Evaluation of the diagnostic validity of noninvasive tests for predicting liver fibrosis stage in chronic hepatitis B patients

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ABSTRACT

Background and study aim **: The aim of this study was to evaluate the effectiveness of noninvasive tests in predicting liver fibrosis levels in chronic hepatitis B (CHB) patients.**

Patients and methods **: A total of 539 treatment naive patients aged 18 years and older with CHB who underwent liver biopsy were included. Patients with coinfections and comorbidities were excluded. Data were obtained retrospectively from patient' follow-up files. Liver biopsy was evaluated according to the Ishak scoring system. SPSS 22.0 program was used for statistical analysis. Diagnostic sensitivity of APRI, FIB-4, NLR, GPR, AAR, RPR, API, King's score, Fibro Q and MPV was determined for predicting ≥F2, ≥F3, ≥F4, ≥F5 groups.**

Results **: The median age of the CHB patients was 41 ±11.57 / year and 49.2% of the patients were female. The distribution of fibrosis stages was : F0, 16.5% ; F1, 26.4% ; F2, 39.7% ; F3, 10.4% ; F4, 4.1% ; F5, 2.4% ; F6 0.4%. Age, AST, ALT, GGT, ALP, RDW, HBV DNA levels were significantly higher, platelet and albumin levels were significantly lower in the ≥F3 group. All noninvasive tests except NLR and AAR predicted ≥F3 adequately (AUROC >0.5). King's score for predicting ≥F2, ≥F5, and GPR for predicting ≥F3 had the highest diagnostic power. The tests predicted the fibrosis stage better, as the fibrosis stage progressed.**

Conclusion **: As a result; most of the noninvasive tests we evaluated could predict significant fibrosis and cirrhosis with significant accuracy. The rate of unnecessary biopsies can be reduced with the help of these noninvasive tests.** (Acta gastroenterol. belg., **2020**, 83, **419-425**).

Keywords : Chronic hepatitis B, liver fibrosis, liver biopsy, noninvasive tests.

Introduction

There are approximately 240 million HBV carriers in the world and it is reported that 686,000 people die each year as a result of cirrhosis and liver cancer caused by HBV (1). According to the World Health Organization (WHO) data, approximately 450 million new HBV infections occur annually and about 25% of them become chronic (2). Biochemical, serological and molecular tests, histopathological examination and imaging methods are used for the diagnosis and staging of chronic hepatitis B. Determining the degree of liver fibrosis in individuals with CHB is the main step in the treatment approach. Liver biopsy is the gold standard method for the evaluation of fibrosis (3). However, being invasive, expensive and complicated are the disadvantages of this procedure (4). Therefore, researchers have focused on noninvasive tests that can be used instead of biopsy in recent years. In March 2015, the aspartate transaminase (AST)-platelet ratio index (APRI) and 4 factors based fibrosis index (FIB-4) were proposed by WHO meta-analysis as noninvasive tools containing only two or three laboratory tests to detect significant fibrosis levels in resource-restricted regions (5). In this meta-analysis, high cut-off value for high specificity and low cut-off value for high sensitivity were determined.

This study was designed to investigate the relationship between necroinflammation and noninvasive diagnostic parameters based on histology of chronic liver diseases. We analyzed the diagnostic values of APRI, FIB-4, neutrophil-lymphocyte ratio (NLR), gamma-glutamyl transpeptidase (GGT)-platelet ratio (GPR), AST-alanine transaminase (ALT) ratio (AAR), red cell distribution width (RDW)-platelet ratio (RPR), age-platelet index (API), King's score, Fibro quotient (Fibro Q), mean platelet volume (MPV) for moderate liver fibrosis (≥F2), significant liver fibrosis (≥F3), advanced liver fibrosis (≥F4) and liver cirrhosis (≥F5) in CHB patients and compared the diagnostic performances of these tests with each other. Furthermore, we determined the sensitivity, specificity and cut-off values of the tests.

Materials and method

Study Population and Design

Treatment naive 539 CHB patients who underwent liver biopsy in a tertiary hospital between August 2010 and August 2017, were included in the study. Demographic data, laboratory values, and clinicopathological data were screened retrospectively from patients' files. Patients with alcohol use (20 g/day), alcoholic liver disease, non-alcoholic fatty liver disease, primary liver cancer, obstructive jaundice, less than 50 000 ($\times 10^9$ L^{-1}) or more than 400 000 ($\times 10^9$ L^{-1}) platelet count, pregnancy, autoimmune disease, malignancy, renal failure, hemolytic anemia co-infections such as HIV, Hepatitis C, Hepatitis D were excluded.

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Ethics Committee Approval and Informed Consent

The study protocol was approved by the Local Ethics Committee of İzmir Tepecik Training and Research Hospital on the 27th of September 2017 and numbered 3. Informed consent was obtained from the patients according to the regulations of the committee. All methods were carried out in accordance with the relevant guidelines, Declaration of Helsinki and regulations of the committee.

Laboratory Tests

Blood sampling and liver biopsy procedures had been applied simultaneously. Blood biochemical parameters; ALT (IU / L), AST (IU / L), alkaline phosphatase (ALP) (IU / L), GGT (IU / L), total bilirubin (mg / dL), direct bilirubin (mg / dL), serum albumin (g / L)) had been analyzed by AU5800 auto-analyzer (Beckman Coulter Inc., CA, USA). Alpha-fetoprotein (AFP) (ng / mL) had been analyzed by DxI 800 auto-analyzer (Beckman Coulter Inc., CA, USA). Prothrombin time (PT) and activated partial thromboplastin time (aPTT) had been determined by an automated coagulation analyzer of the Sysmex® CS-2500 System (SysmexCorporation, Kobe, Japan). International Normalized Ratio (INR) had been calculated by using the ISI formula of INR = (patient's PT / mean normal PT). Hematologic parameters had been determined with Beckman Coulter LH 780 (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). Serum HBsAg, HBeAg, Anti HBe, Anti HBs, Anti HCV, Anti HDV and Anti HIV tests had been evaluated by ELISA (Liaison, Diasonin, Italy). Serum HBsAg quantitative value had been measured by the Abbott ARCHITECT assay (Abbott Diagnostics, Germany; dynamic range (lower limit of quantification, <0.05 IU / mL) HBV DNA level had been measured using real-time PCR (COBAS Ampli Prep / COBAS, TaqMan lower limit of quantification, <20 IU / mL). The calculations of noninvasive tests are shown in Table 1.

Histopathological Evaluation of Liver

Liver biopsy results were evaluated retrospectively. The biopsy had been performed with 18G tru cut biopsy needle (18G x 20 cm, Geotek Medical and Health Services, Ankara, Türkiye). All biopsy materials had been examined by the same pathologist. Biopsy samples had been fixed with 10% neutral buffered formalin for 2 hours. Paraffin-embedded tissues had been cut in series for hematoxylin and eosin, Masson's trichrome and reticulin staining. Fibrosis scores and histological activity indices (HAI) in samples with at least 11 portal areas had been calculated according to Ishak scoring system (6). According to the Ishak score fibrosis stages 2 and above, were considered as mild and above fibrosis, fibrosis stage 3 and above significant fibrosis, and 5 and above cirrhotic. According to the Metavir score, 0 corresponds to 0, 1 to 1, 2 to 2-3, 3 to 4-5, 4 to 6 in the Ishak scoring (5).

Table 1. — **Noninvasive biochemical models and formulas**

APRI	AST (IU/L) /ULN / Platelet count ($\times 10^9$ L^{-1})×100
FIB-4	{Age (year) × AST (IU/L)} / {Platelet count ($\times 10^9$ L^{-1}) × ALT (IU/L)$^{1/2}$}
NLR	Neutrophil ($\times 10^9$ L^{-1}) / Lymphocyte ($\times 10^9$ L^{-1})
GPR	GGT (IU/L) /ULN/Platelet count ($\times 10^9$ L^{-1})×100
AAR	AST (IU/L) /ALT (IU/L)
RPR	RDW (%) / PLT ($\times 10^9$ L^{-1})
API	Age score+Platelet score Age <30=0; 30–39=1; 40–49=2; 50–59=3; 60–69=4; ≥70=5 Platelet count ($\times 10^9$ L^{-1}): ≥225=0; 200–224=1; 175–199=2; 150–174=3; 125–149=4; <125=5
King's score	(Age (year) ×AST (IU/L) ×INR) / Platelet count ($\times 10^9$ L^{-1})
Fibro Q	10 × {Age (year) ×AST (IU/L) ×INR} / {ALT (IU/L) × Platelet count ($\times 10^9$ L^{-1})}

Abbreviations : APRI, aspartate transaminase to platelet radio index ; FIB-4, 4 factors based fibrosis index ; NLR, neutrophil-lymphocyte ratio ; GPR, gamma-glutamyl transpeptidase-platelet ratio ; AAR, aspartate transaminase-alanine transaminase radio ; RPR, red cell distribution width to platelet ratio ; API, age platelet index ; Fibro Q, Fibro quotient ; MPV, mean platelet volume.

Statistical analysis

Data were analyzed using SPSS IBM 22.0 (Statistical Package for Social Sciences 22 version). The characteristics of the study patients, categorical variables were presented as frequency and percentage. The normal distribution of the variables was determined using the Kolmogorov-Smirnov test. Due to their ab-normal distribution, continuous variables were presented as median (min-max). Non-parametric Mann-Whitney U test was used for comparison of variables and Fisher exact test was used for comparison of nominal data. Bivariate Spearman correlation test was used for correlations between numerical values since there was no normal distribution. In order to determine the effectiveness of non-invasive methods, the area under the curve was found by using ROC (Receiver Operating Curves) analysis. AUC (Area under the curve) is defined as a test with excellent diagnostic power between 1-0.9, good between 0.9-0.8, moderate between 0.8-0.7, weak between 0.7-0.6, unworthy between 0.6-0.5. AUC ≤ 0.5 was considered as the test has no diagnostic value (7). All p values were 2-sided and p values less than 0.05 were considered statistically significant.

RESULTS

Study population

The median age of the CHB patients was 41 ±11.57 / year and 49.2% of the patients were female. There was no significant difference between the sexes in the <F3 and the ≥F3 groups (p: 0.211). HBeAg positivity was 7.24%. Median HAI value was 5±3. The distribution of fibrosis stages was : F0, 89 (16.5%) ; F1, 143 (26.4%) ;

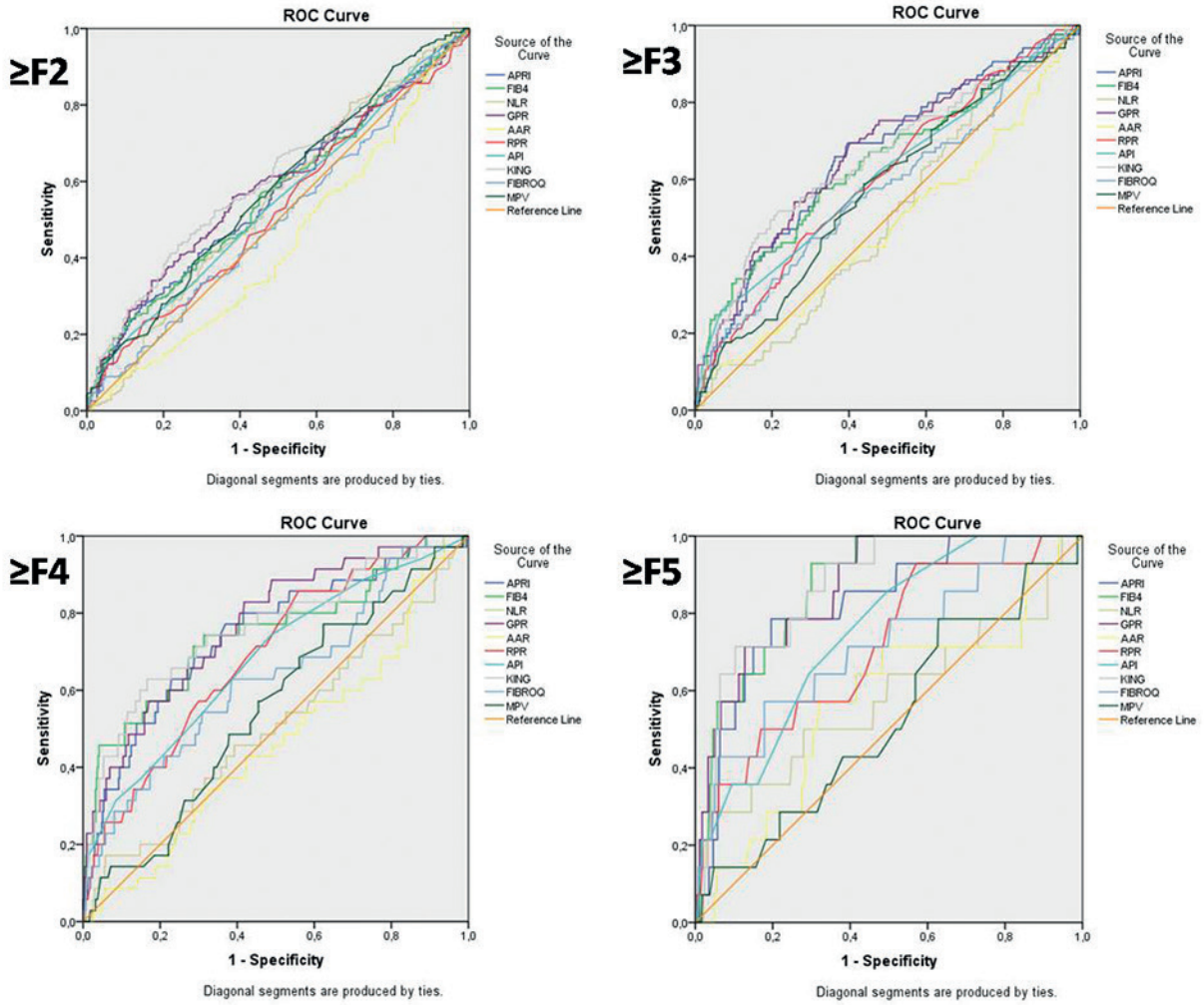

Figure 1. — The ROC Curves of Ten Noninvasive Models for Predicting Moderate Fibrosis (≥F2), Significant Liver Fibrosis (≥F3), Advanced Liver Fibrosis (≥F4) and Liver Cirrhosis (≥F5) in Chronic Hepatitis B Patients.

F2, 214 (39.7%) ; F3, 56 (10.4%) ; F4, 22 (4.1%) ; F5, 13 (2.4%) ; F6 2 (0.4%).

Age, AST, ALT, GGT, ALP, RDW, HBV DNA levels were significantly higher, platelet and albumin levels were significantly lower in the ≥F3 group. Total bilirubin, direct bilirubin, AFP, INR, neutrophil, lymphocyte, HBsAg quantitative levels were not significantly different between ≥F3 and <F3 groups. The median (min-max) values of biochemical, hematological and virological parameters of the whole study group and <F3/≥F3 subgrups and comparisons of demographic and clinical features between these groups are given in Table 2.

The comparisons of diagnostic performance of noninvasive tests in the CHB population

When the median values of the tests was compared between <F3 and ≥F3 groups, APRI, FIB-4, GPR, RPR, API, King's score, Fibro Q, and MPV levels were significantly higher in the ≥F3 group. There was no significant difference in NLR and AAR levels between the groups. The median values and the comparison of the tests are given in Table 3.

When the diagnostic sensitivity of noninvasive tests according to fibrosis stage was investigated, the best diagnostic test was found to be King's score (AUC: 0.599, p: 0.000, CI: 0.555-0.650) in the group ≥F2. The optimal cut-off value of the King's score for the prediction of ≥F2 was 5.16 (sen: 51.5%, spec: 66.4%, NPV: 50.8%). NLR, RPR and Fibro Q did not predict ≥F3 (p≥0.05). The ROC curves of ten noninvasive models for predicting moderate fibrosis (≥F2), significant liver fibrosis (≥F3), and liver cirrhosis (≥F5) in the entire CHB population are shown in Fig. 1. The diagnostic performances of tests are presented in Table 4.

When ROC analysis defining the ≤ F2 group was performed, it was seen that the tests had no diagnostic value since all of the AUC values of the tests were less than 0.5.

In the ≥F3 group, GPR (AUC : 0.666, p : 0.000, CI : 0.599-0.734) ≥F3 was the best diagnostic test. The optimal cut-off value of the GPR for the prediction of ≥F3 was 0.22 (sensitivity (sen) : 69.4%, specifity (spec) : 59.8%, Negative Predictive Value (NPV) : 89.8%). NLR, AAR did not predict ≥F3 (p≥0.05).

Table 2. — **The comparison of demographic and clinical features between mild (<F3) and significant fibrosis (≥F3) in chronic hepatitis B patients**

	All group (n=539) Median (min-max)	<F3 group (n=446) Median (min-max)	≥F3 group (n=93) Median (min-max)	P value
Demographic data				
Age (year)	41(18-77)	40 (18-74)	44 (18-77)	**0.005**
Liver function tests (normal values)				
AST (0-35 IU/L)	25 (10-372)	24 (10-300)	33 (11-272)	**0.000**
ALT (0-35 IU/L)	26 (4-920)	24 (4-920)	37 (7-522)	**0.000**
GGT (0-38 IU/L)	21 (6-224)	21 (6-208)	27 (8-274)	**0.000**
ALP (30-120 IU/L)	81 (32-400)	79 (32-400)	85 (42-309)	**0.004**
Total Bilirubin (0.3-1.2 g/dL)	0.7 (0.26 - 4.3)	0.7 (0.26-3.8)	0.7 (0.4-4.3)	0.374
Direct Bilirubin (0-0.2 g/dL)	0.1 (0.001-1.93)	0.1 (0.001-0.5)	0.11 (0.06-1.93)	0.176
Albumin (3.5-5.2 g/dL)	4.4 (2.9-5.2)	4.4 (2.9-5.2)	4.3 (3.2-5)	**0.02**
AFP (0-9 ng/ml)	2.22 (0.41-107)	2.11 (0.41-83)	2.66 (0.56-107)	0.059
INR (0.8-1.2)	1.01 (0.82-1.38)	1.02 (0.82-1.3)	0.98 (0.83-1.38)	0.063
Hematological parameters (normal values)				
Neutrophil (2-6.9 $\times10^9$ L^{-1})	3.85 (1.4 -11.7)	3.9 (1.4-11.7)	3.7 (1.5-9.9)	0.419
Lymphocyte (0.6-3.4 $\times10^9$ L^{-1})	2.1 (0.6-6.6)	2.1 (0.8-6.6)	2.04 (0.6-3.4)	0.5
Platelet (140-400 $\times10^9$ L^{-1})	222 (91-394)	224 (100-394)	212 (91-346)	**0.004**
RDW (11.6-17.2 %)	13.6 (11.8-26.5)	13.5 (11.8-26.5)	14 (12-19.4)	**0.014**
Virological parameters				
HBV DNA (IU / mL)	11200 (20-170000000)	9055 (20-170000000)	50800 (37-170000000)	**0.002**
HBsAg quantitative	3197.1 (2.99-68513.15)	3264.65 (2.99-68513.15)	2265.97(53.02-22886.1)	0.491

Abbreviations : AST, aspartate transaminase ; ALT, alanine transaminase ; GGT, gamma-glutamyl-transferase ; ALP, alkaline phosphatase ; AFP, alpha-fetoprotein INR, international normalized ratio ; RDW, red cell distribution width ; F, fibrosis ; HbsAg, Hepatitis B virus surface antigen. The data with abnormal distribution were shown as median and min-max. P value was described statistically significant, when it was <0.05 and it was written in bold.

Table 3. — **The comparison of noninvasive serum biomarkers of the <F3 and ≥F3 groups in chronic hepatitis B patients**

	Total (n=539) Median (min-max)	<F3 group (n=446) Median (min-max)	≥F3 group (n=93) Median (min-max)	p value
APRI	0.29 (0.09-7.97)	0.27 (0.1-7.97)	0.37 (0.09-6.95)	**.000**
FIB-4	0.91 (0.21-14.5)	0.87 (0.21-8.56)	1.11 (0.25-14.5)	**.000**
NLR	1.86 (0.53-7.64)	1.84 (0.53-7.64)	1.85 (0.79-5.17)	.846
GPR	0.21 (0.05-3.85)	0.19 (0.05-2.37)	0.28 (0.06-3.85)	**.000**
AAR	0.97 (0.3-5)	1 (0.3-5)	0.96 (0.48-2.56)	.313
RPR	0.06 (0.04-0.18)	0.06 (0.04-0.18)	0.07 (0.04-0.17)	**.001**
API	2 (0-9)	2 (0-9)	3 (0-8)	**.002**
King's score	4.58 (1.07-159.03)	4.4 (1.07- 159.03)	6.74 (1.65-106.31)	**.000**
Fibro Q	1.76 (0.25-48.18)	1.72 (0.26-8.81)	2.02 (0.25-48.18)	**.041**
MPV	8.9 (5.7-14.9)	8.81 (4.7-14.9)	9.28 (6.5-12.9)	**.019**

Abbreviations : APRI, aspartate transaminase to platelet radio index ; FIB-4, 4 factors based fibrosis index ; NLR, neutrophil-lymphocyte ratio ; GPR, gamma-glutamyl transpeptidase-platelet ratio ; AAR, aspartate transaminase-alanine transaminase radio ; RPR, red cell distribution width to platelet ratio ; API, age platelet index ; Fibro Q, Fibro quotient ; MPV, mean platelet volume. P value was described statistically significant, when it was <0.05 and it was written in bold.

In another ROC analysis based on the cut-off values recommended by WHO for APRI and FIB-4 diagnostic values for the prediction of significant fibrosis (≥F3), 0.5 cut-off value (sen: 86.3%, PPV: 86.5%) and 1.5 cut-off value (spec: 96.9%, NPV: 83.4%) for APRI were similar to WHO data (5). For the prediction of cirrhosis, 1 cut-off value (sen: 20%, PPV: 9.7%) for APRI had poorer and 2 cut-off value (spec: 97.9%, NPV: 97.3%) for APRI had better performance than WHO's recommend. However, the diagnostic sensitivity of FIB-4 was similar to those presented in the WHO guidelines (Table 4).

In the ≥F5 group, the King's score was the best diagnostic test (AUC: 0.881, p: 0.000, CI: 0.816-0.949). The optimal cut-off value of the King's score for the prediction ≥F5 was 7.76 (sen: 73.3%, spec: 80.5%, NPV: 99.1%). NLR, AAR, and MPV did not predict ≥F5 (p≥0.05).

DISCUSSION

Early detection of the significant fibrosis is crucial for patients with CHB to decide on antiviral therapy. Although liver biopsy is the gold standard for detecting liver fibrosis, sampling errors, recurrence difficulties and complications limit its use. Therefore, in this study, we compared the diagnostic values of noninvasive tests

Table 4. — **Roc analysis and cut-off values of noninvasive tests for the prediction of liver fibrosis stage in chronic hepatitis B**

Tests	AUC	P value	Cut-off	Sen (%)	Spec (%)	NPV (%)	Youden index
Moderate Fibrosis (≥F2)							
APRI	.549	**.049**	0.48	23.5	87.5	46.3	0.110
FIB-4	.564	**.011**	0.9	55.4	57.8	49.4	0.131
NLR	.548	.055	N/A	N/A	N/A	N/A	N/A
GPR	.586	**.002**	0.21	55.9	61.9	48.8	0.178
AAR	.578	**.002**	1.04	64.2	51.3	52	0.155
RPR	.521	.407	N/A	N/A	N/A	N/A	N/A
API	.552	**.039**	2.5	53.1	54.7	46.9	0.078
King's score	.599	**.000**	5.16	51.5	66.4	50.8	0.178
Fibro Q	.495	.834	N/A	N/A	N/A	N/A	N/A
MPV	.582	**.001**	8.68	67.1	45.7	51.2	0.128
Significant Fibrosis (≥F3)							
APRI	.662	**.000**	0.32 0.5* 1.5*	64.5 86.3 7.5	64.3 35.5 96.9	89.7 35.1 83.4	0.289
FIB-4	.650	**.000**	1.05 1.02-1.7* 2.01-3.25*	58.1 58 20	68.2 68 96.9	88.6	0.262
NLR	.494	.846	N/A	N/A	N/A	N/A	N/A
GPR	.666	**.000**	0.22	69.4	59.8	89.8	0.292
AAR	.530	.367	N/A	N/A	N/A	N/A	N/A
RPR	.607	**.001**	0.06	75.3	41.9	89	0.172
API	.603	**.002**	5.5	23.7	93.7	85.5	0.174
King's score	.657	**.000**	7.1	49.5	80	88.4	0.295
Fibro Q	.565	**.048**	2.58	34.4	79.8	85.4	0.142
MPV	.577	**.019**	8.94	59.1	57	87	0.161
Cirrhosis (≥F5)							
APRI	***.837***	**.000**	0.46 1* 2*	64.9 20 6.7	78.1 94.7 97.9	96.8 97.6 97.3	0.613
FIB-4	***.873***	**.000**	1.13	75.7	69.3	97.5	0.638
NLR	.593	.218	N/A	N/A	N/A	N/A	N/A
GPR	***.867***	**.000**	0.45	82.9	58.2	97.7	0.587
AAR	.479	.78	N/A	N/A	N/A	N/A	N/A
RPR	.712	**.005**	0.06	86.5	44.2	97.8	0.365
API	.749	**.001**	2.5	73	52	96.3	0.380
King's score	***.881***	**.000**	7.76	64.9	84.7	97	0.539
Fibro Q	.682	**.016**	2.69	59.5	61.4	95.4	0.348
MPV	.504	.954	N/A	N/A	N/A	N/A	N/A

Abbreviations : AUC, Area under curve ; APRI, aspartate transaminase to platelet radio index ; FIB-4, 4 factors based fibrosis index ; NLR, neutrophil-lymphocyte ratio ; GPR, gamma-glutamyl transpeptidase-platelet ratio ; AAR, aspartate transaminase-alanine transaminase radio ; RPR, red cell distribution width to platelet ratio ; API, age platelet index ; Fibro Q, Fibro quotient ; MPV, mean platelet volume ; Sen, sentivity ; Spec, specifity ; NPV, negative predictive value. N/A : Not avaliable. Those with AUC> 800 are written in bold and italic. P <0.05 statistically significant ones were written in bold. *threshold recommended by WHO.

and blood biomarkers such as APRI, FIB-4, NLR, GPR, AAR, RPR, API, King's score, Fibro Q, MPV to evaluate liver fibrosis in patients with CHB infection.

Significant fibrosis was detected in 19.3% of the male patients and 15.1% of the female patients, there was no significant difference according to gender. Age was significantly higher in the significant fibrosis group, which was consistent with the literature (4,8).

Age, albumin, platelet, AST, ALT, GGT, INR which are associated with the liver function and level of hepatic disease, are widely used in noninvasive models. In our study, AST, ALT, GGT, ALP levels were significantly higher, platelet and albumin levels were significantly lower in the ≥F3 group. The decrease in platelet counts was associated with increased splenomegaly-induced sequestration and destruction of platelets with the progression of the disease, as well as decreased thrombopoietin production by hepatocytes, and thus reduced platelet production (9). As albumin production is in the liver, it may explain that progression in liver damage reduces albumin levels and this decrease in albumin can be used to predict liver fibrosis (10).

As in the metaanalysis conducted by WHO, which included 77 studies, the APRI and FIB-4 scores were found to be successful in predicting significant fibrosis and cirrhosis, in our study (5). AUC of APRI for significant fibrosis ranged from 0.61 to 0.787 in various studies and cut-off values ranged from 0.47 to 1 (1,11-

14). The cut-off value for significant fibrosis was found to be 0.32, which was lower than the results presented in the literature, but this cut-off value predicted significant fibrosis in more patients than other studies with 89.7% NPV.

GPR had the highest diagnostic sensitivity for prediction significant fibrosis among noninvasive tests. GPR was found to be a more accurate noninvasive test than APRI and FIB-4 for detecting liver fibrosis by Lemoine M et al., as in our study (15). Ren T. et al concluded that GPR predicted all fibrosis stages statistically better than APRI, comparable but not superior to FIB-4 (16). In the meta-analysis conducted by Medline, Embase, Cochrane databases in 2019, the AUC of RPR value for predicting fibrosis in liver diseases including CHB, chronic hepatitis C, primary biliary cirrhosis, nonalcoholic steatohepatitis was determined as 0.71 (17). In our study, it was concluded that the diagnostic value of RPR and API in the prediction of fibrosis and cirrhosis was weak and moderate, respectively. In a study evaluating 17 noninvasive markers in CHB patients, the AUC of API for prediction of ≥F3 was 0.676 and ≥F5 was 0.817 (18). Although Erdoğan et al. stated that the use of API test in predicting significant fibrosis was statistically insignificant, in our study API had moderate diagnostic sensitivity as in many studies in the literature (19).

In a study comparing 30 noninvasive tests in China, for King's score AUC: 0.713 for ≥F3 prediction and AUC : 0.765 for ≥F5 prediction were found in treatment-naive CHB patients (20). Due to the high diagnostic sensitivity of King's score compared to other markers in our study, it may be recommended as the best noninvasive marker in predicting ≥F5. Xiao-Qui Dong's study in untreated patients found AUC: 0.720 of Fibro Q test in predicting ≥F3 and AUC: 0.810 in predicting ≥F5 (20). In our study the diagnostic performance of the Fibro Q score was lower than APRI and FIB-4. For predicting significant fibrosis and cirrhosis, AUCs of Fibro Q were lower than the study results of Hsieh, Minhui Dong, Xiao-Qui Dong's (18,20,21). Although Fibro Q calculated with too many components, it is surprising that its diagnostic performance is not as high as expected.

The use of NLR and AAR in liver fibrosis is controversial. Several studies have reported that NLR can be used to predict the stage of liver fibrosis in CHB patients (22,23). However, our study concluded that NLR is not sufficient to predict any stage of fibrosis. Although Zhang Z. et al., Dong M et al. suggested to use AAR for prediction of significant fibrosis, we concluded that AAR was inadequate to predict ≥F3, ≥F5 (8,18). However, there are studies supporting our results in the literature (11,24). The use of MPV was statistically significant to predict the ≥F3 group with weak diagnostic power. In a study performed by İnci A, in 33 CHB patients with HBV DNA level >2000 IU/ml, patients with fibrosis score <F4 had lower MPV levels than patients with fibrosis score ≥F4 (25). But in our study results, MPV was insufficient to predict advanced fibrosis stages.

Since the AUC values of the 7 tests that we found to be significant in the prediction of ≥F2 remained within the range of 0.5-0.6, the tests were generally considered to be very poor. In 8 tests that we found significant in prediction of ≥F3, the AUC values remained in the range of 0.6-0.7, and the tests were evaluated as weak. GPR, APRI and King's scores had the most accurate diagnostic value for ≥F3 group. Seven out of 10 noninvasive models were able to predict cirrhosis (≥F5) in naive CHB patients successfully. In the prediction of cirrhosis (≥F5), it was concluded that King's score, FIB-4 and GPR had the most powerful predictive values among the models. Since the AUC values of these tests were between 0.9-0.8, they were evaluated as tests with good diagnostic power.

Hepatic fibrogenesis is a dynamic process, in addition to detecting significant fibrosis, these noninvasive markers can also be used to monitor changes in fibrosis that develop over time. APRI, FIB-4, GPR, RPR, API, King's score and Fibro Q predicted the fibrosis stage better, as the fibrosis stage progressed. Close monitoring over time may be more important than assessing the stage of the disease at a specific time point.

However, our study has some limitations; firstly, the most important limitation of this study is being single-center and a having retrospective design. Secondly, since hepatic decompensation, prolongation of coagulation tests and thrombocytopenia were observed during the cirrhosis process, the initiation of treatment without biopsy led to the inclusion of few cirrhosis patients and selection bias. Thirdly, the noninvasive methods investigated in the study were developed for chronic hepatitis C for the first time. Hepatitis C and B are different from each other in terms of virological features, histological changes and fibrosis mechanisms in the liver. Therefore, it may give contradictory results in the prediction of liver fibrosis. Fourthly, in almost all studies in the literature, including our study, patients were not grouped according to the HBV genotype and the genotype was not routinely tested. However, there are studies indicating that the genotype of the virus is also important in hepatocyte damage and developing fibrosis (26).

CONCLUSION

As a result : most of the noninvasive tests that we evaluated could predict significant fibrosis and cirrhosis with significant accuracy. Unnecessary biopsies can be reduced by the use of these tests. The combination of multiple noninvasive tests or the combination of these markers with radiographic imaging may contribute to the ability to assessing the degree of fibrosis. While GPR, APRI and King's scores had the most accurate diagnostic values for predicting significant fibrosis, the value of the tests was weak in prediction of moderate fibrosis. The tests predicted the fibrosis stage better, as the fibrosis stage progressed especially in cirrhotic patients. However, it should be noted that; although there has been

great progress in the evaluation of HBV patients with noninvasive tests, there has no perfect test invented yet to replace liver biopsy.

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Informed consent

Informed consent was obtained from all participants included in the study.

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