Research Article

DOI: 10.4274/vhd.galenos.2026.2026-6-3

Viral Hepat J

Comparison of Non-Invasive Markers with Liver Biopsy for Detecting Fibrosis in Patients with Chronic Hepatitis B

Kronik Hepatit B Hastalarında Fibrozis Belirlenmesinde İnvaziv Olmayan Belirteçlerin Karaciğer Biyopsisi ile Karşılaştırılması

Hande İdil Tüz[1], Nihal Pişkin[2], Güven Çelebi[2], Hande Aydemir[2], Emre Horuz[3], Mustafa Çağatay Büyükuysal[4], Mehmet Ali Tüz[5]

[1]*Balıkesir Atatürk City Hospital, Department of Infectious Diseases and Clinical Microbiology, Balıkesir, Türkiye*

[2]*Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Zonguldak, Türkiye*

[3]*Zonguldak Atatürk State Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Zonguldak, Türkiye*

[4]*Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Biostatistics, Zonguldak, Türkiye*

[5]*Balıkesir University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Balıkesir, Türkiye*

ABSTRACT

Objectives: Liver biopsy is the gold standard for determining liver fibrosis in chronic hepatitis B (CHB); however, alternative methods, such as non-invasive indirect serum markers, are being developed because it is an invasive procedure. This study aimed to compare fibrosis values from liver biopsies of patients with CHB to non-invasive serum markers to determine the efficacy of these markers.

Materials and Methods: Patients with a diagnosis of CHB who underwent a liver biopsy were retrospectively included. According to the Ishak fibrosis staging system, patients were divided into two groups: mild fibrosis (F0-2) and advanced fibrosis (F3-6). Age-platelet index, aspartate aminotransferase (AST)-to-platelet ratio index (APRI), AST/alanine aminotransferase (ALT) ratio (AAR), fibrosis-4 index, Fibro-Q, and King's score were calculated. The markers were compared with respect to their ability to distinguish advanced fibrosis.

Results: A total of 183 patients were included. Of these, mild fibrosis (≤2) was detected in 101 patients and advanced fibrosis (>2) in 82. At the beginning of treatment, ALT, AST, the histological activity index, and HBV-DNA levels were significantly higher in the advanced fibrosis group ($p<0.05$). APRI, King's score, and AAR (inversely) were statistically significant for detecting advanced fibrosis ($p<0.05$). The area under the receiver operating characteristic values for APRI, AAR, and King's score were 0.611, 0.637, and 0.632, respectively.

Conclusion: APRI and King's scores were statistically significant in differentiating advanced from mild fibrosis, but their efficacy was limited.

ÖZ

Amaç: Kronik hepatit B (KHB) enfeksiyonunda karaciğer fibrozisini belirlemede karaciğer biyopsisi altın standart olup, girişimsel bir işlem olması nedeni ile alternatif yöntemler araştırılmaktadır. Çalışmamızda, KHB tanılı hastaların karaciğer biyopsisindeki fibrozis değerlerinin invaziv olmayan serum belirteçleri ile karşılaştırılarak bu belirteçlerin etkinliklerinin saptanması amaçlanmıştır.

Gereç ve Yöntemler: KHB tanılı, karaciğer biyopsisi yapılmış hastalar çalışmaya retrospektif olarak dahil edilmiştir. Hastalar Ishak fibrozis evrelendirme sistemine göre hafif fibrozis (F0-2) ve ileri fibrozis (F3-6) olmak üzere iki gruba ayrıldı. Gruplarda yaş-trombosit (AP) indeksi, aspartat aminotransferaz (AST)/trombosit oranı indeksi (APRI), AST/alanin aminotransferaz (ALT) oranı (AAR), fibrozis-4 indeksi, fibro-katsayısı ve King skoru hesaplanarak ileri fibrozisi ayırt edicilik açısından birbirleriyle karşılaştırıldı.

Bulgular: Kriterleri karşılayan 183 hasta çalışmada değerlendirildi. 101 hastada hafif fibrozis (≤2), 82 hastada ise ileri fibrozis (>2) tespit edildi. İleri fibrozis grubunda ALT, AST, histolojik aktivite indeksi ve tedavi başlangıcındaki HBV-DNA seviyeleri istatistiksel olarak anlamlı düzeyde daha yüksekti ($p<0,05$). APRI, King skoru ve AAR (ters ilişki ile) ileri fibrozisi saptamada istatistiksel olarak anlamlı saptandı ($p<0,05$). Eğri altında kalan alan değerleri sırasıyla; APRI için 0,611, AAR için 0,637 ve King's skor için 0,632 olarak bulundu.

Sonuç: APRI ve King's skorlama sistemleri ileri fibrozisi hafif fibrozisten ayırmada istatistiksel olarak anlamlı bulunmuş ancak bu belirteçlerin

Address for Correspondence: Hande İdil Tüz, MD, Balıkesir Atatürk City Hospital, Department of Infectious Diseases and Clinical Microbiology, Balıkesir, Türkiye

E-mail: hidil233@hotmail.com **ORCID ID:** orcid.org/0000-0003-4483-0906

Received: 24.06.2026 **Accepted:** 16.09.2026 **Epub:** 25.11.2026

Cite this article as: Tüz Hİ, Pişkin N, Çelebi G, Aydemir H, Horuz E, Büyükuysal MÇ, Tüz MA. Comparison of non-invasive markers with liver biopsy for detecting fibrosis in patients with chronic hepatitis B. Viral Hepat J. [Epub Ahead of Print]

Copyright© 2026 The Author(s). Published by Galenos Publishing House on behalf of the Viral Hepatitis Society.

This is an open access article under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

AAR, displaying an inverse relationship, likely reflected inflammatory activity rather than actual fibrosis. Liver biopsy appears to be the gold standard for diagnosing fibrosis in patients with CHB. New studies are needed to develop non-invasive markers.

Keywords: Chronic hepatitis B, fibrosis, biopsy, biomarkers, algorithms

etkinlikleri zayıf görülmüştür. AAR ise ters bir ilişki göstererek fibrozisten ziyade enflamatuvar aktiviteyi yansıtmıştır. KHB hastalarında fibrozis tanısında karaciğer biyopsisi altın standart olmaya devam etmektedir. İnvaziv olmayan belirteçlerin geliştirilmesi için yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kronik hepatit B, fibrozis, biyopsi, biyobelirteçler, algoritmalar

Introduction

Infections caused by the hepatitis B virus (HBV) constitute a major global health problem, affecting approximately 248 million people worldwide and causing about 686,000 deaths annually (1). Liver cirrhosis and hepatocellular carcinoma (HCC), the most significant complications of chronic hepatitis B (CHB) infection, are the primary causes of morbidity and mortality associated with this disease (1). Türkiye, where HBsAg positivity is approximately 4%, is classified as a low- to middle-endemic country for HBV; however, the fact that 40-50% of liver transplants in our country are performed due to HBV-induced liver failure and HCC underscores the severity of the problem (2).

Determining treatment indications and monitoring the course of the disease in CHB patients are based on HBV-DNA levels, alanine aminotransferase (ALT) elevation, and the degrees of necroinflammation and fibrosis in the liver (3). Liver biopsy is still considered the gold standard method for the detection and staging of liver fibrosis (4). Nevertheless, the fact that biopsy is an invasive procedure requiring hospitalization, carries a wide range of potential complications, and demands experienced personnel for its application are significant disadvantages (5).

These limitations have necessitated the investigation of non-invasive methods that carry no risk of complications, are inexpensive, easy to perform, and can be applied repeatedly as an alternative to liver biopsy in evaluating liver fibrosis (4,6). Today, indirect serum markers reflecting changes in liver functions—including platelet count, coagulation parameters, aspartate aminotransferase (AST), and ALT levels—are frequently investigated (6). In the literature, the success of algorithms such as the age-platelet (AP) index, AST to platelet ratio index (APRI), AST/ALT ratio (AAR), fibrosis-4 index (FIB-4), Fibro-Q, and King's score in predicting the fibrosis stage is widely debated (7,8,9,10). In accordance with national clinical guidelines and health insurance reimbursement criteria, non-invasive scoring systems such as APRI and FIB-4 are increasingly used to guide decisions about treatment initiation, especially when liver biopsy is contraindicated or unavailable. However, it is well established that the sensitivity and specificity of these surrogate tests for accurately staging fibrosis—particularly in differentiating intermediate stages—are limited. This limitation underscores the clinical necessity for supportive adjunctive tests and the evaluation of novel scoring models with higher diagnostic accuracy to correctly interpret clinical outcomes and avoid both under- and over-treatment.

In this study, we aimed to compare the fibrosis stages detected by liver biopsy in patients with CHB under follow-up, with the efficacy of the aforementioned non-invasive serum markers.

Materials and Methods

Study Design and Patient Selection

This study retrospectively analyzed patients who were followed up with a diagnosis of CHB between September 15, 2014, and September 15, 2019, at the Infectious Diseases Clinic of the Zonguldak Bülent Ecevit University Health Application and Research Center.

Inclusion criteria were: being older than 18 years of age, having HBsAg positivity for at least 6 months, having undergone a liver biopsy due to CHB, and having laboratory parameters [AST, ALT, platelet, international normalized ratio (INR)] necessary for score calculations measured within the 1-month period prior to the biopsy. Patients with concomitant hepatitis C virus, hepatitis D virus, or human immunodeficiency virus coinfections; those presenting overt signs of cirrhosis (splenomegaly, ascites, esophageal varices); and those receiving specific antiviral treatment for CHB prior to the biopsy were excluded from the study.

Clinical, Laboratory, and Histopathological Evaluation

Patients' demographic data and laboratory parameters were extracted from follow-up files. Liver biopsies were evaluated by the department of medical pathology using the Ishak scoring system. Patients were divided into two groups: "mild fibrosis" (stages 0, 1, 2) and "advanced fibrosis" (stages 3, 4, 5, 6), based on the fibrosis stage detected on biopsy.

The scoring systems were calculated using the following formulas:

• **APRI:** [AST (U/L) / AST upper limit of normal] / [platelet count ($x10^9$/L) x 100]

• **AAR:** AST (U/L) / ALT (U/L)

• **FIB-4:** [Age x AST (U/L)] / [platelet count ($x10^9$/L) x $(ALT)^{1/2}$]

• **Fibro-Q:** [10 x age x AST (U/L) x INR] / [platelet count ($x10^9$/L) x ALT]

• **King's score:** [Age x AST (U/L) x INR] / platelet count ($x10^9$/L)

• **AP index:** Age ≤30=0 points, 31-40=1 point, 41-50=2 points, 51-60=3 points, 61-70=4 points, and ≥71=5 points; platelet count >225,000=0 points, 200,000-224,000=1 point, 175,000-199,000=2 points, 150,000-174,000=3 points, 125,000-149,000=4 points, and

≤124,000=5 points. The score is obtained by summing the points corresponding to age and platelet count.

The upper limit of normal for AST used in the APRI calculation was defined as 40 U/L in our laboratory.

Statistical Analysis

Statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). The conformity of continuous variables to a normal distribution was evaluated using the Shapiro-Wilk test; normally distributed data were expressed as mean ± standard deviation, and non-normally distributed data as median (minimum-maximum). Categorical variables were presented as frequencies and percentages. The independent samples t-test or one-way analysis of variance (ANOVA) was used for group comparisons of normally distributed variables, whereas the Mann-Whitney U or Kruskal-Wallis tests were utilized for non-normally distributed variables. Pearson's chi-square, Yates's chi-square, or Fisher's exact test were employed for intergroup comparisons of categorical variables. A p-value of <0.05 was considered statistically significant. receiver operating characteristic (ROC) curve analysis was applied to evaluate the discriminative ability of the 6 scoring systems to differentiate advanced from mild fibrosis, and the area under the ROC curve (AUROC) was calculated. Cut-off values for relevant parameters were determined using the Youden index. The DeLong test was used for the statistical comparison of the area under the curves (AUCs).

Results

During the specified period, 598 patients with a diagnosis of chronic viral HBV who were under follow-up were identified. A total of 190 of these patients underwent a liver biopsy. Seven patients who did not meet the inclusion criteria were excluded, and the remaining 183 patients were evaluated.

Of the patients, 100 (54.6%) were male and 83 (45.4%) were female, with a mean age of 38.62±12.61 years. Whereas HBeAg positivity was present in 35 patients (19.12%), 146 patients (79.78%) were HBeAg-negative and anti-HBe-positive. Data for HBeAg or anti-HBe were unavailable for 2 patients. The lowest baseline HBV-DNA level, measured before biopsy, was 164 IU/mL; the highest was 1,050,000,000 IU/mL, and the median value was 41,000 IU/mL. Mild fibrosis (≤2) was detected in 101 patients, and advanced fibrosis (>2) in 82 patients.

When the two fibrosis groups were compared with respect to clinical and laboratory data, no statistically significant differences were observed in age, gender, HBeAg status, INR, or platelet values (p>0.05). Conversely, ALT and AST values, histological activity index (HAI) scores, and baseline HBV-DNA levels were significantly higher in the advanced fibrosis (stage >2) group than in the mild fibrosis group (p<0.05) (Table 1).

A detailed evaluation of the cohort revealed that only two patients had baseline HBV-DNA levels <2000 IU/mL. Both patients were HBeAg-negative and anti-HBe-positive. Notably, despite the low viremia, one patient (known to be HBsAg-positive for 8 years) exhibited advanced fibrosis (Stage 3), while the other (HBsAg-positive for 5 years) had mild fibrosis (Stage 1). Although the sample size of this subset is too small for statistical subgroup analysis, the presence of advanced fibrosis in a low-viremic patient highlights the critical clinical need for evaluation by liver biopsy or close monitoring, even at lower HBV-DNA thresholds.

When comparing non-invasive markers, the medians of the APRI and King's scores were significantly higher in the advanced

Table 1. Comparison of demographic data and laboratory tests of patients with mild (≤2) and advanced (>2) fibrosis

		Fibrosis		p
		Mild (≤2) (n=101)	**Advanced (>2) (n=82)**	
Mean age		37.0±11.8	40.6±13.4	0.062
Gender	**Female**	44.6% n=45	46.3% n=38	0.809
	Male	54.4% n=56	53.7% n=44	
HBe	**HBeAg+**	16.8% n=17	22.2% n=18	0.513
	Anti-HBe+	81.2% n=82	78% n=64	0.513
ALT (U/L)	**Median (min-max)**	29 (10-219)	40.5 (11-483)	**0.001**
AST (U/L)	**Median (min-max)**	26 (15-185)	34.5 (11-204)	**0.005**
INR	**Median (min-max)**	1 (0.8-1.29)	1.03 (0.83-1.22)	0.331
PLT (x10^9/L)	**Median (min-max)**	222 (93-388)	220 (124-420)	0.845
HAI	**Median (min-max)**	5 (2-9)	7 (3-16)	**<0.001**
DNA baseline (IU/mL)	**Median (min-max)**	19100 (164-1.05x10^9)	41800 (1510-1.7x10^8)	**<0.001**

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, INR: International normalized ratio, PLT: Platelet, HAI: Histological activity index, HBeAg: Hepatitis B e antigen

fibrosis group (p=0.009 and p=0.002, respectively). The AAR value was significantly lower in the advanced fibrosis group (p=0.001). The median FIB-4 score was higher in the advanced fibrosis group, but the difference did not reach statistical significance (p>0.05). No statistically significant differences in AP and Fibro-Q scores were observed between the mild and advanced fibrosis groups (p>0.05) (Table 2).

In the ROC analysis performed to measure the diagnostic power of the scoring systems in determining advanced fibrosis, APRI (AUC: 0.611, p=0.012), AAR (AUC: 0.637, p=0.001), and King's score (AUC: 0.632, p=0.002) were found to be significant. When the cut-off values were examined, 0.44 for APRI (50% sensitivity, 76.24% specificity); <0.69 for AAR (indicating that values below 0.69 predict advanced fibrosis; 39.02% sensitivity, 85.15% specificity); and 7.74 for King's score (39.02% sensitivity, 85.15% specificity) were determined to be the optimal cut-off points (Table 3). The AUCs of APRI, AAR, King's score, and FIB-4 were compared using the DeLong test, and no statistically significant differences were detected among them (p>0.05). Figure 1 shows the ROC curves for APRI, AAR, King's score, and FIB-4.

Furthermore, we performed multivariate logistic regression analyses to evaluate whether a combination model improves diagnostic accuracy. The combination of APRI, King's score, and AAR yielded an AUROC of 0.660. Since AAR was shown to have an inverse relationship, reflecting necroinflammation rather than fibrosis, we also tested a combined model excluding AAR and incorporating APRI, King's score, and FIB-4. This fibrosis-focused combination model resulted in a maximum AUROC of 0.663.

Discussion

The degree of liver fibrosis in patients with CHB is of great importance in predicting the risk of cirrhosis and HCC and in determining treatment indications (11). In our study, to detect advanced fibrosis in CHB patients, we compared the efficacy of widely studied non-invasive scoring systems with liver biopsy, which remains the gold standard.

In recent years, the current guidelines of international scientific organizations, such as the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases, increasingly emphasize the role of non-invasive tests (NITs) in clinical practice due to the invasive nature, cost, and limitations of liver biopsies (12,13,14). In particular, the current HBV management guidelines of the World Health Organization recommend the use of scores such as APRI and FIB-4 as first-line triage tests in resource-limited regions to increase access to treatment (15). However, the diagnostic power of these serum markers in distinguishing the fibrosis stage in CHB patients, especially in populations with normal or mildly elevated transaminase levels, remains a controversial topic (12,16).

In our study, transaminase levels, the HAI, and HBV-DNA ratios were higher in the advanced fibrosis group, as expected. Conversely, the lack of a significant difference between the groups with respect to INR and platelet counts can be explained by the initial exclusion of overt cirrhosis cases and advanced cirrhotic patients with coagulopathy, who inherently have a contraindication to biopsy.

The APRI score significantly differentiated advanced fibrosis in our study (AUROC: 0.611). In the literature, in a similar study

Table 2. Comparison of the median and min-max values of scoring systems in patients with mild (≤2) and advanced (>2) fibrosis

	Mild fibrosis (n=101) median (min-max)	Advanced fibrosis (n=82) median (min-max)	p
AP	4 (2-9)	5 (2-8)	0.066
APRI	0.323 (0.15-3.30)	0.453 (0.11-2.84)	**0.009**
AAR	0.885 (0.47-2.5)	0.812 (0.37-1.6)	**0.001**
FIB4	0.771 (0.31-3.15)	0.964 (0.29-3.25)	0.065
FibroQ	1.5 (0.49-5.57)	1.510 (0.33-4.56)	0.455
King's score	4.314 (1.85-29.05)	6.026 (1.06-49.5)	**0.002**

AP: Age-platelet, APRI: Aspartate aminotransferase-to-platelet ratio index, AAR: Aspartate aminotransferase/alanine aminotransferase ratio, FIB4: Fibrosis-4 index

Table 3. Results of ROC curve analysis of scoring systems in identifying advanced fibrosis

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	p
AP	5	34.15%	81.19%	59.58%	84.16%	0.578	0.0675
APRI	0.44	50%	76.24%	63.08%	65.24%	0.611	**0.0116**
AAR	0.69	39.02%	85.15%	68.07%	63.17%	0.637	**<0.001**
FIB4	0.73	70.73%	48.51%	52.72%	67.12%	0.578	0.0703
FibroQ	2.13	85.37%	25.74%	48.27%	69.17%	0.532	0.457
King's score	7.74	39.02%	85.15%	68.08%	63.23%	0.632	**<0.001**

APRI: Aspartate aminotransferase-to-platelet ratio index, AAR: Aspartate aminotransferase/alanine aminotransferase ratio, FIB4: Fibrosis-4 index, AUC: Area under the curve, ROC: Receiver operating characteristic, PPV: Positive predictive value, NPV: Negative predictive value

conducted by Ucar et al. (17) using the METAVIR system, the AUROC value (0.662) and efficacy results showed great parallelism with our data. However, the reason why this value remains slightly lower than the figures reported in some meta-analyses (AUROC: ~0.79) may be due to heterogeneities in the age and infection durations of the study populations (18,19). Recent data in the current literature also suggest that the APRI score can be useful as a rule-out test in CHB, but it is insufficient on its own for the definitive diagnosis of moderate-to-advanced fibrosis (12).

AAR score showed a significant relationship with advanced fibrosis in our study (AUROC: 0.69); however, the ratio was paradoxically lower in the advanced fibrosis group. Normally, the AAR tends to rise and exceed 1.0 as the disease progresses toward cirrhosis (20,21). The inverted relationship observed in our cohort (an optimal cut-off of <0.69 for predicting advanced disease) is likely attributable to our study design, which excluded patients with overt cirrhosis. Consequently, in our cohort, the advanced fibrosis group exhibited more pronounced necroinflammation (indicated by significantly higher HAI and ALT levels), which disproportionately elevated ALT and lowered the AAR. Therefore, in this specific setting, AAR may be tracking inflammatory activity rather than actual fibrosis, suggesting that AAR is not a highly reliable independent marker for fibrosis staging in non-cirrhotic CHB patients.

Furthermore, FIB-4, Fibro-Q, and AP scores were not statistically significant predictors of advanced fibrosis in our patient cohort. There are studies in the literature where the FIB-4 score was found to be highly successful (AUROC: 0.81-0.91) (22,23). The main reason for this discrepancy may be that the median AST and ALT levels in our patient population were significantly lower than those in cohorts of studies reporting high success rates. Indeed, large cohort studies incorporating real-world data published in recent years support the finding that non-invasive models such as FIB-4 and APRI, which were originally developed for chronic hepatitis C infection, do not provide a significant advantage in predicting significant inflammation and advanced fibrosis in CHB patients with normal or borderline-high transaminases (19). Likewise, in the study conducted by Zeng et al. (24), similar to our patient cohort, it was reported that the Fibro-Q score was not a significant predictor (AUROC: 0.580). King's score, initially developed for patients with hepatitis C, was one of the more successful models for differentiating advanced fibrosis in our study (AUROC: 0.632). Karacaer et al. (25) reported that King's score was similarly highly significant (AUROC: 0.807) in CHB patients. Minimal differences in cut-off values may reflect differences in mean patient age across studies, as age is a major determinant of this score.

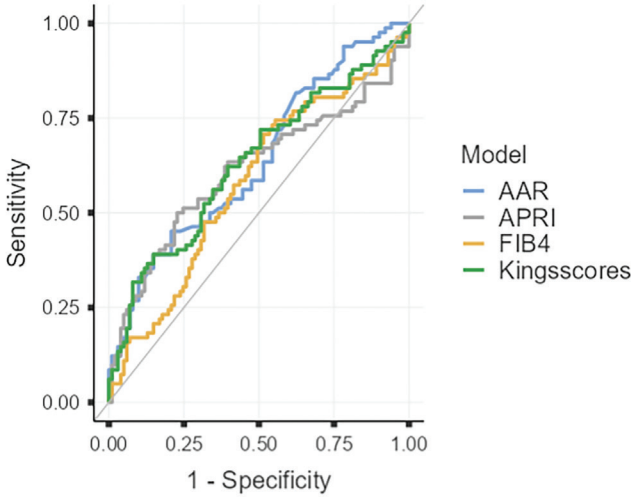

Figure 1. Receiver operating characteristic curves demonstrating the diagnostic performance of APRI, AAR, King's score, and FIB-4 in predicting advanced liver fibrosis in patients with chronic hepatitis B

APRI: Aspartate aminotransferase-to-platelet ratio index, AAR: Aspartate aminotransferase/alanine aminotransferase ratio, FIB4: Fibrosis-4 index

We also investigated whether combining these scores into a single multivariate model could enhance the overall diagnostic accuracy for predicting advanced fibrosis. Although the combination models (e.g., integrating APRI, King's score, and FIB-4) provided a marginal statistical increase in the AUROC (up to 0.663) compared to individual scores, the diagnostic performance remained in the "weak" ategory. This indicates that, even when combined, these indirect serum markers lack the necessary accuracy to confidently bypass liver biopsy and reaffirms that they should not be used as isolated decision-making tools in non-cirrhotic CHB patients.

Study Limitations

The main limitations of this study are its retrospective nature, the possibility that the evaluated biopsies could have been reported by different pathologists across varying clinical routines, and the possibility that the time interval between laboratory sampling and biopsy may have differed slightly. In addition to these, as detailed in the current NITs guidelines of EASL, it is known that combining indirect serum markers with radiological/physiological measurements such as liver stiffness measurement (elastography)—rather than using them alone—significantly increases diagnostic specificity (12). The absence of elastography data in our study and the reliance on single NIT algorithms for evaluation should also be considered limitations. Another major limitation of our study is the lack of evaluation of potential confounding variables. Routine laboratory parameters incorporated into these scoring systems (e.g., AST, ALT, platelet count) can be directly influenced by unmeasured factors such as concurrent alcohol consumption, undiagnosed hyperlipidemia, concomitant use of hepatotoxic medications, and body mass index (body mass index/obesity). The inability to control for these variables may have affected the diagnostic performance of the scoring systems.

Conclusion

Although APRI, AAR, and King's scores were statistically significant in differentiating advanced (≥Stage 3) from mild (≤Stage 2) fibrosis in CHB patients, their overall diagnostic performances remained weak, with AUROC values ranging between 0.611 and 0.637. Furthermore, AAR exhibited an inverse relationship, suggesting that it reflects necroinflammatory activity rather than fibrosis in this cohort.

Consequently, liver biopsy retains its irreplaceable position as the gold standard for accurate fibrosis staging and clinical decision-making. Based on our findings, we suggest that when APRI and King's scores exceed high-risk thresholds, clinicians should strongly consider a liver biopsy regardless of patient age, sex, and baseline HBV-DNA levels to avoid missing advanced fibrosis. Ultimately, there remains a critical need for novel non-invasive tools with higher diagnostic power; prospective studies should prioritize multi-parameter models that combine serum biomarkers with advanced imaging methods.

Ethics

Ethics Committee Approval: This study was approved by the Zonguldak Bülent Ecevit University Clinical Research Ethics Committee on October 16, 2019, under decision no. 2019/16.

Informed Consent: As this is a retrospective study, consent was not obtained from patients; all data were anonymized and analyzed in accordance with standard institutional patient confidentiality principles.

Footnotes

This study was conducted for the purpose of a Turkish Infectious Diseases and Clinical Microbiology specialty thesis.

Authorship Contributions

Surgical and Medical Practices: H.İ.T., N.P., G.Ç., H.A., E.H., Concept: H.İ.T., N.P., Design: H.İ.T., N.P., G.Ç., Data Collection or Processing: H.İ.T., M.A.T., Analysis or Interpretation: H.İ.T., N.P., E.H., M.Ç.B., Literature Search: H.İ.T., N.P., H.A., Writing: H.İ.T., N.P., G.Ç., H.A., E.H., M.Ç.B., M.A.T.

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

Financial Disclosure: The authors declare no financial support.

References

1. Chang MS, Nguyen MH. Epidemiology of hepatitis B and the role of vaccination. Best Pract Res Clin Gastroenterol. 2017;31:239-247.
2. Akarca US, Baykam N, Güner R, Günşar F, İdilman R, Kaymakoğlu S, Köksal İ, Tabak F, Yamazhan T. Eliminating viral hepatitis in Turkey: achievements and challenges. Viral Hepati J. 2022;28:47-54.
3. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-398.
4. Agbim U, Asrani SK. Non-invasive assessment of liver fibrosis and prognosis: an update on serum and elastography markers. Expert Rev Gastroenterol Hepatol. 2019;13:361-374.
5. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. Hepatology. 2009;49:1017-1044.
6. Enomoto M, Morikawa H, Tamori A, Kawada N. Noninvasive assessment of liver fibrosis in patients with chronic hepatitis B. World J Gastroenterol. 2014;20:12031-12038.
7. Poynard T, Bedossa P. Age and platelet count: a simple index for predicting the presence of histological lesions in patients with antibodies to hepatitis C virus. METAVIR and CLINIVIR Cooperative Study Groups. J Viral Hepat. 1997;4:199-208.
8. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38:518-526.
9. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, S Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M; APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43:1317-1325.
10. Cross TJ, Rizzi P, Berry PA, Bruce M, Portmann B, Harrison PM. King's score: an accurate marker of cirrhosis in chronic hepatitis C. Eur J Gastroenterol Hepatol. 2009;21:730-738.
11. Branchi F, Conti CB, Baccarin A, Lampertico P, Conte D, Fraquelli M. Non-invasive assessment of liver fibrosis in chronic hepatitis B. World J Gastroenterol. 2014;20:14568-14580.
12. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021;75:659-689.
13. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2025;83:502-583.
14. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560-1599.
15. World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK614989/
16. Wang Y, Xu MY, Zheng RD, Xian JC, Xu HT, Shi JP, Li SB, Qu Y, Dong YW, Lu LG. Prediction of significant fibrosis and cirrhosis in hepatitis B e-antigen negative patients with chronic hepatitis B using routine parameters. Hepatol Res. 2013;43:441-451.
17. Ucar F, Sezer S, Ginis Z, Ozturk G, Albayrak A, Basar O, Ekiz F, Coban S, Yuksel O, Armutcu F, Akbal E. APRI, the FIB-4 score, and Forn's index have noninvasive diagnostic value for liver fibrosis in patients with chronic hepatitis B. Eur J Gastroenterol Hepatol. 2013;25:1076-1081.
18. 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.
19. Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology. 2015;61:292-302.
20. Eminler AT, Ayyildiz T, Irak K, Kiyici M, Gurel S, Dolar E, Gulten M, Nak SG. AST/ALT ratio is not useful in predicting the degree of fibrosis in chronic viral hepatitis patients. Eur J Gastroenterol Hepatol. 2015;27:1361-1366.
21. Teshale E, Lu M, Rupp LB, Holmberg SD, Moorman AC, Spradling P, Vijayadeva V, Boscarino JA, Schmidt MA, Gordon SC; CHeCS Investigators. 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;21:917-920.
22. Mallet V, Dhalluin-Venier V, Roussin C, Bourliere M, Pettinelli ME, Giry C, Vallet-Pichard A, Fontaine H, Pol S. The accuracy of the FIB-4 index for the diagnosis of mild fibrosis in chronic hepatitis B. Aliment Pharmacol Ther. 2009;29:409-415.
23. Kim BK, Kim DY, Park JY, Ahn SH, Chon CY, Kim JK, Paik YH, Lee KS, Park YN, Han KH. Validation of FIB-4 and comparison with other simple noninvasive indices for predicting liver fibrosis and cirrhosis in hepatitis B virus-infected patients. Liver Int. 2010;30:546-553.
24. Zeng X, Xu C, He D, Li M, Zhang H, Wu Q, Xiang D, Wang Y. Performance of several simple, noninvasive models for assessing significant liver fibrosis in patients with chronic hepatitis B. Croat Med J. 2015;56:272-279.
25. Karacaer Z, Avcı Ö, Yılmaz Karadağ F. King's score may be more effective in the determination of severe fibrosis in chronic hepatitis B infections. Viral Hepat J. 2017;23:20-25.