Research Article

Noninvasive test and chronic HBV

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Evaluation of fibrosis with noninvasive biochemical tests in chronic viral hepatitis B

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Abstract

Background and Aim: Early diagnosis and treatment of chronic hepatitis B (CHB) disease are important for the prevention of complications such as cirrhosis and hepatocellular cancer. Liver biopsy is an invasive, complicated, and expensive diagnostic method, which is the gold standard for detecting fibrosis. The aim of this study was to investigate the role of these tests in predicting liver fibrosis and treatment decision.

Materials and Methods: A total of 1051 patients diagnosed with CHB between 2010 and 2020 in the Gaziantep University Gastroenterology Department were retrospectively evaluated. AAR, API, APRI, FIB-4, KING score, and FIBROQ score were calculated at the time of onset diagnosis. In addition, the Zeugma score, a new formula that is thought to be more sensitive and specific, was determined. Noninvasive fibrosis scores were compared according to the biopsy results of the patients

Results: In this study, the area values under the curve were 0.648 for the API score, 0.711 for the APRI score, 0.716 for the FIB-4 score, 0.723 for the KING score, 0.595 for the FIBROQ score, and 0.701 for the Zeugma score ($p<0.05$). No statistically significant difference was obtained for the AAR score. The KING, FIB-4, APRI, and Zeugma scores were the best indicators for detecting advanced fibrosis. For KING, FIB-4, APRI, and Zeugma scores, the cutoff value for the prediction of advanced fibrosis were ≥8.67, ≥0.94, ≥16.24, and ≥9.63 with a sensitivity of 50.52%, 56.77%, 59.64%, and 52.34%, specificity of 87.26%, 74.96%, 73.61%, and 78.11%, respectively ($p<0.05$). In our study, we compared the globulin and GGT parameters with fibrosis, which we used in the Zeugma score formula. Globulin and GGT mean values were significantly higher in the fibrosis group ($p<0.05$). There was a statistically significant correlation between fibrosis and globulin and GGT values ($p<0.05$, $r=0.230$ and $p<0.05$, $r=0.305$, respectively).

Conclusion: The KING score was found to be the most reliable method for the noninvasive detection of hepatic fibrosis in patients with chronic HBV. The FIB-4, APRI, and Zeugma scores were also shown to be effective in determining liver fibrosis. It was shown that the AAR score was not sufficient for detecting hepatic fibrosis. The Zeugma score, a novel noninvasive test, is a useful and easy tool to evaluate liver fibrosis in patients with chronic HBV and has better accuracy than AAR, API, and FIBROQ.

Keywords: Chronic viral hepatitis B; fibrosis; noninvasive tests.

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Introduction

Despite significant advances in primary prevention, diagnosis, and treatment, hepatitis B virus (HBV) infections continue to be a serious public health problem. Chronic HBV infection is a slow and insidious disease that can progress to cirrhosis and hepatocellular cancer over the years.[1] Early and effective antiviral treatment is one of the most important factors in preventing these complications. Therefore, early detection of fibrosis and effective antiviral treatment should be given to prevent the progression and complications of the disease.[2]

The degree of fibrosis in the liver is very important for the prognosis and treatment management of chronic HBV patients. The gold standard for detecting and grading liver fibrosis is liver biopsy. However, it should be kept in mind that complications such as pain, bleeding, infection, perforation, and, albeit rare, death may occur.[3] There are many scoring systems used to evaluate chronic hepatitis and fibrosis. The most commonly used scoring systems are ISHAK and METAVIR scoring systems. These scoring systems are very helpful in determining prognosis and directing clinical treatment. However, being an invasive method and possible complications are among the biggest limitations of the method. In addition, if fibrosis is not detected in the biopsies, it is necessary to perform a biopsy again in the future in terms of treatment. For this purpose, various noninvasive assessment methods and scoring systems have been developed to predict fibrosis.[4,5]

There are two types of noninvasive methods in the evaluation of fibrosis. The first is the imaging method in which liver stiffness is evaluated. This includes transient elastography (FibroScan), magnetic resonance elastography, and acoustic radiation force impulse imaging. FibroScan is the most commonly used method among these. However, besides being an expensive and not easily accessible method, obesity, pregnancy, and cholestasis are the limitations of this method.[6–8] The second is the serological method in which various serum biomarkers and formulas obtained with biochemical parameters are used. The methods most commonly used are AAR (AST/ALT ratio), APRI (AST/platelet ratio index), FIB-4 score, FibroIndex, Hepascore, KING score, and FibroQ score. These methods are less expensive and easily applicable. Besides, there are also a few noninvasive markers and tests that need expensive instruments for measurement and are difficult to use in clinical practice, such as α2-macroglobulin, haptoglobin, and apolipoprotein A1.[9] Although the sensitivity and specificity of these tests vary considerably according to the cutoff values, an ideal noninvasive test to predict fibrosis has not been defined yet.[10,11] Considering all these limitations, the development of noninvasive and easily applicable practical tests showing liver fibrosis has gained importance in recent years.

It is known that globulin and GGT levels increase and albumin and thrombocyte levels decrease in chronic hepatitis and liver cirrhosis.

It is suggested that these parameters can be very useful in predicting fibrosis. In addition, many studies have shown that globulin and gamma-glutamyl transferase (GGT) levels increase in chronic hepatitis and cirrhosis and may be associated with fibrosis.[9,12] This study aimed to compare liver biopsy, which is the gold standard for predicting liver fibrosis, and noninvasive tests. In addition, it was planned to investigate the effectiveness of a newly developed noninvasive serum model using albumin, platelet, globulin, and GGT.

Materials and Methods

In this study, 1600 patients, who applied to Gaziantep University Hospital Gastroenterology Department between 2010 and 2020 and were diagnosed with chronic hepatitis B (CHB) by serological and histopathological methods and underwent liver biopsy, were evaluated retrospectively.

The inclusion criteria were being older than 18 years of age, having CHB disease, and having a liver biopsy. The diagnosis of CHB was made according to the EASL and AASLD guidelines for HBsAg positive for more than 6 months. Patients with underlying diseases such as liver cirrhosis, cardiac diseases, renal diseases, diabetes mellitus, atherosclerotic disease, chronic infections, history of hypertension, patients with comorbidities that may cause chronic liver disease other than hepatitis B (HCV, HDV, HIV, NASH, Wilson's disease, hemochromatosis, autoimmune hepatitis, alcoholic liver disease, metabolic liver diseases), malignancy, autoimmune disorders, rheumatic diseases, hematological diseases, and chronic obstructive lung diseases, as well as patients taking drugs such as aspirin, warfarin, heparin, antidiabetics, hyperlipidemics, and antihypertensives, were excluded from this study. However, patients with insufficient or missing laboratory parameter data for formulations of noninvasive fibrosis markers to be used in the study were not included. The study flow chart is given in Figure 1.

All complete blood count analysis was performed in the hematology laboratory with the Cell-Dyn 3700 SL analyzer (Abbott Diagnostics, Chicago, IL, USA) in our hospital. Serum levels of AST, ALT, total bilirubin, albumin, and other routine biochemical parameters were determined using automated techniques (Abbott Architect C16000 and Abbott Diagnostics).

The histological evaluation of biopsy specimens was performed in the pathology department of our hospital according to ISHAK's seven-grade staging system. According to the liver biopsy results of the patients included in the study, those with an ISHAK fibrosis score of ≥3 were considered to have significant fibrosis. The liver biopsy was performed on all our patients. The AAR, API, APRI, FIB-4, KING, FibroQ, and our Zeugma scores were used in the noninvasive evaluation of hepatic fibrosis. Scoring formulas were arrived at as follows:

$$\text{AAR} = \frac{\text{AST}}{\text{ALT}},\ \text{API} = \frac{\text{Age}}{\text{Platelet}} \times 100,\ \text{APRI} = \frac{\frac{\text{AST}}{\text{AST (upper limit of normal)}}}{\text{Platelet}} \times 100,\ \text{FIB-4} = \frac{\text{Age} \times \text{AST}}{\text{Platelet} \times \sqrt{\text{ALT}}},$$

$$\text{KING} = \frac{\text{Age} \times \text{AST} \times \text{INR}}{\text{Platelet}},\ \text{FibroQ} = 10 \times \frac{\text{Age} \times \text{AST} \times \text{INR}}{\text{ALT} \times \text{Platelet}},\ \text{ZEUGMA} = \frac{\text{Globuline} \times \text{GGT}}{\text{Albumin} \times \text{Platelet}} \times 100.$$

Noninvasive fibrosis degrees found by the laboratory data of the patients included in the study were analyzed using ROC analysis according to the gold standard ISHAK scoring system. The areas under the curve were calculated for each noninvasive method in the patients included in the study as a result of the ROC analysis (Fig. 2). The ethics committee approval was obtained for the study from Gaziantep University Clinical Research Ethics Committee with the decision numbered 2020/26, and the study was carried out in accordance with the Declaration of Helsinki Principles.

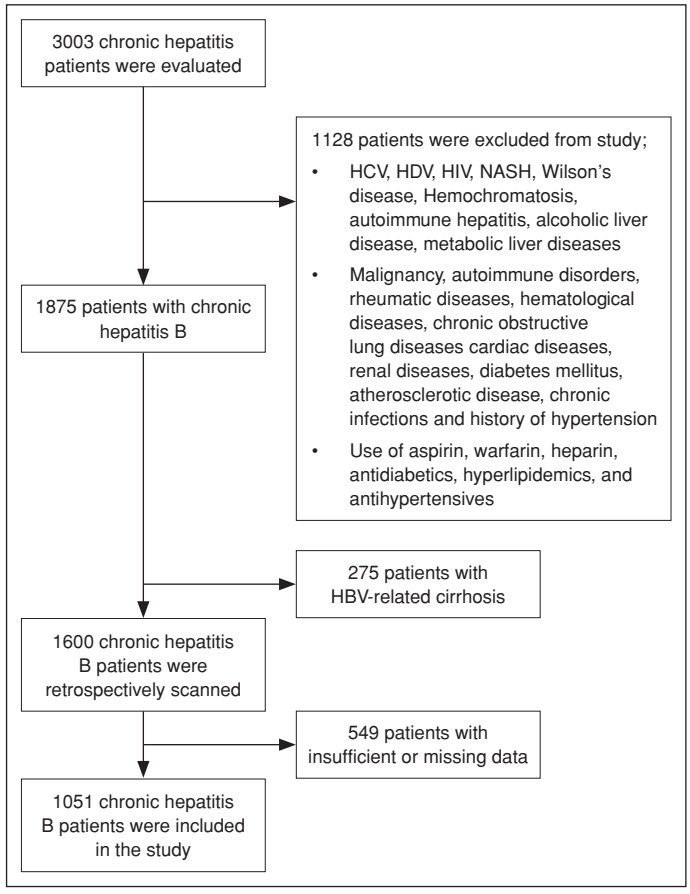

Figure 1. Flow chart of the study.

HCV: Hepatitis C virus; HDV: Hepatitis D virus; HIV: Human immunodeficiency Virus; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B virus.

Statistical Analysis

Demographic data and biochemical parameters obtained from the study were given with descriptive statistics (minimum, maximum, mean, and median) in addition to frequency and percentage distributions. Student's t-test was used to compare biochemical parameters (GGT and globulin) and variables of AAR, API, APRI, FIB 4, KING score, FibroQ, and Zeugma score according to fibrosis groups. The relationship between GGT and globulin variables and fibrosis values was determined with the help of Spearman's correlation analysis. In addition, the ROC analysis was used to determine the cutoff points of AAR, API, APRI, FIB-4, KING score, FibroQ, and Zeugma variables. All analyses were performed using SPSS for windows version 22 and Medcalc. A value of $p<0.05$ was considered statistically significant.

Results

The mean age of the patients included in the study was 36±12.2 years, and 59.9% (n=630) of the patients were males. No fibrosis was detected in 63.5% (n=667) of the patients, while 36.5% (n=384) had significant fibrosis. The distribution according to fibrosis scores was: 9.9% (n=104) of the patients were fibrosis 0, 17.5% (n=184) fibrosis 1, 36.1% (n=379) fibrosis 2, 21.1% (n=222) fibrosis 3, 9.9% (104) fibrosis 4, 4.5% (n=47) fibrosis 5, and 1% (n=11) fibrosis 6. Laboratory characteristics of the patients were

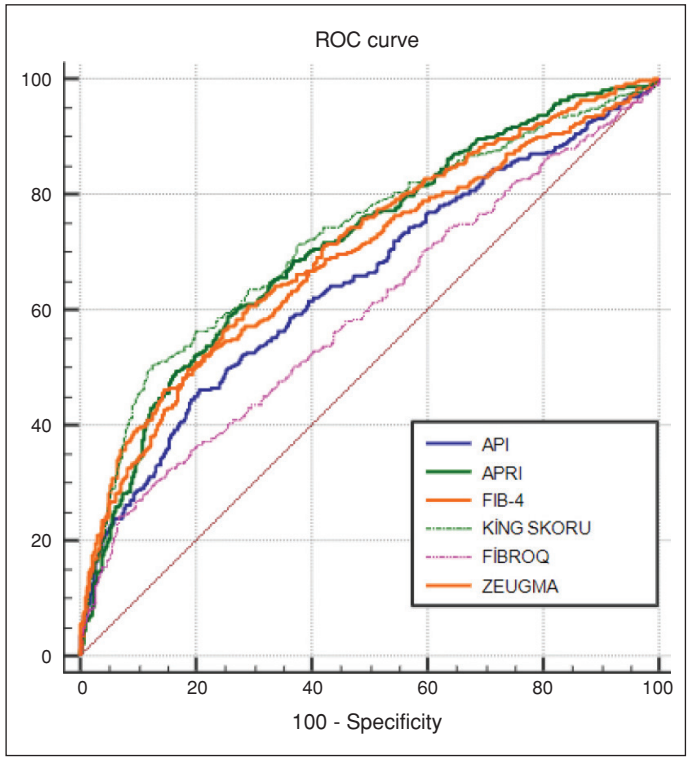

Figure 2. ROC curves for non-invasive scoring system.

ROC: Receiver operating characteristic; API: Age/platelet index; APRI: AST/platelet ratio index; FIB-4: Fibrosis-4 index; FIBROQ: Fibro-quotient.

evaluated. The mean INR level was 1.05±0.12, PLT 223 000±65 350 μL^{-1}, AST 28 U/L (9–1930), ALT 36 U/L (1–2286), ALP 93 U/L (15–844), GGT 22 U/L (4–654), total bilirubin 0.57±0.57 mg/dL, direct bilirubin 0.18±0.39 mg/dL, indirect bilirubin 0.39±0.31 mg/dL, total protein 7.46±0.49 g/dL, globulin 3.00±0.55 g/dL, and albumin 4.41±0.44 g/dL.

Hepatic fibrosis values were calculated separately for all patients using the calculation method with 6 different noninvasive fibrosis scores (AAR, API, APRI, FIB-4 index, KING score, and FibroQ indexes). In addition, the hepatic fibrosis value of the patients was recorded with the Zeugma score we created. The results of the non-invasive fibrosis scoring tests of the patients are shown in Table 1.

Noninvasive fibrosis scoring systems were analyzed by performing the ROC analysis according to the ISHAK scoring system. The area under the curve was 0.529 for the AAR score, 0.648 for the API score, 0.711 for the APRI score, 0.716 for the FIB-4 score, 0.723 for the KING score, 0.595 for the FIBROQ score, and 0.701 for the Zeugma score. Sensitivity and specificity values for the scoring methods were, respectively, 61.72% and 43.78% for the AAR score, 46.09% and 79.31% for the API score, 59.64% and 73.61% for the APRI score, 56.77% and 74.96% for the FIB-4 score, 50.52% and 87.26% for the KING score, 24.22% and 93.10% for the FIBROQ, and 52.34% and 78.11% for the Zeugma score. While the p-value was significant ($p<0.05$) for the API, APRI, FIB-4, KING, FIBROQ, and Zeugma scores, no statistically significant p-value could be obtained for the AAR score (Table 2). A new cutoff value was calculated using the Youden index method in the patients included in our study. The cutoff values were calculated as 0.87 for the AAR score, 20.24 for the API score, 16.24 for the APRI score, 0.94 for the FIB-4 score, 8.67 for the KING score, 8.67 for the FibroQ score, and 9.63 for the Zeugma score.

Globulin and GGT parameters we used in the Zeugma score formula were compared between the two groups. We found a statistically significant difference in the globulin value ($p<0.05$). The mean globulin was higher in the group with fibrosis. When the GGT value was compared according to both groups, it was found that the mean GGT was statistically higher in the fibrosis group ($p<0.05$). A statistically significant, positive, and low correlation was found between fibrosis values and globulin and GGT values ($p<0.05$, $r=0.230$ and $p<0.05$, $r=0.305$, respectively) (Table 3).

Table 2. ROC analysis results of non-invasive scoring systems

Non-invasive scoring system	AUROC	Cut-off	Sensitivity	Specifity	p
AAR	0.529	0.87	61.72	43.78	0.115
API	0.648	20.24	46.09	79.31	0.001*
APRI	0.711	16.24	59.64	73.61	0.001*
FIB-4	0.716	0.94	56.77	74.96	0.001*
King	0.723	8.67	50.52	87.26	0.001*
FİBROQ	0.595	2.72	24.22	93.10	0.003*
Zeugma	0.701	9.63	52.34	78.11	0.001*

ROC: Receiver operating characteristic; AUROC: Area under receiver operating characteristics; AAR: AST/ALT ratio; API: Age/platelet index; APRI: AST/platelet ratio index; FIB-4: Fibrosis-4 index; FIBROQ: Fibro-quotient.

Table 3. Comparison of globulin and GGT averages with fibrosis

	No fibrosis (n=667)	Fibrosis (n=384)	p
Globuline	2.99±0.48	3.25±0.62	<0.05
GGT	27.94±40.47	53.77±82.15	<0.05

GGT: Gama glutamyl transferase.

Table 1. Results of hepatic fibrosis scoring tests

	AAR	API	APRI	FIB-4	King	FIBROQ	Zeugma
Average	0.79	15.86	13.20	0.78	4.84	1.33	6.65
Standard deviation	1.39	9.07	65.15	1.04	25.15	3.10	39.57
Minimum	0.06	3.20	2.62	0.18	0.90	0.13	0.84
Maximum	36.0	73.00	1191.36	14.82	384.73	78.31	665.00

AAR: AST/ALT ratio; API: Age/platelet index; APRI: AST/platelet ratio index; FIB-4: Fibrosis-4 index; FIBROQ: Fibro-quotient.

Discussion

Chronic HBV is one of the most important causes of cirrhosis and hepatocellular carcinoma. Chronic HBV is an important health problem in Turkiye and worldwide. Although the pathway of chronic hepatitis to cirrhosis is not well known, it is estimated that it takes 10–15 years. It is well known as cirrhosis is decompensated and causes fatal complications and significant psychological and economic problems.[13] Although classical laboratory methods used in the diagnosis of chronic HBV partially evaluate the necroinflammation in the liver tissue, they provide little information about fibrosis. Knowing the degree of fibrosis and necroinflammatory activity of this disease in the liver allows us to predict the course of the disease and the results of the treatment. Percutaneous liver biopsy is considered the gold standard for the diagnosis and treatment of progressive chronic liver disease.[14] However, liver biopsy is an invasive procedure, and therefore its risks and benefits should be carefully considered. Percutaneous liver biopsy has 1%–5% risk of complications such as pain, bleeding, infection, and gallbladder perforation.[15]

Noninvasive tests with less risk can be important aids for clinicians. For this reason, we focused on the usability of the Zeugma scoring system. Although the AAR (AST/ALT ratio) is used as an index of liver fibrosis, the data reported so far are conflicting.[16] AAR was the noninvasive fibrosis measurement method with the lowest AUROC value in our study. When the AAR scores of patients with and without fibrosis were compared, no statistically significant difference was found. Our results were similar to the results of the study by Guéchot et al.[17] A total of 590 untreated chronic hepatitis C patients were included in the multicenter prospective study conducted by Guéchot et al.[17] in 2007. Liver fibrosis and necroinflammatory activity were evaluated according to the METAVIR scoring system by biopsy. A weak but significant correlation was found between the METAVIR fibrosis stage and AAR. However, the ROC curve analysis showed that the AST/ALT ratio did not distinguish between significant fibrosis (F2) (AUROC=0.531) and had very poor diagnostic accuracy for severe fibrosis (F≥3) (AUROC=0.584) or cirrhosis (F4) (AUROC=0.626). In addition, in the study of Eminler et al.[16] in 2015 that included 380 viral hepatitis patients (237 with chronic HBV, 143 with chronic HCV), no significant relationship was found between the degree of hepatic fibrosis and AAR score. API (age-platelet index) was one of the first methods used in the noninvasive determination of hepatic fibrosis. In the multicenter study published by Koksal et al.[18] in 2018, 216 chronic HCV patients were included and their APRI, AAR, FIB-4, API, and Forns index were compared in determining liver fibrosis. In patients with significant fibrosis for API, the AUROC value was 0.589, sensitivity 37.3%, and specificity 79.8% ($p<0.05$). In our study, the sensitivity and specificity rates for API were similar to those obtained in Koksal et al.'s[18] study.

The WHO guideline on the management of chronic HBV infection, published in March 2015, recommends the use of APRI as a noninvasive tool to detect liver cirrhosis and significant fibrosis in situations where resources are limited. In the study conducted by Liu et al.[19] in 2016, 1157 HBeAg-positive and 859 HBeAg-negative patients were evaluated. For significant fibrosis, the APRI score was found to be 0.775 in HBeAg-positive patients and 0.744 in HBeAg-negative patients ($p<0.05$). In our study, the AUROC value for the APRI score was found to be 0.711. In addition, in our study, when the cutoff value of 16.24 was taken for APRI, the sensitivity of the test was 59.64% and the specificity was 73.61%.

FIB-4, one of the newer methods for detecting liver fibrosis, has received more attention recently and has been extensively studied for its role in hepatitis B patients. Yin et al.[20] published a meta-analysis on the diagnostic importance of the FIB-4 score in the determination of liver fibrosis in 8274 HBV patients in 2017. In this meta-analysis, the AUROC value for FIB-4 was calculated as 0.720, the sensitivity 77%, and the specificity 66%, when the cutoff value was 0.8–1.1. Similarly, in our study, when we considered the cutoff value as 0.94, the AUROC value for FIB-4 was found to be 0.716. For significant fibrosis, we found the sensitivity of the FIB-4 score to be 56.77% and the specificity as 74.96%. There are also studies showing that FIB-4 has a relatively high diagnostic value for detecting liver fibrosis in hepatitis B patients when the diagnostic threshold is greater than 2.0. It has been shown that the KING score is superior to the AAR, APRI, and FIB-4 scores.[21] In the study of Hamidi et al.,[22] when the cutoff value of 0.661 was taken for the KING score, 0.661 AUROC, 62.9% sensitivity, and 57.6% specificity were obtained. In our study, the highest AUROC value for significant fibrosis was found in the KING score.

The FibroQ score was proposed by Hsieh et al.[23] in 2009. A total of 140 patients with chronic viral hepatitis (Hepatitis B and C) were included in the study. Significant liver fibrosis was defined as >1 (F2–4) METAVIR fibrosis score. When the cutoff value was taken as 1.6, the AUROC value of the FibroQ score for significant fibrosis was 0.783, the sensitivity was 79%, and the specificity was 71%, and it was shown that the FibroQ score was superior to AAR and APRI in determining liver fibrosis. In our study, we calculated the cutoff value of the FibroQ score as 2.72. For significant fibrosis, the AUROC value was 0.595, the sensitivity was 24.2%, and the specificity was 93.1%.

The Zeugma score, which we recommend to predict liver fibrosis, is formulated using a combination of platelet, albumin, globulin, and GGT. It is known that globulin and GGT levels increase and albumin and thrombocyte levels decrease in chronic hepatitis and liver cirrhosis (23–109). On the basis of this information, we created the formula for the Zeugma score. We found that the globulin and GGT values we used in the formula were statistically significantly higher in the fibrosis group compared to the patients without fibrosis ($p=0.001$). There was also a positive correlation between GLB and GGT values and fibrosis ($p<0.05$, $r=0.230$ and $r=0.305$, respectively). That is, as the fibrosis stage increases, both GGT and GLB values increase. When we considered the cutoff value of the Zeugma score as 9.63, we found 0.701 AUROC, 52.34% sensitivity, and 78.11% specificity for significant fibrosis.

As a result, six different noninvasive fibrosis detection methods were compared using patient data. In addition, the effect of the newly created Zeugma score, which is simple, applicable, and easy to calculate, in determining liver fibrosis was investigated and compared with other noninvasive methods. The advantage of our study is the simultaneous evaluation of seven different noninvasive methods and a large number of patients. In our study, the KING score was found to be the most effective noninvasive method in predicting liver fibrosis. At the same time, FIB-4, APRI, and Zeugma scores were also shown to have good efficacy in determining hepatic fibrosis. It was observed that the Zeugma score was superior to AAR, API, and FibroQ indices and had similar effectiveness to the APRI score. The AAR score was the noninvasive fibrosis measurement method that reached the lowest AUROC value in our study, which was shown to be insufficient to determine significant fibrosis in chronic HBV patients. The disadvantages of our study are that the data were obtained retrospectively; therefore, some patients were excluded from the study due to the lack of data, and laboratory data and liver biopsies could not be synchronized in all patients.

Ethics Committee Approval: The Gaziantep University Clinical Research Ethics Committee granted approval for this study (date: 05.02.2020, number: 2020/26).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – AK, MTG; Design – AK, SB; Supervision – AK, MTG; Fundings – AK; Materials – AK, SB; Data Collection and/or Processing – AK, SB; Analysis and/or Interpretation – AK, MTG; Literature Search – AK, SB; Writing – AK, SB; Critical Reviews – SB, MTG.

Conflict of Interest: The authors have no conflict of interest to declare.

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References

1. Trépo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet 2014;384(9959):2053-2063.
2. Furquim d'Almeida A, Ho E, Van Hees S, Vanwolleghem T. Clinical management of chronic hepatitis B: A concise overview. United European Gastroenterol J 2022;10(1):115-123.
3. Hsu CW, Liang KH, Huang SF, Tsao KC, Yeh CT. Development of a non-invasive fibrosis test for chronic hepatitis B patients and comparison with other unpatented scores. BMC Res Notes 2013;6:212.
4. Fiel MI. Pathology of chronic hepatitis B and chronic hepatitis C. Clin Liver Dis 2010;14(4):555-575.
5. 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(4):361-374.
6. Yeh WC, Li PC, Jeng YM, Hsu HC, Kuo PL, Li ML, et al. Elastic modulus measurements of human liver and correlation with pathology. Ultrasound Med Biol 2002;28(4):467-474.
7. Chen SH, Li YF, Lai HC, Kao JT, Peng CY, Chuang PH, et al. Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force ımpulse elastography in patients with chronic hepatitis C. BMC Gastroenterol 2012;12:105.
8. Imajo K, Kessoku T, Honda Y, Tomeno W, Ogawa Y, Mawatari H, et al. Magnetic resonance ımaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography. Gastroenterology 2016;150(3):626-637.e7.
9. Liu XD, Wu JL, Liang J, Zhang T, Sheng QS. Globulin-platelet model predicts minimal fibrosis and cirrhosis in chronic hepatitis B virus infected patients. World J Gastroenterol. 2012;18(22):2784-2792.
10. Park SH, Kim CH, Kim DJ, Suk KT, Cheong JY, Cho SW, et al. Usefulness of multiple biomarkers for the prediction of significant fibrosis in chronic hepatitis B. J Clin Gastroenterol 2011;45(4):361-365.
11. Castera L, Pinzani M. Non-invasive assessment of liver fibrosis: arewe ready? Lancet 2010;375(9724):1419-1420.
12. Li J, Tao H, Zhang E, Huang Z. Diagnostic value of gamma-glutamyl transpeptidase to alkaline phosphatase ratio combined with gamma-glutamyl transpeptidase to aspartate aminotransferase ratio and alanine aminotransferase to aspartate aminotransferase ratio in alpha-fetoprotein-negative hepatocellular carcinoma. Cancer Med 2021;10(14):4844-4854.
13. Rossi E, Adams LA, Bulsara M, Jeffrey GP. Assessing liver fibrosis with serum marker models. Clin Biochem Rev 2007;28(1):3-10.
14. Bhogal H, Sterling RK. Staging of liver disease: which option is right for my patient? Infect Dis Clin North Am 2012;26(4):849-861.
15. Shackel NA, McCaughan GW. Liver biopsy: is it still relevant? Intern Med J 2006;36(11):689-691.
16. Eminler AT, Ayyildiz T, Irak K, Kiyici M, Gurel S, Dolar E, et al. AST/ALT ratio is not useful in predicting the degree of fibrosis in chronic viral hepatitis patients. Eur J Gastroenterol Hepatol 2015;27(12):1361-1366.
17. Guéchot J, Boisson RC, Zarski JP, Sturm N, Calès P, Lasnier E; ANRS HCEP 23 Fibrostar Group. AST/ALT ratio is not an index of liver fibrosis in chronic hepatitis C when aminotransferase activities are determinate according to the international recommendations. Clin Res Hepatol Gastroenterol 2013;37(5):467-472.
18. Koksal I, Yılmaz G, Parlak M, Demirdal T, Kinikli S, Candan M, et al. Diagnostic value of combined serum biomarkers for the evaluation of liver fibrosis in chronic hepatitis C infection: A multicenter, noninterventional, observational study. Turk J Gastroenterol 2018;29(4):464-472.
19. Liu DP, Lu W, Zhang ZQ, Wang YB, Ding RR, Zhou XL, et al. Comparative evaluation of GPR versus APRI and FIB-4 in predicting different levels of liver fibrosis of chronic hepatitis B. J Viral Hepat 2018;25(5):581-589.
20. Yin Z, Zou J, Li Q, Chen L. Diagnostic value of FIB-4 for liver fibrosis in patients with hepatitis B: a meta-analysis of diagnostic test. Oncotarget 2017;8(14):22944-22953.
21. Karacaer Z, Avcı Ö, Karadağ FY. King's score may be more effective in the determination of severe fibrosis in chronic hepatitis B infections. Viral Hep J 2017;23(1):20-25
22. Hamidi AA, Oncul A, Ozguven BY, Sevgi DY, Gunduz A, Uzun N, et al. Diagnostic accuracy of different noninvasive scores for detecting advanced fibrosis in chronic hepatitis B. Eur J Gastroenterol Hepatol 2019;31(11):1439-1443.
23. Hsieh YY, Tung SY, Lee IL, Lee K, Shen CH, Wei KL, et al. FibroQ: an easy and useful noninvasive test for predicting liver fibrosis in patients with chronic viral hepatitis. Chang Gung Med J 2009;32(6):614-622.