Research Article

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Can We Accurately Assess Fibrosis in Chronic Hepatitis B Virus Patients?

Kronik Hepatitis B Virüs Hastalarında Fibrozu Doğru Bir Şekilde Değerlendirebiliyor muyuz?

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ABSTRACT

Objectives: To compare the efficacy of blood biochemical indicators with imaging techniques and biopsy data in detecting liver fibrosis in patients with chronic hepatitis B (CHB).

Materials and Methods: One hundred fifty-three CHB patients followed without treatment in the Infectious Diseases Hepatitis Outpatient Clinic between 2021 and 2023 at Ege University Medical Faculty Hospital. The aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, fibrosis-4 (FIB-4) score, aspartate aminotransferase - platelet ratio index (APRI) score, and platelet (PLT) count were all calculated at the same time as the International Normalized Ratio (INR) level and FIB-4 score. Hepatobiliary system ultrasonography (USG) findings, demographic characteristics, hepatitis B virus (HBV)-DNA levels, ultrasound-based elastographic imaging results, and liver biopsy results were assessed. With serum fibrosis markers, AST/ALT ratio, FIB-4 score, APRI score, INR level, PLT number and gender, age, HBV-DNA, liver damage levels via biopsy and ultrasound-based elastography and hepatobiliary system USG results and their relationship between each other were investigated.

Results: Of the patients, 73 (47.7%) were male. The average age was 47.11±13.47 years. Being female, the AST/ALT ratio of more than 1 and being >40 years were found to be statistically significant. The rate of AST/ALT >1 was found to be significantly higher in patients with normal USG findings. The PLT count was found to be higher in the group with HBV-DNA >2000 IU/mL. The FIB-4 score was found to be higher only in males. There was no statistically significant difference between the genders in the APRI score; however, it was found to be higher in patients aged >40 years.

Conclusion: To predict the progression to cirrhosis or hepatocellular carcinoma in CHB patients who do not match the treatment criteria per the Turkish CHB treatment reimbursement

ÖZ

Amaç: Kronik hepatit B'li (KHB) hastalarda karaciğer fibrozunu tespit etmede kullanılan serum biyokimyasal belirteçlerinin performanslarının, fibrozu saptamaya yönelik olarak kullanılan görüntüleme yöntemleri ve biyopsi sonuçları ile karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Ege Üniversitesi Tıp Fakültesi Hastanesi'nde Ocak 2021-Mart 2023 tarihleri arasında Enfeksiyon Hastalıkları Hepatit Polikliniği'nde tedavi almadan takip edilen 153 KHB hastasının fibrozis-4 (FIB-4) skoru, aspartat aminotransferaz - trombosit oranı indeksi (APRİ) skoru, aspartat aminotransferaz/alanin aminotransferaz oranı (AST/ALT) hesaplanmış, eş-zamanlı Uluslararası Normalleştirilmiş Oran (INR) seviyesi ve trombosit (PLT) sayılarına bakılmıştır. Bu serum belirteçlerinin hesaplanıp, kaydedildiği dönemde sistem kayıtlarından hastaların; demografik özellikleri, hepatit B virüs (HBV)-DNA düzeyleri, ultrason bazlı elastografik görüntüleme sonuçları, hepatobiliyer sistem ultrasonografi (USG) bulguları ve karaciğer biyopsi sonuçları değerlendirilmiştir. Serum fibroz belirteçleri olan; AST/ALT oranı, FIB-4 skoru, APRİ skoru, INR düzeyi, PLT sayısı ile cinsiyet, yaş, HBV-DNA, karaciğer biyopsi hasarı düzeyleri ile ultrason bazlı elastografi görüntüleme sonucu ve hepatobiliyer sistem USG sonuçlarının birbiri ile olan ilişkisi, istatistiksel analizler ile araştırılmıştır.

Bulgular: Hastaların 73'ü (47,7) erkek, 80'i (52,3) kadın olup; yaş ortalaması:47,11±13,479 yıl idi. AST/ALT oranın >1 olması, kadın cinsiyet ve >40 yaş bireylerde istatiksel anlamlı bulunmuştur. Normal USG bulgularına sahip hastalarda AST/ALT >1 olma oranı anlamlı oranda daha yüksek saptanmıştır. HBV-DNA >2000 IU/mL olan grupta PLT değeri daha yüksek bulunmuştur. FIB-4 skoru sadece erkeklerde daha yüksek saptanmış, APRİ skorunda cinsiyetler arasında istatistiksel anlamlı bir fark bulunmamış, ancak >40 yaş hastalarda daha yüksek bulunmuştur.

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guideline, fibrosis risk was assessed using biochemical markers and radiological imaging techniques. However, it was determined that radiological imaging using serum markers is not a reliable way to predict fibrosis in its early stages.
Keywords: Chronic HBV infection, liver fibrosis, non-invasive parameter, liver biopsy

Sonuç: Çalışmamızda Sağlık Uygulama Tebliği'ne göre tedavi kriterlerini sağlamayan KHB hastalarında siroza/hepatosellüler kansere ilerleyişi öngörmek için fibrozis riski, biyokimyasal belirteçler ve radyolojik görüntüleme yöntemleri ile değerlendirilmiştir. Ancak çalışmamızda serum belirteçleri ile radyolojik görüntülemenin, fibrozun erken göstergesi olmadığı sonucuna varılmıştır.
Anahtar Kelimeler: Kronik hepatit B, karaciğer fibrozisi, non-invaziv fibrosis göstergeleri, karaciğer biyopsisi

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Introduction

Detection of fibrosis in patients with chronic hepatitis B (CHB) has become an increasingly important issue in recent years in terms of evaluating the prognosis of the disease and quickly initiating antiviral treatment. The fact that hepatic fibrosis is not an irreversible process as it was accepted in the past, that the progression can be slowed and that it can be resolved to some extent with antiviral treatment has also accelerated the fibrosis diagnosis process (1).

The gold standard for staging hepatic fibrosis is the histopathological analysis of the liver biopsy specimen. Liver biopsy, however, has its own restrictions. The main drawbacks include the need for hospitalization, the difficulty of repeating it, the cost, the potential for deadly complications like hemorrhage and perforation, the capacity to sample just a limited portion of the liver, and the sampling variability and interobserver variability that come with these limitations (1,2,3). Due to these drawbacks, noninvasive techniques to detect hepatic fibrosis have been developed. Non-invasive fibrous testing can be used to determine the start of treatment in specific patient groups according to the 2017 viral hepatitis treatment guideline published by the European Association for the Study of the Liver [with hepatitis B virus (HBV)-DNA level >2000 IU\mL, alanine aminotransferase (ALT) levels normal and refusal to undergo biopsy] (4). These tests were evaluated in two separate groups as imaging and serum markers. In this study, early detection of fibrosis by serum markers and imaging methods and its statistical relationship with findings such as liver biopsy, age, gender, HBV-DNA level, and liver ultrasonography (USG) in CHB patients followed in our outpatient clinic and for whom treatment could not be initiated according to the Turkish CHB treatment reimbursement guideline were investigated.

Materials and Methods

The study included 153 CHB patients who did not receive treatment and were evaluated in the Infectious Diseases Hepatitis Outpatient Clinic at Ege University Hospital between January 2021 and March 2023. Demographic features, fibrosis-4 (FIB-4) (1.45-3.25) score, [aspartate aminotransferase - platelet ratio index (APRI) (0.5-2)] score, ratio of aspartate aminotransferase to alanine aminotransferase (AST/ALT >1) were calculated, International Normalized Ratio (INR), platelet (PLT) count, HBV-DNA levels [Cobas® 6800 (Roche Molecular Diagnostics, Switzerland)], ultrasound-based elastographyimaging, hepatobiliary system USG findings and liver biopsy results were recorded retrospectively. HBV-DNA levels were classified as having HBV-DNA >2000 IU/mL at some point in life or having all measurements. Liver biopsy results were grouped as mild, moderate, and severe according to grade and stage values in the Ishak fibrosis staging. USG findings were divided into normal and abnormal (additional adiposity, increase in paraenchymal echogenicity, increase in portal vein diameter, etc.) ≤2000. The AST/ALT ratio, FIB-4 score, APRI score, INR number, and PLT number values; age (>40, sex ≤40), HBV-DNA (>2000 ve ≤2000), liver biopsy result (mild, moderate, severe), ultrasound-based elastography imaging result (F0, F1, F2), and hepatobiliary system USG result (normal, abnormal) were statistically compared with each other and analyzed.

The study was planned in accordance with the Helsinki Declaration decisions and the patient rights regulation, and the Turkish CHB treatment reimbursement guideline (HBV-DNA >2000 IU/mL or $>10^4$ copy/mL and Ishak fibrosis score ≥2/6 or Histology Activity Index ≥6/18). Ethics committee approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: E-99166796-050.06.04-1197109, date: 27.03.2023).

Statistical Analysis

The SPSS statistical analysis program was used to evaluate the data. For numerical variables, first to fit the normal distribution Kolmogorow-Smirnov and Shaphiro-Wilk tests were performed. If the p (statistical significance) value was greater than 0.05 in both tests, it was accepted that the data had a normal distribution. T-test was used for the variables with a normal distribution, and the Mann-Whitney U test was used for those who did not. Statistically, $p<0.05$ was considered significant.

Results

When 153 CHB patients who were followed up between January 2021 and March 2023 and who did not receive treatment were analyzed 73 (47.7). Of the patients, 73 (47,7.3%) were

male and the mean age was 47.11±13.48 years. The mean ALT, AST, PLT, and INR values of the patients were, respectively; 24.06±25.42 U/L, 20.81±12.24 U/L, 240.91±53.97 10^3µL, and the INR value was 0.96±0.06. A serum marker AST/ALT ratio of more than 1 was found to be statistically significantly higher in females and individuals aged more than 40 years (p=0.00003, 0.0072, respectively). Contrary to expectations, the AST/ALT >1 rate was higher in patients with normal USG findings. (p=0.0146). When the PLT count was evaluated, there was no significant difference between the groups, but the platelet PLT was found to be higher in the group with HBV-DNA >2000 IU/mL (p=0.00154). The FIB-4 score was found to be higher only in males (p=0.0457), and no statistically significant difference was found in other parameters. There was no statistically significant difference between the genders in the APRI score, but it was found to be higher in patients aged more than 40 years (p=0.04). Contrary to expectations, the APRI score was found to be statistically significantly higher in patients with normal USG findings. The INR value was found to be high in patients aged 40 years (p=0.0055). Comparison data between groups are summarized in Table 1, 2.

Discussion

Liver biopsy is the gold standard method in the determination of fibrosis in CHB patients and is a necessary and mandatory practice in Turkey to initiate treatment for naive patients. In the last decade of hepatology, the determination of liver fibrosis by non-invasive diagnostic methods without biopsy and early initiation of treatment in certain groups by considering individual risk factors has been included in the guidelines and accepted internationally (4,5,6,7).

In this research, we did not encounter a patient in our chronic HBV patient group for whom we could not start treatment according to the Turkish CHB treatment reimbursement guideline, and we thought it necessary to start treatment with non-invasive serum fibrous markers and ultrasound-based elastography methods. This situation is mainly due to the analyzed patient group, we attribute ALT, AST, PLT, and INR values to the patients with mild disease according to their HBV-DNA mean. In addition, the young age and female gender predominance of the patient group were also effective in this result.

Williams and Hoofnagle (8) showed in a retrospective study that AST/ALT ≥1 is significant for cirrhosis in a population of patients with non-alcoholic liver disease. Reedy et al. (9), on the other hand, stated in their study that the AST/ALT ratio evaluated before the treatment of chronic HCV infection could not accurately predict the presence of cirrhosis and the need for liver biopsy continued. Although AST/ALT ratio more than 1 was found to be higher in the female gender and >40 age group in our study, it was unexpectedly found to be statistically higher in individuals with normal USG findings. The lack of a statistically significant relationship between biopsy and elastography results might be due to the insufficient number of the study group.

Low PLT count and especially recently prolonged INR have been mentioned in many publications as important markers of cirrhosis and advanced fibrosis (10,11). Gold standard liver biopsy and non-invasive serum fibrous markers were compared retrospectively in 464 patients who underwent surgical resection for hepatocellular cancer. Where ISHAK score and 10 different non-invasive fibrous markers were compared, no significant correlation was found between tests and biopsy scores (12). The fact that such a result was obtained even in the patient group with high fibrosis is supportive in terms of the accuracy of the results of our study, in which patients with mild fibrosis were predominant.

FIB-4 and APRI scoring systems have been routinely used in recent years to determine fibrosis. In this respect Shin et al. (13) showed that the APRI score is a reliable method for estimating fibrosis. Another study in patients with chronic HCV concluded that the APRI score was more reliable in predicting fibrosis in women than in men (14). Yilmaz et al. (15), in their study on 207 CHB, 108 CHC and 140 NAFLD patients, showed results that correlated with liver biopsy, with APRI score showing significant fibrosis in all three patient groups. In the study of Sayar et al. (16), the diagnostic performance of the FIB-4 index in determining cirrhosis was found to be good. Kaya et al. (17) found that the negative predictive value of FIB-4 index was high.

Wai et al. (18) compared the biopsy results with the APRI score in untreated patients with chronic HBV and demonstrated that the APRI score was successful in identifying patients with significant fibrosis and cirrhosis. In the study of Lin et al. (19), on the other hand, they found that APRI could identify fibrosis associated with CHB with moderate accuracy. At the latest, in a publication in which high patient data such as 69,106 were reviewed retrospectively, the diagnostic value of FIB-4 and APRI test results in determining fibrosis was found to be low. In this publication, it was reported that 86% and 67% of patients with fibrous F3-F4 scores, respectively, with FIB-4 and APRI scores were misdiagnosed as F1-F2 (20,21). Statistically significant in our study, in patients with APRI score >40 years; FIB-4 score was found to be higher in males; It was found to be compatible with some literature, but there are also studies reporting different results.

Imaging techniques, one of the noninvasive methods that detect fibrosis, have taken their place in the guides in terms of diagnosis (4). Studies have reported that fibroscan and serum biomarkers have similar performance in detecting fibrosis in hepatitis patients with significant fibrosis (22). Although the combination of fibroscan and serum biochemical markers is more effective than the combination of the two serum markers, its higher cost draws attention in studies (4,23,24). In our study, fibroscan and biopsy findings did not yield statistically significant results with non-invasive biochemical tests. We think that our patient group consisted of patients with m, and fibrosis and the comparison of fibroscan and biopsy results in a few patients is probably responsible for this situation.

In our study, the APRI score and AST/ALT ratio were found to be higher in individuals with normal USG findings, contrary to expectations. We think that the reason for this is that our patients are in the young age group with mild disease without advanced liver damage. Another problem is that USG evaluations were made at different times and by different radiologists. USG is the first preferred imaging method because it is inexpensive and easily accessible in detecting chronic liver damage (25). Demir et al.

(26) investigated the value of ultrasound in the diagnosis of early cirrhosis by comparing the histopathological findings of patients with chronic viral hepatitis with ultrasound changes in the liver. In this study, it was determined that the most sensitive finding in the diagnosis of early cirrhosis was the irregularity of the liver parenchyma. In another study, it was reported that ultrasound had a diagnostic accuracy of 84-87% for the diagnosis of significant fibrosis, 89-91% for the diagnosis of severe fibrosis, and 92-93% for the diagnosis of liver cirrhosis (27).

Table 1. Intergroup analysis of AST/ALT ratio, APRI score, and PLT count

Mann-Whitney U test		**n**	**Median**	**Minimum**	**Maximum**	**Asymp. sig. (2-tailed)**
AST/ALT	Male	73	0.864	0.375	2,5	0.00003
	Female	80	1,071	0.455	2,625	
	<=40 years	54	0.915	0.375	2	0.0072
	>40 years	99	1,045	1,04545	2,625	
	HBV-DNA <=2000	73	One	0.455	2,625	0.645
	HBV-DNA >2000	80	One	0.375	1,889	
	Abnormal	49	0.888	0.375	2	0.014
	Normal	67	One	0.444	2,625	
	F0	24	0.968	0.571	1,615	0.975
	F1	4	0.974	0.714	1,429	
T-test biopsy		**n**	**Mean**	**SD**		**Sig. (2-tailed)**
AST/ALT	Mild	24	1,015	0.3064		0.035
	Moderate	4	0.655	0.2334		
T-test		**n**	**Mean**	**SD**		**Sig. (2-tailed)**
PLT (10^3µL)	Male	73	219.23	44.76		7,358
	Female	80	260.7	54,299		
	<=40 years	54	237.61	56.62		0.577
	>40 years	99	242.72	52,681		
	HBV-DNA <=2000	73	226.62	48,141		0.00154
	HBV-DNA >2000	80	253.96	55,961		
	Abnormal	49	250.45	55,238		0.1896
	Normal	67	237.3	51,341		
	F0	24	229	61,163		0.3144
	F1	4	264.75	86,102		
	Mild	24	255.92	56,083		0.693
	Moderate	4	244.25	37,322		
Mann-Whitney U test		**n**	**Median**	**Minimum**	**Maximum**	**Asymp. sig. (2-tailed)**
APRI	Male	73	0.401	0.156	1,689	0.354
	Female	80	0.42	0.169	1,651	
	<=40 years	54	0.383	0.156	1,361	0.04
	>40 years	99	0.426	0.191	1,689	
	HBV-DNA <=2000	73	0.439	0.191	1,689	0.109
	HBV-DNA >2000	80	0.3885	0.156	1.05	
	Abnormal	49	0.375	0.156	0.922	0.01099
	Normal	67	0.439	0.169	1,689	
	F0	24	0.439	0.287	1.05	0.635
	F1	4	0.4125	0.209	0.611	
T-test	**Biopsy**	**n**	**Mean**	**SD**		**Sig. (2-tailed)**
APRI	Mild	24	0.43679	0.183567		0.092
	Moderate	4	0.271	0.091902		

AST/ALT: Aspartate aminotransferase/alanine aminotransferase, APRI: Aspartate aminotransferase - platelet ratio index, PLT: Platelet, HBV: Hepatitis B virus, SD: Standard deviation

Table 2. Intergroup analysis of FIB-4 score and INR value

Mann-Whitney U test		**n**	**Median**	**Minimum**	**Maximum**	**Asymp. sig. (2-tailed)**
INR	Male	73	0.96	0.85	1.16	0.463
	Female	80	0.965	0.86	1.15	
	<=40 years	54	0.975	0.9	1.16	0.0055
	>40 years	99	0.95	0.85	1.15	
	HBV-DNA <=2000	73	0.97	0.88	1.16	0.79
	HBV-DNA >2000	80	0.96	0.85	1.1	
	Abnormal	49	0.955	0.86	1.1	0.157
T-test		**n**	**Mean**	**SD**		**Sig. (2-tailed)**
INR	F0	23	0.97565	0.050075		0.741
	F1	4	0.985	0.061914		
	Mild	23	0.95826	0.051756		0.051
	Moderate	4	1,015	0.047958		
Mann-Whitney U test		**n**	**Median**	**Minimum**	**Maximum**	**Asymp. sig. (2-tailed)**
FIB-4	Male	73	0.83	0.37	3.25	0.0457
	Female	80	0.745	0.24	3.17	
	<=40 years	54	0.61	0.24	1.33	2,267
	>40 years	99	0.97	0.262	3.25	
	HBV-DNA <=2000	73	0.92	0.24	3.25	0.0647
	HBV-DNA >2000	80	0.74	0.262	2.05	
	Abnormal	49	0.94	0.262	1.95	0.801
	Normal	67	0.76	0.295	3.25	
T-test		**n**	**Mean**	**SD**		**Sig. (2-tailed)**
FIB-4	F0	24	0.89308	0.323162		0.114
	F1	4	0.62	0.161038		
	Mild	24	0.90133	0.40718		0.996
	Moderate	4	0.9025	0.422641		

FIB-4: Fibrosis-4, HBV: Hepatitis B virus, INR: International Normalized Ratio

Study Limitations

The limitations of our study are that we have biopsy and fibroscan results from a limited number of patients and that these results are not concurrent with serum fibrous markers.

Conclusion

We think that this study is an original study in terms of complicating the possibility of early treatment by comparing serum fibrous markers and imaging tests used to detect liver fibrosis with the factors of the patient.

The risk of fibrosis was assessed with noninvasive biochemical and radiological tests, and their superiority over liver biopsy was investigated in CHB patients who did not receive treatment because they did not meet the current treatment criteria in order to prevent progression to cirrhosis and hepatocellular cancer. We could not uncover any results in our study that supported our hypothesis that these technologies, which are affordable, simple, and accessible, can prevent both patients and doctors from an intrusive operation such as a biopsy. Our research has led us to believe that non-invasive fibrous indicators are not yet a viable substitute for liver biopsies, but they do have a negative predictive value when deciding whether to begin treatment.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2023-033623-3T/25, date: 16.02.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Y., H.P., T.Y., Concept: N.Y., H.P., T.Y., Design: N.Y., H.P., T.Y., Data Collection or Processing: N.Y., A.K., G.Ş.İ., M.M.V., H.P., T.Y., Analysis or Interpretation: N.Y., A.K., H.P., T.Y., Literature Search: N.Y., H.P., T.Y., Writing: N.Y., H.P., T.Y.

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