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Predictive Value of Laboratory, Radiological, and Non-invasive Tests for Liver Biopsy Findings in Treatment-naive, HBeAg-negative Chronic Hepatitis B Patients

Tedavi Naif HBeAg-negatif Kronik Hepatit B Hastalarında Karaciğer Biyopsi Bulgularının Öngörülmesinde Laboratuvar, Radyolojik ve Non-invaziv Testlerin Değeri

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ABSTRACT

Aim: Chronic hepatitis B (CHB) remains a major cause of liver-related morbidity and mortality worldwide. Liver biopsy is considered the reference standard for assessing significant histopathological abnormality (SHA); however, its invasive nature and potential complications limit routine use. This study aimed to evaluate the diagnostic performance of laboratory, radiological, and non-invasive indices in predicting significant histopathological abnormalities in treatment-naïve, HBeAg-negative CHB patients.

Materials and Methods: In this retrospective single-center study, adult HBeAg-negative, treatment-naïve CHB patients who underwent liver biopsy between 2010 and 2024 were evaluated. Liver histology was assessed using the Ishak fibrosis score and Knodell histological activity index (HAI). Significant histological activity was defined as HAI ≥6 and/or fibrosis stage ≥2. Several non-invasive indices were calculated. Multivariable logistic regression analyses were performed to identify independent predictors of high HAI and significant fibrosis. Diagnostic performance was assessed using ROC curve analysis.

Results: A total of 148 patients were included. Higher hepatitis B virus DNA levels were independently associated with both high HAI [odds ratio (OR): 1.7 per $\log_{10}$ increase, p=0.002] and significant fibrosis (OR: 1.3 per $\log_{10}$ increase, p=0.044). Lower serum albumin levels were independently associated with high HAI (p=0.025). Among non-invasive markers, aspartate aminotransferase to platelet ratio index (APRI), showed the highest accuracy for predicting high HAI [area under the curve (AUC): 0.785; sensitivity 68.2%, specificity 85.0% at a cut-off >0.35]. The KING score demonstrated the best performance for predicting significant fibrosis (AUC: 0.768; sensitivity 61.5%, specificity 87.8%). GUCI and Fibrosis-4 index also showed good discriminatory ability.

Conclusion: Simple, routinely available non-invasive indices particularly APRI and KING scores demonstrate good diagnostic performance in identifying SHA in HBeAg-negative CHB patients. These tools may help reduce the need for liver biopsy in selected patients and support clinical decision-making, especially in settings where biopsy access is limited.

Keywords: APRI, chronic hepatitis B, KING score, liver biopsy, non-invasive markers

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ÖZ

Amaç: Kronik hepatit B (KHB), dünya genelinde karaciğer ilişkili morbidite ve mortalitenin başlıca nedenlerinden biri olmaya devam etmektedir. Karaciğer biyopsisi, anlamlı histopatolojik anormalliğin (SHA) değerlendirilmesinde referans standart olarak kabul edilmekle birlikte, invaziv yapısı ve olası komplikasyonları nedeniyle rutin kullanımını sınırlamaktadır. Bu çalışmada, tedavi almamış, hepatit B e antijeni negatif KHB hastalarında anlamlı histopatolojik anormalliğin öngörülmesinde laboratuvar, radyolojik ve non-invaziv indekslerin tanısal performansının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmada, 2010-2024 yılları arasında karaciğer biyopsisi yapılan erişkin, HBeAg-negatif, tedavi almamış KHB hastaları değerlendirildi. Karaciğer histolojisi, Ishak fibrozis skoru ve Knodell histolojik aktivite indeksi (HAI) kullanılarak değerlendirildi. Anlamlı histolojik aktivite HAI ≥6 ve/veya fibrozis evresi ≥2 olarak tanımlandı. Çeşitli non-invaziv indeksler hesaplandı. Yüksek HAI ve anlamlı fibrozisin bağımsız belirleyicilerini saptamak amacıyla çok değişkenli lojistik regresyon analizleri yapıldı. Tanısal performans ROC eğrisi analizi ile değerlendirildi.

Bulgular: Toplam 148 hasta çalışmaya dahil edildi. Daha yüksek hepatit B virüs (HBV) DNA düzeyleri, hem yüksek HAI [olasılık oranı (OR): $\log_{10}$ artış başına 1,7; p=0,002] hem de anlamlı fibrozis (OR: $\log_{10}$ artış başına 1,3; p=0,044) ile bağımsız olarak ilişkili bulundu. Daha düşük serum albümin düzeyleri yüksek HAI ile bağımsız olarak ilişkiliydi (p=0,025). Non-invaziv belirteçler arasında aspartate aminotransferaz/trombosit oranı indeksi (APRI), yüksek HAI'yi öngörmede en yüksek doğruluğu gösterdi [eğri altında kalan alan (AUC): 0,785; >0,35 kesim değerinde duyarlılık %68,2, özgüllük %85,0]. KING skoru ise anlamlı fibrozisi öngörmede en iyi performansı gösterdi (AUC: 0,768; duyarlılık %61,5, özgüllük %87,8). GUCI ve FIB-4 de iyi ayırt edici performans sergiledi.

Sonuç: Özellikle APRI ve KING skoru olmak üzere, kolay uygulanabilen ve rutin olarak kullanılabilen non-invaziv indeksler, HBeAg-negatif KHB hastalarında anlamlı histopatolojik anormalliklerin belirlenmesinde iyi tanısal performans göstermektedir. Bu araçlar, uygun hastalarda karaciğer biyopsisi gereksinimini azaltmaya yardımcı olabilir ve özellikle biyopsiye erişimin kısıtlı olduğu merkezlerde klinik karar verme sürecini destekleyebilir.

Anahtar Kelimeler: APRI, kronik hepatit B, KING skoru, karaciğer biyopsisi, non-invaziv belirteçler

INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global public health challenge. As reported by the World Health Organization in its latest update from July 2025, an estimated 254 million people were living with chronic hepatitis B (CHB) worldwide in 2022. Additionally, HBV-related complications, including cirrhosis and hepatocellular carcinoma (HCC), accounted for approximately 1.1 million deaths during the same year[1]. In Türkiye according to Viral Hepatitis Prevention and Control Program for 2018-2023, there have been approximately 3.3 million patients with CHB infection[2].

Chronic HBV infection is classified into five distinct clinical phases based on a combination of serological markers, liver function tests, HBV DNA levels, and liver biopsy findings. The decision to initiate antiviral therapy is primarily guided by serum alanine aminotransferase (ALT) levels and HBV DNA concentrations. In cases where these criteria are not clearly met, liver biopsy is recommended to assess the degree of hepatic inflammation and fibrosis[3].

Percutaneous liver biopsy is widely regarded as the gold standard for assessing the extent of liver injury. However, its application is limited due to its invasive nature and the risk of serious complications, including bleeding, pneumothorax, hemothorax, organ perforation, bile peritonitis, infections such as bacteremia, abscess formation, or sepsis, as well as hemobilia and neuralgia[4].

In Türkiye, antiviral treatment is covered by national health insurance for patients with evidence of cirrhosis or those with contraindications to liver biopsy, such as coagulopathy. In most other cases histopathological evaluation through liver biopsy is required to access reimbursed HBV treatment. The aim of this retrospective study is to evaluate the effectiveness of non-invasive methods in assessing liver damage, with the ultimate goal of reducing the need for liver biopsy.

MATERIALS AND METHODS

Study Setting and Patients

Patients who presented to the infectious diseases and clinical microbiology outpatient clinic between June 1, 2010, and June 1, 2024, were retrospectively evaluated. Adult patients (≥18 years) who were hepatitis B surface antigen (HBsAg) positive, hepatitis B e antigen (HBeAg) negative, treatment-naïve, and who had undergone liver biopsy were eligible for inclusion. During the study period, a total of 435 HBsAg positive patients were identified.

Patients were excluded if they had hepatitis C virus co-infection (n=3), human immunodeficiency virus co-infection (n=4), malignancy (n=4), insufficient clinical or laboratory data (n=45), HBeAg positivity (n=31), unavailable HBeAg records (n=41), or follow-up without liver biopsy (n=159). After applying these exclusion criteria, the final study cohort consisted of 148 treatment-naïve adult patients with HBeAg-negative CHB infection who underwent liver biopsy after a minimum follow-up period of one year.

Demographic characteristics (age and sex), laboratory parameters [hemoglobin, platelet count, aspartate aminotransferase (AST), ALT, total bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), international normalized ratio

(INR), alpha-fetoprotein (AFP) and albumin], virological data (HBV-DNA levels), and histopathological findings were obtained from patients' medical records. At the hospital where the study was conducted, the upper limit of normal for AST and ALT was defined as 40 IU/L.

Liver biopsy specimens were evaluated using the Ishak fibrosis score and the Knodell histological activity index (HAI) to assess fibrosis and necroinflammation[5]. Under the regulations of the Turkish Social Security Institution Healthcare Implementation Communiqué, histopathological criteria constitute a valid indication for initiating antiviral therapy in Türkiye. Patients meeting the definition of significant histological activity (fibrosis stage ≥2 and/or necroinflammatory activity grade ≥6) are considered eligible for treatment.

This study was approved by the Ethics Committee for Non-interventional Research of Tekirdağ Namık Kemal University by (decision no: 2025.215.11.12, date: 25.11.2025) in accordance with the Declaration of Helsinki.

Non-invasive İndices of Liver Fibrosis

- AST to platelet ratio index (APRI) = [(AST/AST upper limit of normal (U/L)/platelet count (10^9/L)] × 100,
- AST-ALT ratio = (AAR): AST (U/L)/ALT(U/L),
- Age-GGT-AST-platelet score AGAP) = [AST (U/L) x GGT (U/L)] × [age/platelet count^2 (10^9/L)],
- Fibrosis-4 index (FIB-4) = [age × AST (U/L)]/[platelet count (10^9/L) × √ALT (U/L)],
- Fibro alpha =1.35 + [AFP (μg/L) × 0.009584] + [AST (U/L)/ALT (U/L) × 0.243] - [platelet count (10^9/L) × 0.001624],
- Fibro Q = [(10 × age × AST (U/L) × INR)/(platelet count (10^9/L)] × ALT (U/L),
- Fibrosis-cirrhosis index (FCI) = [(ALP (U/L) × bilirubin (mg/dL)/[(albümin (g/dL) × platelet count (10^9/L)],
- DOHA score = 8.5 - [0.2 × albümin (g/dL) + [0.01× (AST (U/L)] - [0.02 ×platelet count (10^9/L)],
- GUCI = Normalized AST (U/L) x INR x 100/platelet count (10^9/L),
- KING's score = age x AST (U/L) x INR/platelet count (10^9/L)

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for MacOS, version 30.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages [n (%)], while continuous variables were summarized as median and interquartile range [median (IQR)]. Group comparisons were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, where appropriate. Multivariable logistic regression analyses were conducted to identify factors associated with high HAI (HAI ≥6) and fibrosis (fibrosis ≥2). Variables that were clinically relevant and found to be significant in univariable analyses were included in the multivariable models. To avoid collinearity, the AST/ALT ratio was used instead of AST and ALT individually, and HBV DNA levels were log-transformed ($\log_{10}$ HBV DNA) to represent viral replication better. Platelet count was included as a marker of portal hypertension, and serum albumin level was included as an indicator of hepatic functional reserve. To evaluate the diagnostic performance of non-invasive tests, widely used biochemical indices in CHB, including APRI, FIB-4, GUCI, KING, AGAP, DOHA, and Fibro-Q scores, were assessed using ROC curve analysis. The area under the curve (AUC), optimal cut-off values, sensitivity, and specificity were calculated for each score. A p-value <0.05 was considered statistically significant.

RESULTS

The distribution of demographic and clinical characteristics of patients according to low (HAI<6) and high (HAI ≥6) HAI scores is presented in Table 1. Patients in the high HAI group had significantly higher HBV DNA levels compared with those in the low HAI group (p<0.001). Markers of hepatocellular injury, including AST and ALT were also significantly elevated in the high HAI group (p<0.001). Furthermore, categorical analysis of ALT levels demonstrated that higher ALT strata were markedly more frequent among patients with high HAI scores (p<0.001). Although platelet counts tended to be lower in the high HAI group, this difference did not reach statistical significance (p=0.066). Serum albumin levels were significantly higher in the low HAI group (p=0.007), suggesting a relative preservation of hepatic functional reserve in patients with less severe histological inflammation. With regard to non-invasive liver injury indices, APRI, KING, GUCI, and AGAP scores were all significantly higher in patients with high HAI scores (p<0.001).

The demographic and clinical characteristics of patients with low (F<2) and high fibrosis (≥F2) scores are summarized in Table 2. Patients with high fibrosis had significantly higher HBV DNA levels(age and sex). Platelet counts were significantly lower in the high fibrosis group (p=0.010). Among the non-invasive tests, FIB-4, APRI, Fibro Q, KING, GUCI, DOHA and AGAP scores were significantly higher in patients with high fibrosis (p<0.001).

Each 1 $\log_{10}$ increase in HBV DNA levels was associated with an approximately 1.7-fold higher risk of having a high HAI score (≥6) (p=0.002). Patients with an AST/ALT ratio ≥1 had a nearly 60% lower likelihood of high HAI compared with those with an AST/ALT ratio <1 (OR: 0.4; p=0.034). Each 1 g/dL decrease in serum albumin level was associated with a significantly lower likelihood of high HAI (OR: 0.2; p=0.025) (Table 3).

Table 1. Comparison of laboratory and radiological findings of patients with HAI <6 and HAI ≥6

Parameters (n=148)	**HAI<6 (n=60)**	**HAI≥6 (n=88)**	**p-value**
	n (%) or median (IQR)	**n (%) or median (IQR)**	
Gender			**0.018**
Male	30 (50)	61 (69.3)	
Female	30 (50)	27 (30.7)	
Age (years)	45.5 (36.5-52)	46 (38.5-56.5)	0.228
HBV DNA (IU/L)	13126 (4372,5-55377)	293024 (12372-8189502)	**<0.001**
Fibrosis score			**<0.001**
<2	53 (88.3)	24 (27.3)	
≥2	7 (11.7)	64 (72.7)	
Hemoglobin (g/dL)	13.7 (12.9-15)	14.8 (13.3-15.3)	**0.032**
Platelet count (mm^3)	212 (178-251)	198 (164-235)	0.066
AST (IU/L)	21 (17-25.9)	35 (24-58)	**<0.001**
ALT (IU/L)	21 (16-30)	49.5 (28.5-100.1)	**<0.001**
<40	49 (81.7)	32 (36,4)	**<0.001**
40-80	7 (11.7)	26 (29.5)	
>80	4 (6.7)	30 (34.1)	
AST/ALT ratio			**<0.001**
<1	31 (51.7)	72 (81.8)	
≥1	29 (48.3)	16 (18.2)	
ALP (IU/L)	70.5 (53.5-88)	77 (63-95.5)	0.120
GGT (IU/L)	17 (12-23)	17.5 (12-27)	0.542
AFP (μg/L)	2.4 (1.6-3.7)	2.7 (1.7-4.2)	0.327
INR	1 (0.9-1.1)	1 (0.9-1.1)	0.496
Total bilirubin (mg/dL)	0.5 (0.3-0.7)	0.5 (0.3-0.8)	0.480
Albumin (g/L)	4.6 (4.4-4.8)	4.5 (4.2-4.6)	**0.007**
Ultrasonography			**0.006**
Normal	39 (65)	57 (64.8)	
Hepatic steatosis 1-2	20 (33.3)	15 (17)	
Hepatic steatosis 3-4	1 (1.7)	10 (11.4)	
Irregularity in liver contours	0 (0)	6 (6.8)	
Non-invasive tests			
FIB-4	0.9 (0.6-1.2)	1.1 (0.7-1.7)	**0.005**
APRI	0.2 (0.2-0.3)	0.5 (0.3-0.8)	**<0.001**
Fibro Q	1.5 (1-1.9)	1.8 (1.1-2.6)	0.106
AAR	1 (0.7-1.1)	0.7 (0.6-0.8)	**<0.001**
DOHA	3.6 (2.7-4.3)	4 (3.5-5)	**0.006**
Fibro alpha	1.3 (1.2-1.3)	1.2 (1.2-1.3)	0.202
FCI	0.04 (0.02-0.05)	0.05 (0.02-0.09)	**0.027**
GUCI	0.37 (0.27-0.49)	0.74 (0.44-0.12)	**<0.001**
KING	4.1 (2.7-6)	7.7 (4.6-16.3)	**<0.001**
AGAP	0.3 (0.2-0.8)	0.9 (0.4-2.2)	**<0.001**

AFP: Alpha-fetoprotein, AGAP, age-GGT-AST-platelet score, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, APRI: Aspartate aminotransferase to platelet ratio index, AST: Aspartate aminotransferase, AAR, AST/ALT ratio, FCI: Fibrosis-cirrhosis index, GGT: Gamma-glutamyl transferase, HBV: Hepatitis B virus, FIB-4: Fibrosis-4 index, INR: International normalized ratio, IQR: Interquartile range, significance set at p<0.05

Table 2. Comparison of laboratory and radiological findings of patients with fibrosis <2 and fibrosis ≥2

Parameters (n=148)	Fibrosis <2 (n=77)	Fibrosis ≥2 (n=71)	p-value
	n (%) or median (IQR)	n (%) or median (IQR)	
Gender			**0.013**
Male	40 (51.9)	51 (71.8)	
Female	37 (48.1)	20 (28.2)	
Age (years)	45 (35-53)	47 (39-57)	0.095
HBV DNA (IU/L)	16879 (5688-124233)	188239 (12372-8189502)	**<0.001**
HAI			**<0.001**
<6	53 (68.8)	7 (9.9)	
≥6	24 (31.2)	64 (90.1)	
Hemoglobin (g/dL)	13.8 (12.8-15)	14.9 (13.9-15.4)	**0.009**
Platelet count (mm^3)	213 (182-250)	193 (157-233)	**0.010**
AST (IU/L)	22 (18.3-32)	34 (24-65)	**<0.001**
ALT (IU/L)	24 (18-42)	49 (27-108)	**<0.001**
<40	56 (72.7)	25 (35.2)	**<0.001**
40-80	13 (16.9)	20 (28.2)	
>80	8 (10.4)	26 (36.6)	
AST/ALT ratio			**0.007**
<1	46 (59.7)	57 (80.3)	
≥1	31 (40.3)	14 (19.7)	
ALP (IU/L)	74 (54-90)	76 (61-96)	0.189
GGT (IU/L)	17 (12-22)	18 (12-30)	0.181
AFP (µg/L)	2.5 (1.6-3.7)	2.7 (1.7-4.6)	0.323
INR	1 (1-1.1)	1 (0.9-1.1)	0.286
Total bilirubin (mg/dL)	0.5 (0.3-0.7)	0.6 (0.3-0.7)	0.450
Albumin (g/L)	4.5 (4.4-4.7)	4.5 (4.3-4.6)	0.168
Ultrasonography			0.060
Normal	51 (66.2)	45 (63.4)	
Hepatic steatosis 1-2	22 (28.6)	13 (18.3)	
Hepatic steatosis 3-4	3 (3.9)	8 (11.3)	
Irregularity in liver contours	1 (1.3)	5 (7)	
Non-invasive tests			
FIB-4	0.9 (0.6-1.2)	1.2 (0.8-1.8)	**<0.001**
APRI	0.3 (0.2-0.4)	0.5 (0.3-0.8)	**<0.001**
Fibro Q	1.4 (0.9-1.8)	2.1 (1.4-3.2)	**<0.001**
AAR	0.9 (0.7-1.1)	0.7 (0.6-0.9)	**0.006**
DOHA	3.6 (2.8-4.3)	4.2 (3.5-5.1)	**0.001**
Fibro alpha	1.2 (1.2-1.3)	1.2 (1.2-1.3)	0.533
FCI	0.03 (0.02-0.06)	0.05 (0.03-0.08)	**0.029**
GUCI	0.43 (0.30-0.61)	0.75 (0.41-1.40)	**<0.001**
KING	4.5 (3.2-6.4)	8.2 (4.5-17.3)	**<0.001**
AGAP	0.4 (0.2-0.8)	0.9 (0.4-2.3)	**<0.001**

AFP: Alpha-fetoprotein, AGAP, age-GGT-AST-platelet score, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, APRI: Aspartate aminotransferase to platelet ratio index, AST: Aspartate aminotransferase, AAR, AST/ALT ratio, FIB-4: Fibrosis-4 index, GGT: Gamma-glutamyl transferase, HAI: Histological activity index, HBV: Hepatitis B virüs, INR: International normalized ratio, IQR: Interquartile range, significance set at p<0.05

Each 1 log₁₀ IU/mL increase in HBV DNA levels was independently associated with an approximately 1.3-fold increased risk of advanced fibrosis (p=0.044) (Table 4).

Among the non-invasive markers, the APRI score demonstrated the highest discriminatory ability for predicting high HAI scores, with an AUC of 0.785 (95% CI: 0.710-0.860). Using a cut-off value of >0.350 for APRI, the sensitivity and specificity were 68.2% and 85.0%, respectively. GUCI and KING scores also showed good discriminatory performance, with AUC values of 0.753 (95% CI: (0.673-0.833) and 0.740 (95% CI: 0.659-0.820), respectively (Figure 1). The KING score demonstrated the highest discriminatory ability for predicting advanced fibrosis, with an AUC of 0.768 (95% CI: 0.667-0.869). Using a cut-off value of >6.995, the sensitivity and specificity were 61.5% and 87.8%, respectively. The APRI [AUC: 0.756; (95% CI: 0.654-0.857); sensitivity: 66.7%, specificity: 75.5%] and FIB-4 [AUC: 0.747; (95% CI: 0.640-0.854); sensitivity: 69.2%, specificity: 79.6%] scores also showed comparably good performance in distinguishing fibrosis (Figure 2).

Table 3. Multivariable logistic regression analysis for HAI ≥6

Variables	OR (95% CI)	p-value
Gender		
Female	Reference	-
Male	2.0 (0.8-4.7)	0.118
HBV DNA (log)	1.7 (1.2-2.4)	**0.002**
AST/ALT ratio		
<1	Reference	
≥1	0.4 (0.2-0.9)	**0.034**
Platelet count (mm³)	1.0 (0.9-1.1)	0.812
Albumin (g/dL)	0.2 (0.1-0.8)	**0.025**
KING	1.0 (0.9-1.1)	0.933

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBV: Hepatitis B virus, HAI: Histological activity index, OR: Odds ratio, CI: Confidence interval, significance set at p<0.05

Table 4. Multivariable logistic regression analysis for fibrosis ≥2

Variables	OR (95% CI)	p-value
Gender		
Female	Reference	-
Male	1.8 (0.8-4.0)	0.118
HBV DNA (log)	1.3 (1.1-1.8)	**0.044**
AST/ALT ratio		
<1	Reference	
≥1	0.6 (0.3-1.5)	0.304
Platelet count (mm³)	1.0 (0.9-1.1)	0.477
Albumin (g/dL)	0.2 (0.1-0.8)	0.449
KING	1.0 (0.9-1.1)	0.394

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBV: Hepatitis B virus, HAI: Histological activity index, OR: Odds ratio, CI: Confidence interval, significance set at p<0.05

DISCUSSION

In this study, the demographic, laboratory, radiological, and non-invasive test characteristics of 148 patients diagnosed with CHB who underwent liver biopsy were evaluated. We aimed to retrospectively investigate the predictive factors for liver fibrosis or/and high HAI referred to as significant histopathological abnormality (SHA), in order to indicate the need for treatment. Multivariate analysis identified HBV-DNA as a significant predictor for detecting SHA in CHB infection. Additionally, ROC analysis showed that the APRI score demonstrated the highest discriminatory power for predicting significant histological activity, while the KING score was the most effective in identifying advanced fibrosis. GUCI score also exhibited good overall performance.

CHB represents a dynamic disease state resulting from the complex and evolving interaction between HBV replication and the host immune response[3]. Patients receiving antiviral therapy have been shown to experience a 40-60% reduction in the risk of developing HCC compared with untreated individuals[6]. Liver biopsy remains the gold standard for assessing the degree of hepatic fibrosis in patients with CHB; however, its invasive nature, potential for serious complications, high cost, and limitations related to the heterogeneous distribution of histopathological changes within the liver parenchyma have prompted the search for alternative assessment methods. Given the critical role of liver fibrosis in guiding treatment decisions and predicting complications in CHB, non-invasive, simple, and cost-effective scoring systems have been developed to facilitate fibrosis evaluation without the need for biopsy.

When our results were compared with those of Abdo et al.[7], who investigated predictors of highfibrosis (≥F2), notable similarities were observed. In both studies, advanced age, elevated AST levels, and reduced serum albumin and platelet counts emerged as independent predictors of significant fibrosis. In addition, Ozdemir et al.[8] demonstrated significant correlations between HAI scores and AST, ALT, and HBV DNA levels. Diktas et al.[9] reported significant correlations between HAI scores and AST, ALT, and HBV DNA levels in HBeAg-negative patients with CHB. In this study, several of these associations were corroborated. Higher AST and ALT levels, elevated HBV DNA, and particularly an AST/ALT ratio <1 were identified as predictors of significant histological activity in univariate analysis. In multivariate analysis, HBV DNA emerged as the main independent predictive factor. Previous studies have demonstrated a negative correlation between platelet count and the degree of fibrosis[10-12]. Consistent with these findings, our study showed lower platelet counts in patients with higher fibrosis scores (p=0.01). In addition, several studies have reported that reduced serum albumin levels are significant determinants in predicting the extent of liver damage[13,14]. In

Variables	AUC (95% CI)	p-value	Cut-off	Sensitivity (%)	Specificity (%)
AGAP	0.702 (0.616-0.789)	<0.001	>0.499	68.2	71.7
APRI	0.785 (0.710-0.860)	<0.001	>0.350	68.2	85.0
DOHA	0.633 (0.541-0.724)	0.004	>3.645	68.2	56.7
FIB-4	0.636 (0.546-0.726)	0.003	>1.265	40.9	86.7
GUCI	0.753 (0.673-0.833)	<0.001	>0.574	64.8	83.3
King	0.740 (0.659-0.820)	<0.001	>6.958	58.0	85.0

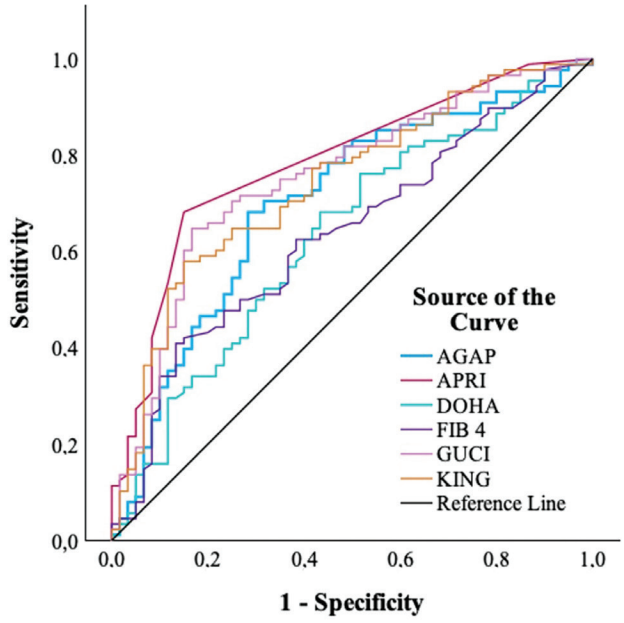

Figure 1. ROC curves of non-invasive scores for predicting high histological activity (HAI ≥6)

AGAP, age-GGT-AST-platelet score, AUC: Area under the curve, CI: Confidence interval, APRI: Aspartate aminotransferase to platelet ratio index, GGT: Gamma-glutamyl transferase, CI: Confidence interval, FIB-4: Fibrosis-4 index, HAI: Histological activity index, AST: Aspartate aminotransferase, GUCI: Gothenburg University Cirrhosis index, significance set at p<0.05

this study, serum albumin levels were found to be significantly lower in patients with HAI ≥6 in multivariate analysis (p=0.025).

Previous studies have reported that the AUC values of APRI for predicting significant fibrosis range from 0.61 to 0.787, with cut-off values varying between 0.47 and 1[15-18]. In this study, the cut-off value for significant fibrosis was determined to be 0.35, which is lower than those reported in the literature. In a study conducted by Lee et al.[14], APRI and FIB-4 scores were shown to have performance comparable to liver biopsy in risk stratification for liver-related morbidity and mortality among patients with non-alcoholic fatty liver disease. In a multicenter study conducted by Korkmaz et al.[15] in patients with CHB, APRI and FIB-4 were identified as the non-invasive models with the highest diagnostic accuracy for fibrosis staging. In the present study, APRI was found to have a particularly strong predictive value for identifying SHA.

In the study by Karacaer et al.[19] 277 patients were divided into two groups according to the Ishak fibrosis score: the first group included patients with mild fibrosis (0-2), and the second group comprised those with advanced fibrosis (3-6). In that study, GUCI, KING, APRI, and FIB-4 scores were found to be statistically significant in differentiating between the two groups. In a study conducted by Dong et al.[20] KING score was found to be the most successful scores in distinguishing significant fibrosis in patients with CHB. According to thisstudy, GUCI and KING scores were effective in differentiating advanced significant fibrosis from mild HAI in patients with CHB, with AUROC values of 0.731 and 0.768, respectively. In previous studies, both GUCI and KING scores also demonstrated significant discriminative ability, as reflected by their AUROC values, in distinguishing patients with advanced fibrosis from those with no or low-grade fibrosis[18,19]. In our study, ROC analysis demonstrated that the KING score was significantly effective in predicting fibrosis stage ≥2, with

Variables	AUC (95% CI)	p-value	Cut-off	Sensitivity (%)	Specificity (%)
AGAP	0.739 (0.633-0.846)	<0.001	>0.499	71.8	73.5
APRI	0.756 (0.654-0.857)	<0.001	>0.350	66.7	75.5
FIB-4	0.747 (0.640-0.854)	<0.001	>0.995	69.2	79.6
FIBRO-Q	0.706 (0.594-0.819)	<0.001	>1.825	61.5	77.6
GUCI	0.731 (0.624-0.838)	<0.001	>0.587	61.5	79.6
KING	0.768 (0.667-0.869)	<0.001	>6.995	61.5	87.8

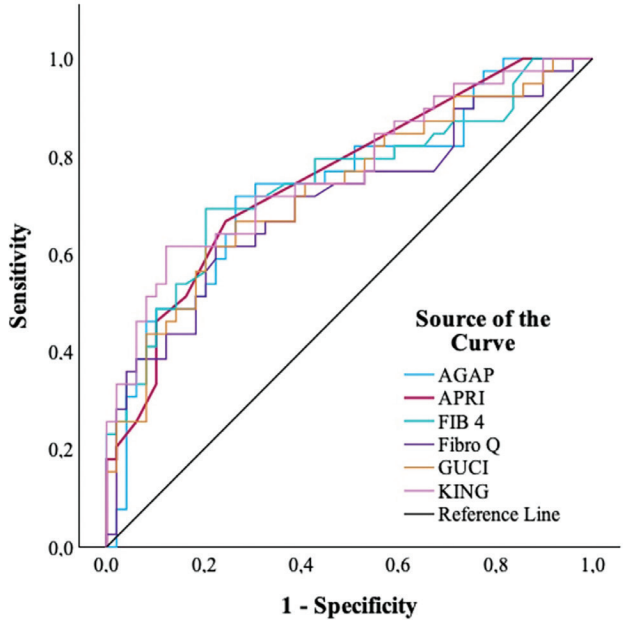

Figure 2. ROC curves of non-invasive scores for predicting significant fibrosis (fibrosis ≥2)

AGAP, age-GGT-AST-platelet score; AUC: Area under the curve, CI: Confidence interval, APRI: Aspartate aminotransferase to platelet ratio index, GGT: Gamma-glutamyl transferase, CI: Confidence interval, FIB-4: Fibrosis-4 index, AST: Aspartate aminotransferase, GUCI: Gothenburg University Cirrhosis index, significance set at p<0.05

an AUC of 0.768, and HAI ≥6, with an AUC of 0.740. Similarly, the GUCI score showed significant discriminative ability for both fibrosis stage ≥2 and HAI ≥6, yielding high AUC values of 0.731 and 0.758, respectively. In a study conducted by Xiao-Qiu Dong in treatment-naive patients, the Fibro-Q test demonstrated an AUC of 0.720 for predicting ≥F3 fibrosis and an AUC of 0.810 for predicting ≥F5 fibrosis[19]. In this study, the diagnostic performance of the Fibro-Q score for predicting SHA was found to be lower than that of other non-invasive tests.

Study Limitations

This study has several limitations. First, its single-center and retrospective design represents the most important limitation, which may restrict the generalizability of the findings. In addition, the inability to apply non-invasive methods across large and diverse patient populations, the use of different fibrosis scoring systems, variability in histopathological assessment by pathologists with differing levels of expertise, and heterogeneity in patient ethnicity and viral genotypes have hindered the standardization of any single non-invasive marker.

CONCLUSION

In conclusion, although the number of studies investigating non-invasive methods as alternatives to liver biopsy has increased in recent years, an adequate level of diagnostic accuracy has not yet been achieved. In addition to APRI, we believe that the King score is particularly valuable for providing insight into significant histological activity of the liver and may serve as a useful adjunct in the non-invasive assessment of disease severity. These findings suggest that simple, APRI and KING scores may serve as valuable tools in the clinical evaluation of CHB patients, potentially reducing unnecessary liver biopsy in selected patients.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee for Non-interventional Research of Tekirdağ Namık Kemal University by (decision no: 2025.215.11.12, date: 25.11.2025) in accordance with the Declaration of Helsinki.

Informed Consent: The study is a retrospective study.

Footnotes

Authorshıp Contribution

Concept: M.N.Ö., N.T., İ.E., Design M.N.Ö., N.T., İ.E., S.B., Data Collection or Processing: B.E., B.S.S., M.Ö., A.Ç., İ.E. Analysis or Interpretation: B.E., B.S.S., M.Ö., A.Ç., İ.E., Literature Search: M.N.Ö., N.T., S.B., İ.E., Writing: M.N.Ö., İ.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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