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Research Article

Noninvasive Tests to Assess Liver Stiffness in Patients with Chronic Hepatitis B: APRI, FIB-4, and FIB-5 Scores

Aysun Yakut[1] **and Murat Aladag**[2]

[1]*Department of Gastroenterology, Istanbul Medipol University Sefakoy Health Practice Research Center, Istanbul, Türkiye*
[2]*Department of Gastroenterohepatology, Turgut Ozal University Faculty of Medicine Hospital, Malatya, Türkiye*

Correspondence should be addressed to Aysun Yakut; aysun.yakut@istanbul.edu.tr

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Background. Invasive percutaneous liver parenchymal biopsy is the best test used to evaluate liver stiffness and fibrosis in the follow-up and treatment of chronic hepatitis B (CHB) patients. In this study, we aimed to indirectly evaluate the severity of liver parenchymal fibrosis with tests used in the laboratory. *Methods*. This retrospective study was conducted with 201 patients diagnosed with CHB who underwent liver biopsy between 2021 and 2022. Preprocedural examination information, laboratory tests, and histopathological data of the patients were taken from the hospital database and examined. "Aspartate aminotransferase (AST)-platelet ratio index" (APRI), "4 factor-based fibrosis index" (FIB-4) score, and "5 factor-based fibrosis index" (FIB-5) score were calculated and compared with liver histopathological features. *Results*. Of the 201 CHB patients, 76 were females and 125 were males. The average age of the patients was 38.05 ± 12.63 years. A weak, statistically significant correlation was observed between FIB-4 and APRI scores. The patients' significant fibrosis scores were 31.3% and 33.8%, respectively ($r = 0.313$; $r = 0.338$; $p = 0.001$; $p < 0.01$). The very weak negative correlation of 17.4% between the patients' FIB-5 score and fibrosis score was statistically significant ($r = -0.174$; $p = 0.014$; $p < 0.05$). *Conclusions*. According to the data we obtained in our study, while the APRI score and FIB-4 score can be used safely, more comprehensive studies are needed for the reliability of the FIB-5 score.

1. Introduction

Chronic hepatitis B virus (CHB) is a chronic disease that can progress to liver fibrosis and cirrhosis. Liver cirrhosis can cause potentially life-threatening complications. The degree of fibrosis needs to be determined in the prognosis and treatment plans of CHB patients. The reliable and gold standard test for grading liver fibrosis is percutaneous liver biopsy. A liver biopsy is histopathologically important in the evaluation of inflammation, necrosis, and fibrosis [1]. However, this process is a costly, laborious method that carries the risk of serious complications and may cause sampling errors [2, 3]. The fact that liver biopsy carries these risks has led us to investigate noninvasive tests (NITs). The use of noninvasive laboratory and radiological methods in the evaluation of liver stiffness has become an alternative to liver biopsy in the follow-up and treatment of CHB patients. According to current guidelines, we can identify liver fibrosis based on laboratory or radiological tests with NIT systems. Among laboratory tests, the "aspartate aminotransferase (AST)-platelet ratio index" (APRI) and "4 factor-based fibrosis index" (FIB-4) scoring systems are two widely used scoring systems in determining chronic liver diseases [4]. The "5-factor fibrosis index" (FIB-5) scoring system is a scoring system that has recently started to be used in CHB patients and needs to be studied further [5]. Although APRI, FIB-4, and FIB-5 scoring systems have low sensitivity, their use in patient follow-up is an alternative to an unnecessary liver biopsy. Due to its positive predictive values, it has been found in some studies to be insufficient to distinguish early stage fibrosis from advanced fibrosis [6]. Our study was planned to evaluate how effective the APRI, FIB-4, and FIB-5

scoring systems are in predicting significant fibrosis in CHB patients who underwent liver biopsy, which is the gold standard in treatment decisions.

2. Methods

2.1. Patients and Study Design. This retrospective study was conducted with 201 patients followed in the gastroenterology outpatient clinic between 2021 and 2022. All adult patients over the age of 18 who participated in the study were diagnosed with CHB and had previously undergone liver parenchymal biopsy. Exclusion criteria of the study included patients coinfected with hepatitis C virus, delta virus, or human immunodeficiency virus; patients with alcohol-related liver disease; patients with nonalcoholic fatty liver disease; patients with autoimmune liver disease; patients with primary or secondary liver tumors; patients with portal vein or hepatic vein thrombosis; patients whose laboratory values could not be obtained before biopsy; patients who refuse liver biopsy or have any contraindications to liver biopsy; and patients with decompensated cirrhosis. The body mass index of the patients was between 25 and 30.

2.2. Liver Biopsy and Pathological Evaluation. Each patient included in the study had a percutaneous liver biopsy performed by a gastroenterologist using a Menghini needle (Hepafix kit 1.4 or 1.6 mm, Braun) under ultrasound guidance, which we routinely apply. While patients with at least 8–10 portal areas in their biopsy materials were included in the study, those with portal areas below this value were not included in the study. Biopsy materials were evaluated by a hepatopathologist blinded to the patient's clinical and laboratory data. The evaluation was made according to the internationally accepted modified Knodell scoring system [7]. Liver fibrosis (F) was graded on a scale of 0–6: F0—no fibrosis; F1—fibrous expansions in some portal areas; F2—fibrous expansions in most portal areas; F3—fibrous expansion in most portal areas with some bridging from portal to portal; F4—fibrous expansion with prominent bridging in most portal areas; F5—nodular bridging rarely (incomplete cirrhosis); and F6—cirrhosis with significant bridging. When evaluating the fibrosis stage, we divided it into two: nonsignificant low-grade fibrosis and significant high-grade fibrosis.

2.3. Noninvasive Evaluation. Demographic characteristics, anamnesis, physical examination, and laboratory tests such as a complete blood count, liver function tests, and abdominal ultrasound were examined for all patients who underwent liver parenchymal biopsy. The degree of fibrosis in liver biopsies and NIT ("aspartate aminotransferase (AST)-platelet ratio index" (APRI), "4-factor-based fibrosis index" (FIB-4) score, "5-factor-based fibrosis index" (FIB-5), and AST\ALT ratio (AAR)) results were evaluated statistically. Blood tests of CHB patients before biopsy: alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet (PLT), alkaline phosphatase (ALP), and albumin values were taken from the hospital automation system and recorded. In addition, the AAR, APRI score, FIB-4 score, and FIB-5 score calculated from these values were calculated and recorded.

2.4. Noninvasive Tests We Evaluated in Our Study. AAR = AST\ALT ratio [8].

APRI score = [(AST/upper limit of normal AST range) × 100]/platelet count [9].

FIB-4 score = age (years) × AST (U/L)/[PLT(10^9/L) × $ALT^{1/2}$ (U/L)] [10].

FIB-5 score = albumin (g/l) × 0.3 + platelet count (10^9/l) × 0.05 − alkaline phosphatase (IU/l) × 0.014 + AST/ALT ratio × 6 + 14 [5].

2.5. Research Ethics. This study was approved by the local ethics committee (Turgut Özal University Ethics Committee, acceptance: decision dated 04.04.2022 and numbered 2022\65). The guidelines of the Declaration of Helsinki were followed.

2.6. Statistical Analysis. The SPSS 26 (Statistical Package for the Social Sciences) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used when evaluating the study data. The suitability of quantitative data for normal distribution was tested using the Shapiro–Wilk test and graphical analysis. Student-t test was used for comparisons of normally distributed quantitative variables between two groups, and the Mann–Whitney *U* test was used for comparisons of nonnormally distributed quantitative variables between two groups. Spearman correlation analysis was used to evaluate the relationships between quantitative variables. Diagnostic screening tests (sensitivity, specificity, PPV, and NPV) and ROC analysis were used to determine the predictive value of the parameters. Statistical significance was accepted as $p < 0.05$ (Table 1).

Sensitivity: the quality of the test to identify patients among real patients.

Specificity: the quality of the test to detect healthy people among truly healthy people.

Positive predictive value (PPV): a measure of the conditional probability that the subject is truly sick when the test returns a positive (sick) result.

Negative predictive value (NPV): the probability that the subject is truly healthy when the test gives a negative (healthy) result.

3. Results

This study was carried out with a total of 201 patients diagnosed with CHB, 37.8% ($n = 76$) of whom were female and 62.2% ($n = 125$) of whom were male, who applied to the gastroenterology outpatient clinic between 2021 and 2022. The ages of the participants in the study ranged between 18 and 68 years, and the average was 38.05 ± 12.63 years. The average FIB-4 score of the patients participating in the study

Table 1: Rule considered when interpreting the size of the correlation coefficient.

r	Comment
0.00–0.19	Very weak
0.20–0.39	Weak
0.40–0.59	Medium
0.60–0.79	Strong
0.80–1.00	Very strong

Evans, J. D. (1996). Straightforward statistics for the behavioral sciences. Pacific Grove, CA: Brooks/Cole Publishing.

was 1.11 ± 1.18, the average APRI score was 0.83 ± 1.91, the average FIB-5 score was 5.00 ± 4.03, and the average liver fibrosis was 1.25 ± 1.08 (Table 2).

A weak positive correlation of 31.3% between the patients' FIB-4 score and fibrosis score (as the FIB-4 score increases, the fibrosis score increases) was found to be statistically significant ($r = 0.313$; $p = 0.001$; $p < 0.01$) (Figure 1(a)). A weak positive correlation of 33.8% between the patients' APRI score and fibrosis score (as the APRI score increases, the fibrosis score increases) was found to be statistically significant ($r = 0.338$; $p = 0.001$; $p < 0.01$) (Figure 1(b)). A very weak negative correlation of 17.4% was found between the patients' FIB-5 score and fibrosis score (as the FIB-5 score increases, the fibrosis score decreases) ($r = -0.174$; $p = 0.014$; $p < 0.05$). A weak positive correlation was found between the patients' ALT and AST measurements and their fibrosis scores (as ALT and AST values increase, the liver fibrosis score increases) at a level of 20.8% and 28%, respectively ($r = 0.208$; $p = 0.003$; $p < 0.01$) ($r = 0.280$; $p = 0.001$; $p < 0.01$) (Figure 1(c)). A very weak negative correlation of 19.6% was found between the patients' PLT measurements and fibrosis score (as the PLT value increases, the fibrosis score decreases) ($r = -0.196$; $p = 0.005$; $p < 0.01$). A very weak negative correlation of 16.9% was found between the patients' albumin measurements and fibrosis score (as albumin value increases, fibrosis score decreases) ($r = -0.169$; $p = 0.016$; $p < 0.05$) (Table 3).

The FIB-4 score, APRI score, and AST value of patients with significant liver fibrosis were found to be statistically significantly higher than those of patients with nonsignificant fibrosis ($p = 0.001$; $p < 0.01$). Again, the ALT value of patients with significant liver fibrosis was found to be statistically significantly higher than that of patients with nonsignificant fibrosis ($p = 0.008$; $p < 0.01$). However, the patients' FIB-5 score, AAR, PLT, ALP, and albumin measurements did not show a statistically significant difference according to liver fibrosis levels ($p > 0.05$) (Table 4).

The cutoff point for the FIB-4 score according to liver fibrosis levels was 0.90 and above. For the FIB-4 score cutoff value of 0.90, the sensitivity was 62.5% and the specificity was 63.5% (PPV = 44.4%, NPV = 78.4%). The area under the ROC curve obtained was 65.6%, with a standard error of 4.3% (Figure 2(a)). The cutoff point for the APRI score according to liver fibrosis levels was 0.29 and above. For the APRI score cutoff value of 0.29, the sensitivity was 87.5% and the specificity was 46.72% (PPV = 43.40%, NPV = 88.90%). The area under the ROC curve obtained was 68.9%, with a standard error of 3.9% (Figure 2(b)). The cutoff point for

Table 2: Distribution of descriptive characteristics.

	Mean ± Sd
FIB-4 score	1.11 ± 1.18
APRI score	0.83 ± 1.91
FIB-5 score	5.00 ± 4.03
HAI	6.07 ± 2.49
Liver fibrosis	1.25 ± 1.08
ALT (U/L)	108.67 ± 209.72
AST (U/L)	65.64 ± 129.56
PLT (cell/mL)	227.37 ± 63.30
ALP (IU/l)	84.35 ± 26.05
Albumin (g/dL)	4.42 ± 0.41
AAR	0.73 ± 0.27

FIB-4: 4-factor-based fibrosis index; APRI: aspartate aminotransferase (AST)-platelet ratio index; FIB-5: 5-factor-based fibrosis index; HAI: histological activity index; ALT: alanine transferase; AST: aspartate aminotransferase; PLT: platelet; ALP: alkaline phosphatase; AAR = AST\ALT ratio.

ALT measurement according to liver fibrosis levels was 37 and above. For the ALT measurement cutoff value of 37, the sensitivity was 79.69% and the specificity was 42.34% (PPV = 39.20%, NPV = 81.70%). The area under the ROC curve obtained was 61.6%, with a standard error of 4.1% (Figure 3(a)). The cutoff point for AST measurement according to the liver fibrosis levels was 34 and above. For the AST measurement cutoff value of 34, the sensitivity was 68.75% and the specificity was 59.85% (PPV = 44.4%, NPV = 80.4%). The area under the ROC curve obtained was 65.9%, with a standard error of 4% (Figure 3(b)) (Table 5).

4. Discussion

Because liver biopsy has limitations such as being invasive and sampling inaccurately, various NITs have been developed [11–19]. NITs are not as accurate enough as liver parenchymal biopsy in evaluating liver stiffness and fibrosis in CHB patients [20]. Although NITs such as Fibroscan are very useful in demonstrating liver stiffness and fibrosis, these devices are not available in every clinic [21]. Most guidelines recommend assessing and monitoring liver stiffness and fibrosis with inexpensive and accessible NITs [22]. AAR, APRI, and FIB-4 scores derived as an alternative to liver parenchymal biopsy were the first NITs identified based on laboratory tests [23]. Following these NITs, publications have been published stating that the FIB-5 score, which evaluates liver stiffness and fibrosis based on blood tests, can also be used in studies [24, 25]. The FIB-6 score, which is also used to evaluate liver fibrosis, is the NIT created as a result of the integration of blood tests with artificial intelligence [26]. These NITs are tests developed as an alternative to liver parenchymal biopsy and aim to find optimal accuracy in the early detection of patients with cirrhosis [20]. Recent studies and meta-analyses have highlighted that NITs with optimal threshold values, good diagnosis, and accuracy for measuring liver fibrosis at different stages in CHB patients have not been identified [27, 28]. The large discrepancy between significant liver fibrosis cutoff values in NIT is due to the number of samples in the studies, fibrosis score differences,

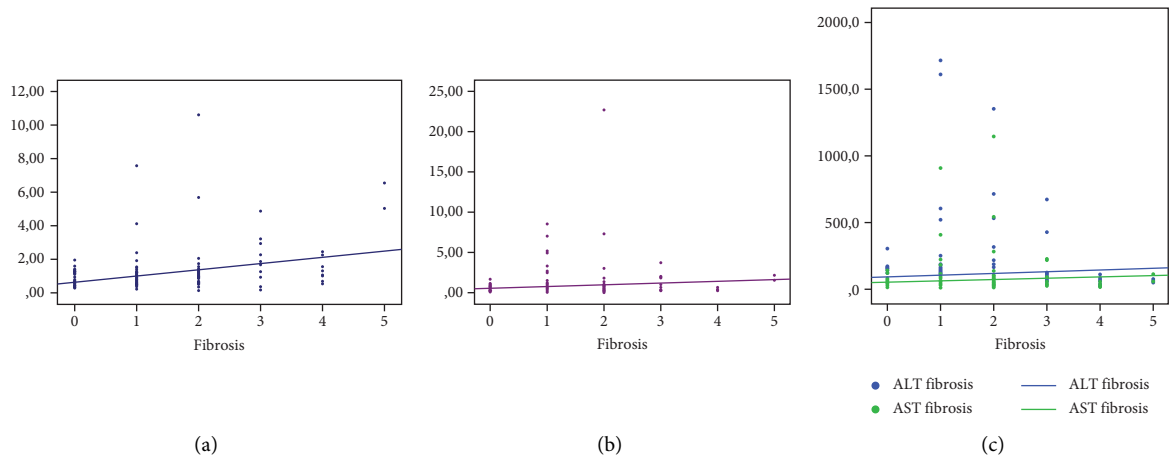

Figure 1: (a) Relationship between liver fibrosis and the FIB-4 score. (b) Relationship between liver fibrosis and APRI score. (c) Relationship between liver fibrosis and AST and ALT measurements.

Table 3: Evaluation of the relationship between noninvasive markers according to liver fibrosis and HAI scores.

	Liver fibrosis		HAI	
	r	*p*	*r*	*p*
FIB-4 score	0.313	**0.001****	0.429	**0.001****
APRI score	0.338	**0.001****	0.548	**0.001****
FIB-5 score	−0.174	**0.014***	−0.185	**0.0011***
ALT (U/L)	0.208	**0.003****	0.437	**0.001****
AST (U/L)	0.28	**0.001****	0.534	**0.001****
PLT (cell/mL)	−0.196	**0.005****	−0.241	**0.001****
ALP (IU/l)	0.059	**0.409**	0.107	**0.142**
Albumin (g/dL)	−0.169	**0.016***	−0.211	**0.003****
AST/ALT	−0.017	**0.811**	−0.102	**0.161**

r = Spearman's correlation coefficient. * $p < 0.05$; ** $p < 0.01$. While there was a positive relationship between the participants' APRI score, FIB-4 score, ALT measurements, and AST measurements and liver fibrosis, there was a weak negative relationship between the FIB-5 score, albumin value, and PLT value. Similarly, while there was a positive relationship between the pathologically evaluated histological activity index and APRI score, FIB-4 score, ALT measurements, and AST measurements, there was a weak negative relationship between FIB-5 score, albumin value and PLT value.

Table 4: Sensitivity of noninvasive tests according to liver fibrosis grading.

	Liver fibrosis		
	Nonsignificant fibrosis ($n = 136$)	Significant fibrosis ($n = 64$)	*p*
FIB-4 score	0.91 ± 0.77	1.54 ± 1.7	[a]**0.001****
APRI score	0.66 ± 1.14	1.21 ± 2.92	[a]**0.001****
FIB-5 score	5.43 ± 3.52	4.15 ± 4.87	[b]**0.063**
ALT (U/L)	98.97 ± 210.52	129.44 ± 208.13	[a]**0.008****
AST (U/L)	57.62 ± 114.74	82.81 ± 156.29	[a]**0.001****
PLT (cell/mL)	232.76 ± 59.83	215.65 ± 69.32	[b]**0.076**
ALP (IU/l)	83.61 ± 27.22	85.94 ± 23.47	[a]**0.439**
Albumin (g/dL)	4.44 ± 0.43	4.38 ± 0.35	[a]**0.052**
AST/ALT	0.72 ± 0.26	0.73 ± 0.3	[a]**0.918**

[a]Mann–Whitney *U* Test; [b]Student-*t* test; ** $p < 0.01$. The FIB-4 score, APRI score, ALT measurement, and AST measurement in cases with significant fibrosis are significantly higher than those with nonsignificant fibrosis.

more severe hepatic necroinflammatory events, and differences in laboratory values [27, 28]. The lack of a significant cutoff value in noninvasive tests has led us to conduct new studies. We referenced the fibrosis degree of 201 patients according to the modified Knodell score and compared it with laboratory values before the biopsy. We found a statistically significant correlation between liver fibrosis and the 37 cutoff value of the ALT measurement ($p = 0.002$, $p < 0.01$). We predicted that the risk of having an ALT value of 37 and above was 2,880 times higher in patients with

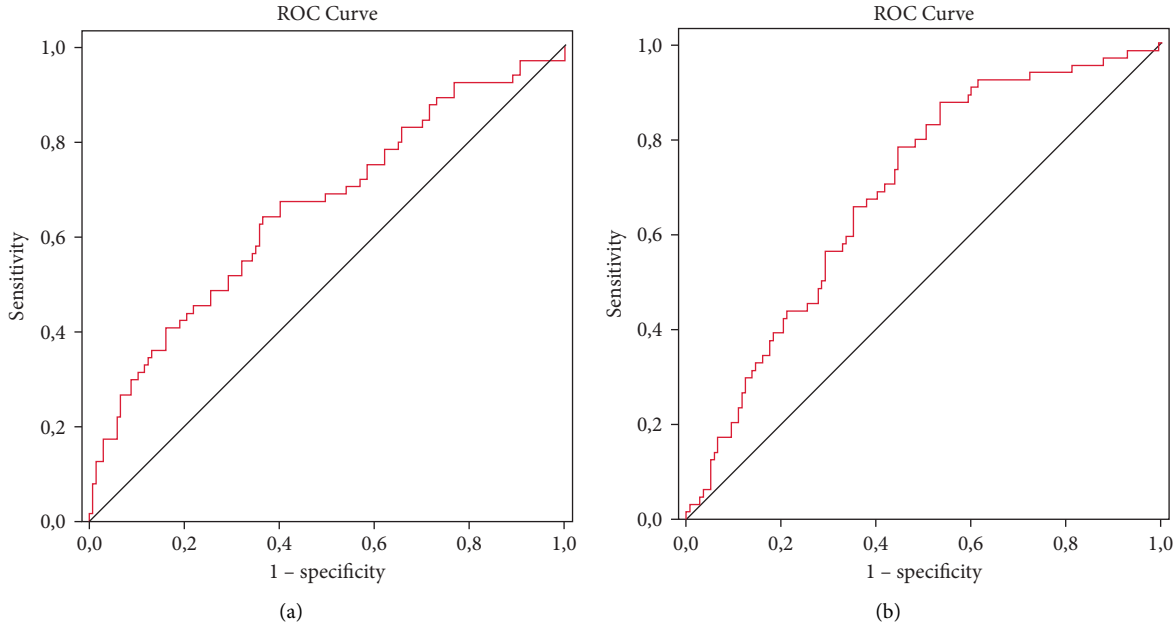

Figure 2: (a) ROC curve for FIB-4 score vs. liver fibrosis score. (b) ROC curve for APRI score vs. liver fibrosis score.

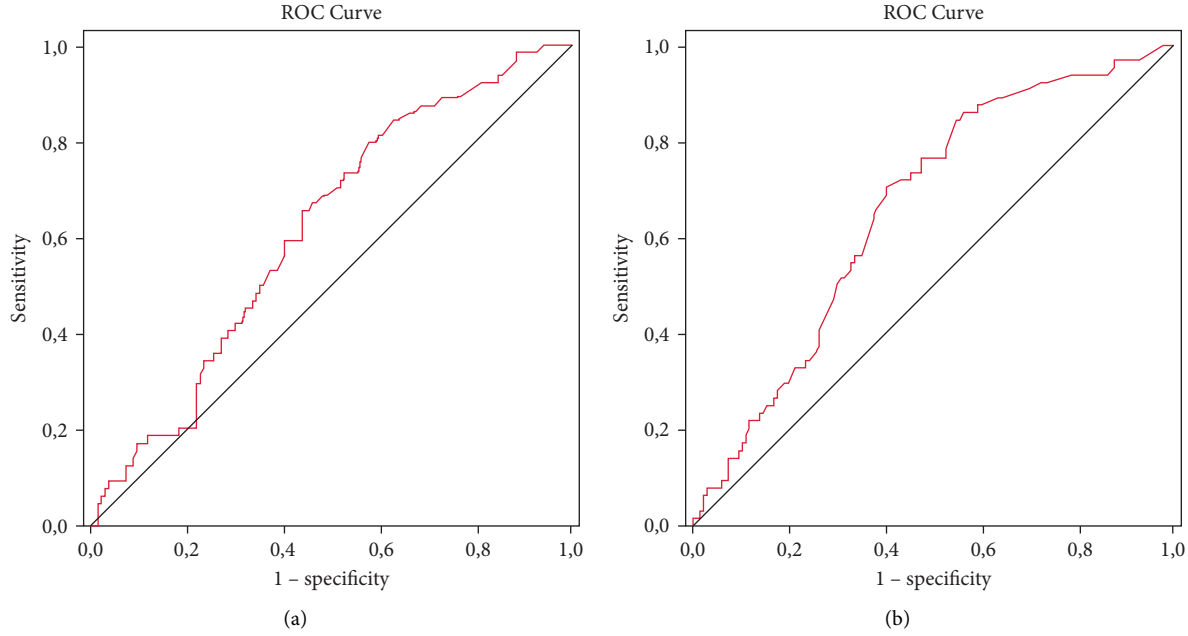

Figure 3: (a) ROC curve for ALT measurement by fibrosis score. (b) ROC curve for AST measurement by fibrosis score.

significant fibrosis. The odds ratio for ALT measurement was 2.880 (95% CI: 1.435–5.782). We found a statistically significant correlation between liver fibrosis and the 34 cutoff values of the AST measurement ($p = 0.001$, $p < 0.01$). We predicted that the risk of having an AST value of 34 and above was 3.531 times higher in patients with significant fibrosis. The odds ratio for AST measurement was 3.531 (95% CI: 1.870–6.669). We found a statistically significant correlation between liver fibrosis and the 0.29 cutoff value of the APRI score ($p = 0.001$; $p < 0.01$). We predicted that the risk of having an APRI score of 0.29 or above was 6.137 times higher in patients with significant fibrosis. The odds ratio of the APRI score was 6.137 (95% CI: 2.721–13.841). We found a statistically significant correlation between liver fibrosis and the 0.90 cutoff value of the FIB-4 score ($p = 0.001$; $p < 0.01$). We predicted that the risk of having a FIB-4 score of 0.90 or above was 3.102 times higher in patients with significant fibrosis. The odds ratio of the FIB-4 score was 3.102 (95% CI: 1.672–5.753). In our study, AAR and FIB-5 scores did not show a statistically significant difference according to the liver fibrosis levels of the patients ($p = 0.918$; $p > 0.05$; $p = 0.063$; $p > 0.05$, respectively). For

Table 5: ROC curve results of diagnostic and screening tests according to liver fibrosis levels.

	Diagnostic scan					ROC curve		
	Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area	95% confidence interval	*p*
FIB-4 score	**≥0.90**	62.5	63.5	44.4	78.4	**0.656**	0.573–0.739	**0.001****
APRI score	**≥0.29**	87.5	46.72	43.04	88.9	**0.689**	0.613–0.765	**0.001****
ALT (U/L)	**≥37**	79.69	42.34	39.2	81.7	**0.616**	0.536–0.696	**0.008****
AST (U/L)	**≥34**	68.75	59.85	44.4	80.4	**0.659**	0.582–0.737	**0.001****

** $p < 0.01$. According to the fibrosis level, the cut-off value of 0.90 and above was found to be significant for the FIB-4 score (sensitivity 62.5 specificity 63.5 PPV:44.40 NPV:78.4 area under the ROC curve 65.6% standard error 4.3%), while the cut-off value of 0.29 and above was found to be significant for the APRI score (sensitivity 87.5 specificity 46.72 PPV:43.04 NPV:88.9 area under the ROC curve is 68.9%, standard error is 3.9%). Again, according to the fibrosis level, the cut-off value of 37 and above was found to be significant for ALT measurement (sensitivity 79.69 specificity 42.34 PPV:39.20 NPV:81.70 area under the ROC curve 61.6% standard error 4.1%), while the cut-off value of 34 and above was found to be significant for AST measurement (sensitivity 68.75 specificity 59.85 PPV:44.40 NPV:80.40 area under the ROC curve 61.6% standard error 4%).

this reason, the ROC curve could not be drawn and the cutoff value could not be determined. In our study, the sensitivity and specificity of the APRI score in predicting significant fibrosis in CHB patients were 87.5% and 46.72%, respectively, for an APRI score of 0.29 (PPV = 43.40%, NPV = 88.90%). The resulting area under the ROC curve was 68.9%, with a standard error of 3.9%.

In other studies, the sensitivity and specificity of the APRI score in predicting significant fibrosis in CHB patients were 73.3% and 55.9%, respectively, for the APRI score of 0.4 [24]. In another meta-analysis, APRI score sensitivity and specificity values in patients diagnosed with CHB with advanced fibrosis and cirrhosis were; fibrosis within the APRI cutoff value of 0.5, 1, and 1.5 was reported as 70% and 60%, 50% and 83%, 36.9% and 92.5% [28]. In a meta-analysis of the FIB-4 score, the area under the ROC curve for significant fibrosis was 0.78 (95% CI = 0.74–0.81) [20]. The recommended cutoff value ranged from 1.45 to 1.62. The area under the ROC curve for patients with cirrhosis was 0.89 (95% CI = 0.85–0.91), and the recommended cutoff value was 2.9–3.6 [20]. In a study on FIB-5 scores in CHB patients, when the cutoff value was determined as 7.05, the specificity in distinguishing significant fibrosis was found to be 98.8% and the sensitivity was 23.1% [25]. However, in our study, the power and cutoff value of the FIB-5 score to detect significant fibrosis could not be determined. On the other hand, one of the factors that may affect the relationship between the FIB-5 score and liver fibrosis is the score's relationship with ALP. It should not be ignored that ALP may be affected by many bone metabolism diseases, such as vitamin D deficiency, and may cause erroneous results in the FIB-5 score.

Although it is important for the clinician that NITs eliminate the need for percutaneous liver biopsy, the lack of predictive values and lack of sensitivity and specificity cause clinicians to have difficulties in patient follow-up and treatment. In many publications and in our own study, although the APRI score and FIB-4 score are not specific and sensitive, they are effective NITs in predicting the severity of liver fibrosis. However, since there are not enough data on other liver diseases, especially CHB, more prospective, multicenter studies are needed on the usability of the FIB-5 score.

The most important limitations of our study are that it is a retrospective study, our number of patients is small, and it does not include liver fibrosis in CHB patients at different stages. Additionally, another limitation of our study is that there are no globally accepted standard cutoff values for the APRI score, FIB-4, and FIB-5 score tests. This has limited us in terms of not having standards to which we can take reference. Therefore, multicenter, large sample sizes, and prospective studies are needed to standardize NITs that we can use in the follow-up and treatment of liver fibrosis and cirrhosis in CHB patients.

5. Conclusion

NITs such as the APRI score and FIB-4 score have been reported in various guidelines for the detection of liver fibrosis in CHB patients, although standardized cutoff values have not been optimized. In our study, we did not find a significant relationship with the FIB-5 score, which is the NIT, in evaluating the liver fibrosis of patients diagnosed with CHB.

Data Availability

The dataset utilized and analyzed in the current research is accessible from the corresponding authors upon reasonable request.

Ethical Approval

This retrospective study was approved by the Turgut Ozal University Ethics Committee with the decision dated April 4, 2022, and numbered 2022\65. Helsinki Declaration: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects.

Consent

Since it was a retrospective study, a voluntary consent form was not taken.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

A.Y. was responsible for concept and design, data collection, and original draft preparation. A.Y. and M.A. were responsible for critical feedback and revision of the manuscript and data analysis and interpretation.

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