Research Article

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Comparison of Non-Invasive Methods and Liver Biopsy for Detecting Liver Fibrosis Associated with Chronic Hepatitis B

Kronik Hepatit B'ye Bağlı Fibrozisin Saptanmasında Non-İnvaziv Yöntemlerle Karaciğer Biyopsisinin Karşılaştırılması

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ABSTRACT

Objectives: Serological tests and elastography have recently been used more commonly for the detection of liver fibrosis. The aim of this study was to compare the histopathologically confirmed liver fibrosis stage with serological tests and point shear wave elastography (pSWE) in chronic hepatitis B (CHB) patients.

Materials and Methods: Patients who underwent liver biopsy for CHB in the infectious diseases clinic were included. Demographic characteristics, laboratory results, and pSWE measurements were recorded retrospectively. pSWE measurements were evaluated according to the guidelines of the European Federation of Ultrasound Societies in Medicine and Biology.

Results: Thirty-five patients were included in the study, 23 (65.7%) of whom were male. The mean age was 47.2±12.6. Significant fibrosis was found in 15 patients (42.9%) on histopathological evaluation. The mean pSWE value of patients with mild fibrosis was 1.6±0.5 m/sec and with significant fibrosis was 2.2±0.5 m/sec. Significant fibrosis risk was shown to be associated with mean pSWE values (p=0.002) and the accuracy rate was calculated 62.8% (the area under the curve: 0.807). When the cut-off value of pSWE was taken as 1.77 m/sec to determine significant fibrosis (likelihood ratio: 2.67), the sensitivity was 80% and the specificity was 70% (p=0.002). The correlation between pSWE median values with age (r=0.452, p<0.01), body mass index (r=0.673, p<0.01), grade of steatosis (r=0.534, p<0.01), and stage of fibrosis (r=0.633, p<0.01) was calculated.

ÖZ

Amaç: Son zamanlarda karaciğer fibrozisinin tespitinde serolojik testler ve elastografi daha yaygın olarak kullanılmaktadır. Bu çalışmanın amacı kronik hepatit B (KHB) hastalarında histopatolojik olarak doğrulanan karaciğer fibrozisi evresini serolojik testler ve point shear wave elastografi (pSWE) ile karşılaştırmaktır.

Gereç ve Yöntemler: Enfeksiyon hastalıkları kliniğinde KHB nedeniyle karaciğer biyopsisi yapılan hastalar çalışmaya dahil edildi. Demografik özellikler, laboratuvar sonuçları ve pSWE ölçümleri retrospektif olarak kaydedildi. pSWE ölçümleri, Avrupa Tıp ve Biyolojide Ultrason Dernekleri Federasyonu yönergelerine göre değerlendirildi.

Bulgular: Çalışmaya dahil edilen 35 hastanın 23'ü (%65,7) erkekti. Ortalama yaş 47,2±12,6 idi. Histopatolojik değerlendirmede 15 hastada (%42,9) belirgin fibrozis saptandı. Hafif fibrozisli hastaların ortalama pSWE değeri 1,6±0,5 m/sn, belirgin fibrozisli hastaların ise 2,2±0,5 m/sn idi. Belirgin fibrozis riskinin ortalama pSWE değerleriyle ilişkili olduğu gösterildi (p=0,002) ve doğruluk oranı %62,8 olarak hesaplandı (Eğri altında kalan alan: 0,807). Belirgin fibrozisin belirlenmesi için pSWE'nin eşik değeri 1,77 m/sn alındığında (olasılık oranı: 2,67) testin duyarlılığı %80 ve özgüllüğü %70 olarak bulundu (p=0,002). PSWE medyan değerleri ile yaş (r=0,452, p<0,01), vücut kitle indeksi (r=0,673, p<0,01), hepatosteatoz derecesi (r=0,534, p<0,01) ve histopatolojik fibrozis skorları (r=0,633, p<0,01) arasında orta seviyede pozitif ve anlamlı bir korelasyon olduğu gösterildi.

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Conclusion: pSWE is promising; however, it is thought that the method will develop further if pSWE is used more frequently in clinical practice.
Keywords: Chronic hepatitis B, liver fibrosis, point shear wave elastography

Sonuç: pSWE ümit vericidir; ancak pSWE'nin klinik uygulamada daha sık kullanılması durumunda yöntemin daha da gelişeceği düşünülmektedir.
Anahtar Kelimeler: Kronik hepatit B, karaciğer fibrozisi, point shear wave elastografi

Introduction

Hepatitis B virus (HBV) is a global health problem. Regular follow-up of this disease is important because it causes serious complications such as cirrhosis, hepatocellular cancer (HCC), and death in chronic cases (1).

The stage of liver fibrosis in patients is determined by biopsy, the gold standard method. In recent years, non-invasive methods have been used more frequently due to liver biopsy being invasive in nature, risk of complications, difficulty in repeating, and high cost (2).

Non-invasive methods consist of two categories: serological tests and elastography. Serological tests [Aspartate aminotransferase (AST) platelet ratio index (APRI), Fibrosis-4 (FIB-4), FibroTest/FibroSure (Labcorp, United States) etc.] are used more frequently because of ease of administration. However, there are not enough studies related to serological tests that have accurate sensitivity and specificity that can replace histopathological evaluation directly in the literature (3,4). Therefore, it is generally recommended to use these markers in combination with elastography. Elastography is an alternative to biopsy and gives an idea about liver fibrosis according to the degree of hardness of the tissue (5).

This study was conducted to compare the histopathologically confirmed liver fibrosis stage with serological tests and point shear wave elastography (pSWE) in chronic hepatitis B (CHB).

Materials and Methods

Study Design and Ethical Statement

This study was conducted between 01.09.2021 and 01.09.2022 as a descriptive retrospective study. Ethics committee approval was obtained from the Clinical Research Ethics Committee (approval number: 2022/133, date: 12.10.2022). The study was conducted in accordance with the Declaration of Helsinki.

Clinical Data

The inclusion criteria for the studywere as follows: (I) being followed up due to CHB in the infectious diseases clinic between 01.09.2021 and 01.09.2022, (II) having undergone liver biopsy in the interventional radiology, (III) being between the ages of 18 and 85, and (IV) having hepatitis B surface antigen positivity for more than six months. Patients with a diagnosis of viral hepatitis other than HBV infection and incomplete clinical or laboratory data were excluded from the study.

Data Sources, Measurement, and Variables

All patients' age, body mass index (BMI), gender, laboratory results, and pSWE measurements were retrospectively analyzed from hospital records. The test results of all patients obtained immediately before the biopsy day were recorded. Serological fibrosis scores were calculated using the following formulas (5):

FIB-4 = Age (years) × AST (U/L)/[platelet count (10^9/L) × (U/L)]

APRI = [(AST/upper limit of normal AST range) x100]/platelet count

Forn's index = 7.811-3.131 × log (platelet count) + 0.781 × log [gamma-glutamyl transferase (GGT) (U/L)] + 3.467 × log (age) -0.014 × (total cholesterol)

NAFLD = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glucose or diabetes mellitus (yes = 1, no = 0) + 0.99 × AST/alanine aminotransferase (ALT) ratio - 0.013 × platelet count (×10^9/L) - 0.66 × albumin (g/dL).

All patient measurements were made by the same radiologist who was unaware of patient information. A Siemens Acuson S3000 ultrasound device and curvilinear probe were used for pSWE.

pSWE measurement was performed at a depth of 2-7 cm of the liver capsule from the intercostal space while the patient was in the supine position and holding breath at the end of expiration. Ten measurements were performed for each patient, and the median value of these measurements was given as the pSWE result. pSWE measurements were performed in accordance with the European Federation of Societies for Ultrasound in Medicine and Biology (6).

Grouping Methods for Participants and Definitions

Patients were divided into two groups according to their Metavir fibrosis scores. Patients with pSWE 1.35 m/sec (F0 and F1) were grouped as having mild fibrosis, and patients with 1.35 m/sec and above (F2 and above) were grouped as significant fibrosis (6).

Histopathological evaluation of biopsies is performed according to the Ishak scoring system in our hospital. The patients were divided into two groups according to Ishak fibrosis scores. Patients with fibrosis scores of 0 and 1 were grouped as having mild fibrosis; patients with a fibrosis score of 2 or more were grouped as having significant fibrosis.

Statistical Analysis

SPSS version 22.0 program was used for statistical evaluation. The Kolmogorov-Smirnov "Test of Normality" was used to analyze the conformity of the data to normal distribution, and those with $p>0.05$ were considered to be normally distributed. Risk prediction to distinguish significant fibrosis from mild fibrosis was evaluated using receiver operating characteristic (ROC) analysis. The cut-off value was determined after calculating the likelihood ratio (LR) in the ROC analysis for pSWE measurement. The p-values for all tests were calculated at the $\alpha<0.05$ significance level.

Results

Thirty-five patients who met the inclusion criteria were enrolled in the study. Twenty-three (65.7%) patients were male and 12 (34.3%) were female. The mean age of the patients was 47.2±12.6.

According to the Ishak fibrosis scoring system, mild and significant fibrosis was detected in 20 (57.1%) and 15 (42.9%) patients, respectively. In addition, five or six fibrosis scores were not detected in any patient.

A comparison of the demographic characteristics, laboratory parameters, and pSWE measurements of the patients according to their Ishak fibrosis scores is shown in Table 1. The risk of significant fibrosis increased significantly with age and BMI (p=0.018 and p=0.032). A statistically significant relationship was not found between Ishak fibrosis scores and laboratory parameters and serological tests.

The mean pSWE value of patients with mild fibrosis was 1.6±0.5 m/sec and with significant fibrosis was 2.2±0.5 m/sec. Significant fibrosis risk was associated with mean pSWE values (p=0.002). According to PSWE measurements, mild and significant fibrosis was detected in 7 (20%) and 28 (80%) patients, respectively.

A cross-table of patients with mild and significant fibrosis according to Ishak fibrosis scores and pSWE measurements was performed (p=0.012). The sensitivity and specificity of the pSWE measurements were calculated as 100% and 35%, respectively. The positive predictive value was 53.5%, whereas the negative predictive value was 100%. The accuracy rate of the test was 62.8%.

To analyze the diagnostic performance of pSWE, ROC curve was used based on the fibrosis score determined by histopathological evaluation (Figure 1).

In the ROC curve analysis, which was performed to predict the risk of significant fibrosis, the area under the curve (AUC) was calculated as 0.807 (95% confidence interval: 0.663-0.951). According to the study, when the cut-off value of pSWE was taken as 1.77 m/sec to determine significant fibrosis (LR: 2.67), the sensitivity of the test was 80% and the specificity was 70% (p=0.002).

According to the ultrasound records of the patients, hepatic steatosis was found in 16 patients (45.7%). Five of the patients (14.3%) had grade 1 steatosis and 11 (31.4%) had grade 2 steatosis. Spearman's test was performed to investigate the correlation between the patients' Ishak fibrosis scores and pSWE median measurements, age, BMI, and grade of hepatic steatosis

Table 1. Comparison of the demographic characteristics, laboratory parameters, serological tests, and pSWE measurements of patients according to Ishak fibrosis scores

	Mild fibrosis, (n=20, 57.1%)	**Significant fibrosis, (n=15, 42.9%)**	**Total (n=35)**	**p-value**
Demographic characteristics				
Age (mean ± SD)	43±12.6	53±10.4	47.2±12.6	0.018*
BMI (mean ± SD)	25.7±4.8	29.5±5.1	27.3±5.2	0.032*
Gender (n, %)				
Female	5 (14.3%)	7 (20%)	12 (34.3%)	0.181
Male	15 (42.8%)	8 (22.9%)	23 (65.7%)	
Laboratory parameters median (min.-max.)				
AST, U/L	27.5 (14-122)	25 (14-175)	27 (14-175)	0.505
ALT, U/L	38.5 (15-203)	29 (13-304)	35 (13-304)	0.484
GGT, U/L	22 (12-146)	22 (12-40)	22 (12-146)	0.125
Total cholesterol, mg/dL	174.5 (97-258)	161 (142-290)	166 (97-290)	0.739
Laboratory parameters (mean ± SD)				
Platelet, x10^3/uL	216.1±70.8	238.6±60.2	225.7±66.5	0.328
Albumin, g/dL	4.3±0.2	4.2±0.3	4.3±0.3	0.294
Serological tests median (min.-max.)				
FIB-4	1.1 (0.4-4.3)	0.9 (0.3-3.1)	0.9 (0.3-4.3)	0.443
APRI	0.3 (0.1-1.7)	0.2 (0.1-3)	0.3 (0.1-3)	0.907
Serological tests (mean ± SD)				
Forn's index	4 ± 1.4	4.8±1.5	4.3±1.5	0.125
NAFLD score	0.1±1.2	0.5±0.8	0.3±1.1	0.208
Radiology results (mean ± SD)				
pSWE measurements, m/s	1.6±0.5	2.2±0.5	1.9±0.6	0.002*

*p<0.05 was considered statistically significant; n: number of patients. BMI: Body mass index, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, FIB-4: Fibrosis-4, APRI: AST platelet ratio index, NAFLD: Nonalcoholic fatty liver disease, SD: Standard deviation, min.: Minimum, max.: Maximum, pSWE: Point shear wave elastography

(Table 2). There was a positive and significant correlation between the variables. The strongest relationship was found between the pSWE median values and BMI (Figure 1).

Discussion

Anyone living with CHB infection should be followed up regularly at 3-6 months intervals because of the risk of developing cirrhosis, liver failure, and HCC (7). To prevent cirrhosis and HCC in patients with CHB, it is critical to identify risk factors that may be associated with fibrosis. In a study by Wu et al. (8), the parameters that predict fibrosis in CHB patients were evaluated. As a result; male gender, ≥18 years of age, high α-fetoprotein level and CHB disease with hepatitis B e antigen negative are found as the associated risk factors (8). In another study, advanced age (≥50 years), being overweight (BMI ≥28 kg/m^2), and high triglyceride and ALT levels were found to be independent risk factors for septal fibrosis (9). In our study, it was also shown that the risk of fibrosis increases significantly with age and BMI, significantly (p=0.018 and p=0.032).

In a review, serological tests such as APRI, FIB-4, and FibroSure can also be used for liver fibrosis scoring in patients who cannot undergo biopsy because they are clinically unsuitable. Nevertheless, it also warns that the accuracy rates of these tests are variable in previous studies (10).

In Kim et al. (11), 575 patients evaluated the performance of the APRI and FIB-4 tests in patients who underwent biopsy. While APRI and FIB-4 test results at the beginning of treatment were similar to those of the Ishak scoring system (p<0.01), they were found to be lower in patients followed 240 weeks after treatment. For this reason, it has been emphasized that APRI and FIB-4 scores are not sufficient in the evaluation of liver fibrosis, especially in the treatment follow-up (11). Therefore, it is generally recommended to use these markers in combination with elastography (5).

A meta-analysis by Jiang et al. (12) compared the diagnostic accuracy of pSWE and transient elastography in predicting liver fibrosis. The rate of failed measurement was found to be more than ten times greater for transient elastography than for pSWE (12). In another study, transient elastography was found to perform better than pSWE in detecting significant and advanced fibrosis (13). Studies have shown that the diagnostic accuracy of imaging methods is better, especially in advanced fibrosis stages. The superiority of transient elastography and pSWE has not yet been clearly demonstrated.

In a prospective multicenter study in patients who underwent biopsy for chronic liver disease conducted by Sande et al. (14), the role of factors such as age, gender, and hepatic steatosis in addition to pSWE measurements in the prediction of liver fibrosis was evaluated using logistic regression analysis, and modeling was performed to detect fibrosis. According to the logistic regression analysis applied to all variables in the model, it has been shown that pSWE and hepatic steatosis are variables that contribute to the predictive power of the model. The AUC was calculated as 0.91 when only pSWE was used in the detection of significant fibrosis, whereas it was calculated as 0.944 when hepatic steatosis and pSWE were used together. It has been shown that the diagnostic accuracy of pSWE significantly increases with the inclusion of hepatic steatosis (14).

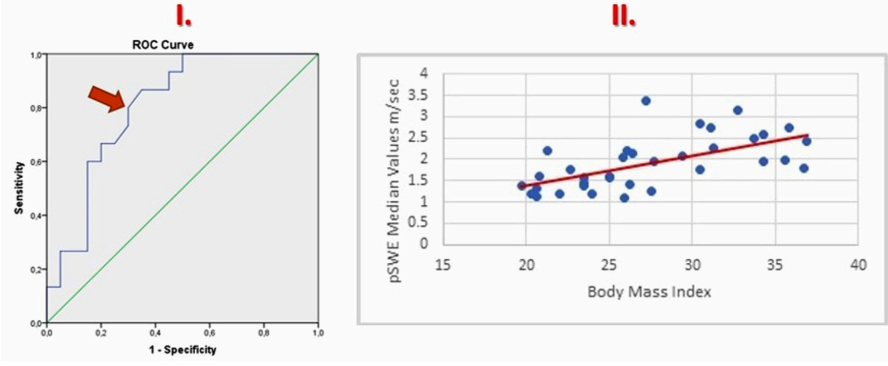

Figure 1. (I) ROC curve for significant fibrosis risk calculated from patients' pSWE measurements (the cut-off value is marked with red arrow.) (II) Correlation graph of BMI and pSWE median values (r=0.673, p<0.01).

ROC: Receiver operating characteristic, pSWE: Point shear wave elastography

Table 2. Correlation between variables

	Age	BMI	Grading of liver steatosis	pSWE median values	Ishak fibrosis scores
Age	1				
BMI	0.561**	1			
Grading of liver steatosis	0.636**	0.591**	1		
pSWE median values	0.452**	0.673**	0.534**	1	
Ishak fibrosis scores	0.520**	0.382*	0.392*	0.633**	1

**p<0.01, *p<0.05 were considered statistically significant. BMI: Body mass index, pSWE: Point shear wave elastography

In Beland et al. (15), 50 patients who underwent liver biopsy were evaluated. When the threshold value for pSWE was taken as 1.89 m/sec in the detection of F2 or higher fibrosis stage in patients followed up with CHC, the sensitivity and specificity were found to be 75% and the AUC was found to be 0.85. A 5% increase in measurements was noted in patients with hepatic steatosis. However, in the multivariate analysis, they could not show a significant correlation between the grade of hepatic steatosis, fibrosis score, and pSWE values (p>0.05) (15). While the cut-off value of pSWE is defined as 1.35 m/sec for detecting F2 or higher fibrosis in guidelines, the cut-off value was calculated as 1.77 m/sec in our study (AUC: 0.807) (6). Therefore, Spearman's correlation test was applied to evaluate the correlation between the variables. There was a moderately positive and significant correlation between pSWE median values and age (r=0.452, p<0.01), BMI (r=0.673 , p<0.01), and grade of hepatic steatosis (r=0.534 , p<0.01). In our study, it was also shown that there was an increase in measurements when patients had hepatic steatosis.

Study Limitations

The limitations of our study are that it was conducted with some patients and was retrospective.

Conclusion

Because liver biopsy has various limitations, non-invasive methods are being investigated more recently. In our study, the diagnostic performance of serological tests and pSWE was evaluated by referring to liver biopsy in patients followed up with CHB. Although serological tests did not give statistically significant results in detecting fibrosis, there was a significant relationship between the significant fibrosis risk and the pSWE median values. pSWE, which can be performed during routine ultrasound imaging with devices of appropriate technology, is promising; however, it is thought that the method will develop further with the new information to be obtained by conducting studies involving more patients.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Clinical Research Ethics Committee (approval number: 2022/133, date: 12.10.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Concept: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Design: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Data Collection or Processing: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Analysis or Interpretation: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Literature Search: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Writing: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G.

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