scores were 1.030, -2.650 and 3.226, respectively, and the sensitivity and specificity were found to be 70.3% and 72.9%, 67.6% and 59.7%, and 67.6% and 72%, respectively. In previous studies, the cut-off values of 1.0, -2.7, 2.69-3.3 for the GUCI, ALBI and FibroQ scores were similar to the values in our study, but the sensitivity values were low [21-23,26]. In our study, the cut-off values of King's and Lok scores were 16.7 and 0.385. In the studies conducted, the cut-off values for both King's and Lok scores were 5.76-7.76 and 0.46, respectively, and were lower compared to the results of our study. However, the sensitivity and specificity values of these scores were similar to our study [20,22,26]. The cut-off values for FI and Fibroindex in our study were 2.215 and 0.984. The cut-off values were 10.34 and 3.25 in previous studies and were higher than our study, but their sensitivity and specificity values were similar [16,25]. In our study, from non-invasive fibrosis scores, FCI AUROC value was 0.751, cut-off values were 0.171 and the sensitivity and specificity were 70.3% and 72.9%, respectively. There was a significant difference between the advanced fibrosis and no/low grade fibrosis group.

In our study, the AUROC values of FCI score was 0.751 and the cut-off value, sensitivity and specificity were 0.171, 70.3%, 72.9%, respectively, but in the literature, there was no study comparing advanced fibrosis and no/low grade fibrosis groups in patients with chronic

hepatitis B. Instead, there was a significant difference in the literature on patients with chronic hepatitis C compared to the advanced fibrosis and no/low grade fibrosis group [28].

5. Conclusion

In our study, non-invasive fibrosis markers; Fib-4, APRI, GPR, AGAP, GUCI, KING, ALBI, FI, FCI, FibroQ, Lok and Fibroindex were shown to be successful in the differentiation of advanced fibrosis in patients with CHB. However, the other score, AAR, was found to be unsuccessful in detecting fibrosis. In our study, the most successful of the 12 scores used in the differentiation of fibrosis was the AGAP score that we developed. The AUROC value, sensitivity and specificity, positive predictive and negative predictive values and accuracy rates of this score were very successful compared to other scores. However, more extensive and detailed studies are needed regarding these scores. This AGAP score that we developed is quite sensitive, simple and has a low-cost in differentiation of advanced fibrosis in patients with CHB.

Author contributions

All authors have contributed to the reporting of the work described in the article.

Conflicts of interest

The authors have no conflict of interest to declare.

References

- Razavi-Shearer D, Gamkrelidze I, Nguyen MH, Chen DS, Damme PV, Abbas Z, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018;3(6):383–403. [https://doi.org/10.1016/S2468-1253\(18\)30056-6](https://doi.org/10.1016/S2468-1253(18)30056-6).
- James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1789–858. [https://doi.org/10.1016/S0140-6736\(18\)32279-7](https://doi.org/10.1016/S0140-6736(18)32279-7).
- Bonder A, Tapper E, Afdhal NH. Contemporary assessment of hepatic fibrosis. *Clin Liver Dis* 2015;19(1):123–34. <https://doi.org/10.1016/j.cld.2014.09.007>.
- Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. *Hepatology* 2009;49:1017–44. <https://doi.org/10.1002/hep.22742>.
- Agbim U, Asrani SK. Non-invasive assessment of liver fibrosis and prognosis: an update on serum and elastography markers Non-invasive assessment of liver fibrosis and prognosis: an update on serum and elastography markers. *Expert Review of Gastroenterology & Hepatology* 2019;13:361–74. <https://doi.org/10.1080/17474124.2019.1579641>.
- Jin W, Lin Z, Xin Y, Jiang X, Dong Q, Xuan S. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis B-related fibrosis: A leading meta-analysis. *BMC Gastroenterol* 2012;12:14. <https://doi.org/10.1186/1471-230X-12-14>.
- Kim W, Berg T, Asselah T, Flisiak R, Fung S, Gordon SC, et al. Evaluation of APRI and FIB-4 scoring systems for non-invasive assessment of hepatic fibrosis in chronic hepatitis B patients. *J Hepatol* 2016;64:773–80. <https://doi.org/10.1016/j.jhep.2015.11.012>.
- Teshale E, Lu M, Rupp LB, Holmberg SD, Moorman AC, Spradling P, et al. APRI and FIB-4 are good predictors of the stage of liver fibrosis in chronic hepatitis B: The Chronic Hepatitis Cohort Study (CHecs). *J Viral Hepat* 2014;21:1917–20. <https://doi.org/10.1111/jvh.12279>.
- Lemoine M, Shimakawa Y, Nayagam S, Khalil M, Suso P, Llyold J, et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. *Gut* 2016;65:1369–76. <https://doi.org/10.1136/gutjnl-2015-309260>.
- Dong M, Wu J, Yu X, Li J, Yang S, Qi X, et al. Validation and comparison of seven noninvasive models for evaluating liver fibrosis in Chinese hepatitis B patients. *Liver Int* 2018;38:1562–70. <https://doi.org/10.1111/liv.13688>.
- Branchi F, Conti C, Baccarin A, Lampertico P, Conte D, Fraquelli M. Non-invasive assessment of liver fibrosis in chronic hepatitis B. *World J Gastroenterol* 2014;20(40):14568–80. <https://doi.org/10.3748/wjg.v20.i40.14568>.
- Ishak K, Bapista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;22:696–9. [https://doi.org/10.1016/0168-8278\(95\)80226-6](https://doi.org/10.1016/0168-8278(95)80226-6).
- Bedossa P, Patel K, Castera L. Histologic and noninvasive estimates of liver fibrosis. *Clin Liver Dis* 2015;6(1):5–8. <https://doi.org/10.1002/cld.481>.
- Li J, Mao R, Li X, Zheng J, Qi X, Yuan Q, et al. A novel noninvasive index for the prediction of moderate to severe fibrosis in chronic hepatitis B patients. *Dig Liver Dis* 2018;50(5):482–9. <https://doi.org/10.1016/j.dld.2017.12.028>.
- Wang R-Q, Zhang Q-S, Zhao S-X, Niu X-M, Du J-H, Du H-J, et al. Gamma-glutamyl transpeptidase to platelet ratio index is a good noninvasive biomarker for predicting liver fibrosis in Chinese chronic hepatitis B patients. *J Int Med Res* 2016;44:1302–13. <https://doi.org/10.1177/0300060516664638>.
- Wu D, Rao Q, Chen W, Ji F, Xie Z, Huang K, et al. Development and validation of a novel score for fibrosis staging in patients with chronic hepatitis B. *Liver Int* 2018;38:1930–9. <https://doi.org/10.1111/liv.13756>.
- Kayadibi H, Yilmaz S, Yeniova AO, Koseoglu H, Simsek Z. Development and evaluation of a novel noninvasive index for predicting significant fibrosis, advanced fibrosis, and cirrhosis in patients with chronic hepatitis B infection. *Eur. J Gastroenterol Hepatol* 2020 Online ahead of print. <https://doi.org/10.1097/MEG.0000000000001973>.
- Hu YC, Liu H, Liu XY, Ma LN, Guan YH, Luo X, et al. Value of gamma-glutamyl-transpeptidase-to-platelet ratio in diagnosis of hepatic fibrosis in patients with chronic hepatitis B. *World J Gastroenterol* 2017;23(41):7425–32. <https://doi.org/10.3748/wjg.v23.i41.7425>.
- Sha FR, Uddin M, Abuelezz NZ, Pervin R, Talukder RI, Begum M, Rahman M. Investigating the Efficiency of APRI, FIB-4, AAR and AARPRI as Noninvasive Markers for Predicting Hepatic Fibrosis in Chronic Hepatitis B Patients in Bangladesh The Open Microbiology. *Journal* 2019;13:34–40. <https://doi.org/10.2174/1874285801913010034>.
- Karaca er Z, Avci O, Karadağ FY. King's Score may be More Effective in the Determination of Severe Fibrosis in Chronic Hepatitis B Infections. *Viral. Hepat J* 2017;23(1):20–5. <https://doi.org/10.4274/vhd.09326>.
- Sebastiani G, Vario A, Guido M, Alberti A. Sequential algorithms combining non-invasive markers and biopsy for the assessment of liver fibrosis in chronic hepatitis B. *World J Gastroenterol* 2007;13(4):525–31. <https://doi.org/10.3748/wjg.v13.i4.525>.
- Celik D, Tatar B, Köse Ş, Ödemiş İ. Evaluation of the diagnostic validity of noninvasive tests for predicting liver fibrosis stage in chronic hepatitis B patients. *Acta Gastroenterol Belg* 2020;83(3):419–25.
- Alsebaey A, Badr R, Omar Amer EAM, Eljaky MA, El-Azab G, et al. King's Fibrosis, Fibrosis Index, GPR, and ALBI Score Are Useful Models for Liver Fibrosis in Chronic Hepatitis B Patients Pre-and Post-Treatment. *Hepat Mon* 2019;19(11):e96081. <https://doi.org/10.5812/hepatmon.96081>.
- Said M, Eletreby R, Omar H, Dabees H, Abdelghafour R, El-Serafy M, et al. Fibroindices versus liver stiffness for prediction of significant fibrosis in hepatitis B virus-infected Egyptian patients; a single-center experience. *Expert Rev Gastroenterol Hepatol* 2020;14:221–7. <https://doi.org/10.1080/17474124.2020.1723415>.
- Sayar S, Atalay R, Çakmak S, Ayrancı G, Kürbüz K, Kahraman K, et al. Diagnostic performance of Non-invasive fibrosis Indexes in Hepatitis B Related fibrosis. *Viral Hepatitis Journal* 2020;26(2):78–84. <https://doi.org/10.4274/vhd.galenos.2020.2019.0038>.
- Wang HW, Peng CY, Lai HC, Su WP, Lin CH, Chuang PH, et al. New noninvasive index for predicting liver fibrosis in Asian patients with chronic viral hepatitis. *Sci Rep* 2018;8(1):6062. <https://doi.org/10.1038/s41598-018-24186-5>.
- Huang R, wang G, Tian C, Liu Y, Jia B, Wang J. Gama-glutamyl-transpeptidase to platelet ratio is not superior to APRI, FIB-4 and RPR for diagnosing liver fibrosis in CHB patients in China. *Sci Rep* 2017;17(1):8543. <https://doi.org/10.1038/s41598-017-09234-w>.
- Ahmad W, Ijaz B, Javed FT, Gull S, Kausar H, Sarwar MT, et al. A comparison of four fibrosis indexes in chronic HCV: development of new fibrosis-cirrhosis index (FCI). *BMC Gastroenterol* 2011;11:44. <https://doi.org/10.1186/1471-230X-11-44>.