



Evaluation of Portal Venous Flow as a Non-invasive Method for Diagnosing Liver Fibrosis in Patients with Chronic Hepatitis B

Kronik Hepatit B'li Hastalarda Karaciğer Fibrozunun Teşhis Edilmesi İçin Non-invaziv Bir Yöntem Olarak Portal Venöz Debinin Değerlendirilmesi

Uğur Kesimal¹, Şenay Öztürk Durmaz², Tansu Pınarbaşıllı³,

¹Recep Tayyip Erdoğan University Training and Research Hospital, Clinic of Radiology, Rize, Turkey

²Kepez State Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Antalya, Turkey

³Kepez State Hospital, Clinic of Radiology, Antalya, Turkey

ABSTRACT

Objectives: This study aimed to evaluate the relationship between portal venous flow (PVF), which could be measured non-invasively with Doppler ultrasound, and the degree of fibrosis obtained by biopsy in patients with chronic hepatitis (CHB).

Materials and Methods: The study included 133 patients with CHB. During the Doppler evaluation, PVF was calculated in addition to routine measurements. The patients were divided into two groups according to the degree of fibrosis based on the biopsy results: F0 and F1 (first group) and F2, F3 and F4 (second group). The Doppler ultrasound findings obtained from all patients were compared with the pathology results.

Results: The mean PVF was measured as 688.38±608.2 mL/minute. An inverse correlation was detected between PVF and liver fibrosis degree ($p<0.0001$, Spearman's correlation coefficient 0.47). In the receiver-operating characteristic analysis, the area under the curve was 71.1% (95% confidence interval: 55.6%-83.6%). The cut-off value for PVF was calculated as 480 mL/minute, at which it had a sensitivity of 57.8% and specificity of 100%.

Conclusion: We considered that the decrease we showed in PVF in our study could be used as a non-invasive evaluation method in the differentiation of mild and significant fibrosis in non-cirrhotic patients.

Keywords: Chronic hepatitis B, Doppler ultrasonography, non-invasive fibrosis test

ÖZ

Amaç: Bu çalışmada, kronik hepatit B (KHB) hastalarında non-invaziv olarak Doppler ultrason ile ölçülebilen portal venöz akım (PVA) ve biyopsi ile elde edilen fibrozis derecesi arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya KHB hastası 133 hasta dahil edildi. Doppler değerlendirmesi sırasında rutin ölçümlere ek olarak PVA hesaplandı. Hastalar biyopsi sonuçlarına göre fibrozisin derecesine göre F0 ve F1 (birinci grup) ve F2, F3 ve F4 (ikinci grup) olmak üzere iki gruba ayrıldı. Tüm hastalardan elde edilen Doppler ultrason bulguları patoloji sonuçları ile karşılaştırıldı.

Bulgular: Ortalama PVA 688,38±608,2 mL/dakika olarak ölçüldü. PVA ile karaciğer fibrozisi derecesi arasında ters korelasyon saptandı ($p<0,0001$, Spearman korelasyon katsayısı 0,47). ROC analizinde eğrinin altında kalan alan %71,1 idi (%95 güven aralığı: %55,6-%83,6). PVA için cut-off değeri 480 mL/dakika olarak hesaplandı ve bu değerde duyarlılığı %57,8 ve özgüllüğü %100 idi.

Sonuç: Çalışmamızda PVA'da gösterdiğimiz azalmanın, sirotik olmayan hastalarda hafif ve anlamlı fibrozisin ayırımında non-invaziv bir değerlendirme yöntemi olarak kullanılabileceğini düşündük.

Anahtar Kelimeler: Kronik hepatit B, Doppler ultrasonografi, non-invaziv fibrozis testi

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Introduction

Clinical manifestations due to hepatitis B virus (HBV) emerge as an important global health problem, and the most common of these conditions is chronic hepatitis B (CHB). In CHB patients, the treatment decision is made according to HBV-DNA and alanine aminotransferase (ALT) levels, and the degree of necroinflammation and degree of fibrosis in the liver biopsy. A liver biopsy is the gold standard in evaluating liver fibrosis; however, due to complications, such as pain, bleeding, and pneumothorax, variable pathology interpretations, and these risks being repeated in each biopsy required, researchers have begun to seek non-invasive tests for detecting fibrosis (1,2,3,4,5,6).

Doppler ultrasonography (US) is a widely accepted imaging method due to its easy accessibility, non-invasiveness, reproducibility when desired, and low cost, despite possible errors in the evaluation of chronic hepatitis patients and differences between practitioners. A Doppler US assessment is widely used in the follow-up of chronic hepatitis patients to obtain useful information about hepatic parenchymal morphology and hemodynamic changes (7,8).

Although there are trials and studies on the use of non-invasive fibrosis markers in patients with chronic hepatitis C, the data on the use of these markers in CHB patients remain limited (9,10,11,12,13). This study aimed to determine whether portal venous flow (PVF) detected by Doppler US was related to the degree of fibrosis obtained from percutaneous biopsies in CHB patients.

Materials and Methods

This study was conducted with the approval of the Clinical Research Ethics Committee of our university (approval number: 9/15, date: 18.06.2020). A prospective diagnostic accuracy study was conducted in our hospital between December 2018 and December 2019, involving 133 CHB patients. All patients provided written informed consent.

The inclusion criteria were being aged 18-70 years and having a diagnosis of chronic hepatitis serologically related to HBV according to the biopsy result. Patients that were hepatotoxic and those using drugs that could cause hemodynamic changes in liver Doppler flow were excluded from the study. Further excluded were patients with coagulation disorders or heart failure, and pregnant women.

Automatic pistol needle biopsies (16 W x 15 cm, ESTACOR to, GEOTEK Medical, Ankara, Turkey) were performed through intercostal access under ultrasound guidance in the interventional radiology unit. The patients' demographic characteristics, ALT and HBV-DNA levels, platelet counts, and pathology reports were obtained from the electronic hospital files and by screening epicrises.

In order to clinically evaluate the chronic hepatitis stage and correlate it with the Doppler data, the patients were divided into two groups according to the degree of fibrosis: the first group that did not have significant fibrosis (F0 and F1) (n=42) and the second group with a high degree of fibrosis (F2, F3 and F4) (n=91). In liver biopsies, the histopathological evaluation was made according to the METAVIR scoring system.

All 133 patients were examined with Doppler and grayscale US using a 2-5 MHz frequency convex ultrasound probe (Canon

Aplio 500, Canon Medical System Corporation, Tokyo, Japan). The patients underwent the ultrasound evaluation in the supine position in the morning after fasting for 10 to 12 hours. All ultrasounds were performed by the same radiologist. All segments of the liver were examined with grayscale and Doppler US. Patients with structural abnormalities in hepatic vascular structures and focal parenchymal lesions were excluded from further analysis. Ultrasound parameters were obtained within one week after the biopsy procedure. Doppler portal vein parameters were obtained during apnea at the beginning of inspiration to avoid changes caused by deep inspiration. The smallest possible pulse repetition frequency setting was chosen to minimize measurement errors. Care was taken to ensure that the angle between the ultrasound beam and the vein to be examined was always below 60. Portal vein measurements were performed at the inferior vena cava level with the least variability between practitioners, using an intercostal and subcostal approach. To calculate PVF, the mean portal venous velocity and cross-sectional area were measured in the transverse plane. PVF was automatically obtained from these values as a function of the Doppler device.

Statistical Analysis

Statistical analyses were performed using the SPSS, version 15 (SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used to evaluate the conformance of continuous variables to normal distribution. Descriptive statistics were expressed as mean, standard deviation, frequency and percentages. During statistical analysis, the correlation between Spearman's rank correlation coefficient and data was evaluated. A p-value of less than 0.05 was considered statistically significant.

Results

Of the 133 patients included in the study, 88 were men and 45 were women. The mean age of all patients was calculated as 41.82 ± 12.48 years. ALT levels in seven men and four women were above the cut-off value of 35 IU/L. The fibrosis value indicated F2 to F4 level of fibrosis in 91 patients. In 42 patients, the fibrosis value was reported as F0 or F1; i.e., low degree of fibrosis. Portal and splenic vein diameters were calculated as 10.56 ± 1.64 and 4.7 ± 1.64 mm, respectively. The mean PVF was measured as 688.38 ± 608.2 mL/min. The descriptive, laboratory and pathology findings of the sample are shown in Table 1, and portosystemic hemodynamic parameters in Table 2.

There was no statistically significant correlation between the histological activity index and hemodynamic parameters of the patients. In the correlation evaluation between the PVF and liver fibrosis degree of the patients, a statistically significant

Table 1. Descriptive, laboratory and pathology results		
	Mean	Standard deviation
Age	41.82	12.49
Platelet count ($10^3/\mu\text{L}$)	218.91	58.06
Alanine aminotransferase (U/L)	30.56	15.15
Fibrosis degree	2.22	0.74
Histological activity index	7.67	2.49

inverse relationship was found ($p < 0.0001$, Spearman's correlation coefficient: 0.47). Apart from this, there was no correlation between the portosystemic hemodynamic parameters and the degree of fibrosis. The p-values of the correlation analysis between the pathological and portosystemic hemodynamic data of the patients are shown in Table 3. We used the ROC curve to determine the PVF cut-off value in the diagnosis of significant liver fibrosis in CHB patients. In this analysis, the area under the curve was 71.1% (95% confidence interval: 55.6%-83.6%). The cut-off value for PVF was calculated as 480 mL/min, at which this parameter had 57.8% sensitivity and 100% specificity (Figure 1).

Discussion

HBV infection is one of the leading causes of chronic liver disease worldwide (14). The aim of HBV treatment is to prevent HBV replication, decrease necroinflammatory activity, and stop the progression of fibrosis. The evaluation of the degree of liver fibrosis in HBV patients plays a key role for better clinical management since the treatment decision is usually made according to the degree of necroinflammation (15). It is also very important to

	Mean	Standard deviation
Portal vein diameter (mm)	10.56	1.64
Portal venous flow (mL/minute)	688.38	608.21
Splenic vein diameter (mm)	4.70	1.64
Spleen size	102.91	16.77

	Fibrosis	Histological activity index
Portal vein diameter	0.465	0.620
Portal venous flow	0.003*	0.922
Splenic vein diameter	0.746	0.212
Spleen size	0.627	0.324

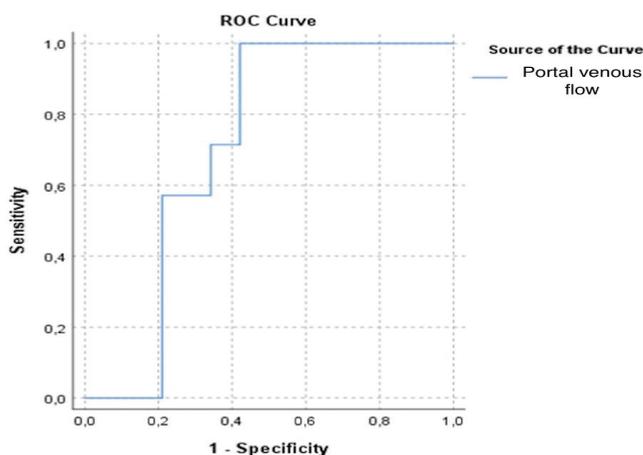


Figure 1. ROC curve for portal venous flow
ROC: Receiver-operating characteristic

evaluate the early stages of liver fibrosis, especially in patients with chronic viral hepatitis because the prognosis is mainly determined by the degree of fibrosis (16). Despite its contraindications and complications, a liver biopsy is still considered as the gold standard for defining the degree of liver fibrosis and guiding treatment (17).

Many new laboratory and imaging methods are being investigated for a non-invasive evaluation of liver fibrosis (17). Doppler US is a non-invasive method for evaluating liver hemodynamics and can be easily performed at the same time as routine upper abdominal US. However, due to limited data and conflicting results (18,19,20,21), the clinical role of Doppler measurements in evaluating non-cirrhotic liver disease remains controversial (18,19,22,23,24). In this regard, Doppler US methods have been the subject of several publications (18,24,25). These methods include the measurement of maximum and minimum velocities of the portal vein, PVF, congestive index, and portal venous index (15).

In the pathology of liver diseases within the range of chronic hepatitis to decompensated cirrhosis, there are various changes, such as hepatocellular inflammation, necrosis, development of regenerative nodules, collagen deposition, and lobule reconstruction. These pathological changes may result be gradual, with increasing intensity at each stage, with the increase in resistance to the portal vein, a decrease in its velocity, and an enlargement of its diameter. The enlargement of the portal vein diameter can counteract the reduction in portal vein velocity, and thus a certain degree of stability can be achieved in PVF to maintain hepatic perfusion (26).

Modifications occur in the usual architecture of the liver associated with sinusoidal vascular impairment due to HBV infection. As a result, various degrees of liver inflammation and fibrosis are known to occur. These changes can theoretically lead to alterations in intrahepatic and extrahepatic vascular impedance, which can be detected by the Doppler examination of the portal vein, hepatic vein, and hepatic artery. Several Doppler ultrasound parameters have been investigated to identify hemodynamic changes in the liver, but there is still no consensus on which option is best for determining the degree of liver fibrosis (27,28,29).

In a study by Su et al. (26), a statistically significant difference was found between the control group and chronic hepatitis patients, as well as between chronic hepatitis and compensated cirrhotic patients in terms of the portal vein diameter and velocity, but no difference was observed in terms of PVF. Similarly, Zheng et al. (30), evaluating cirrhotic patients, reported that the degree of fibrosis was associated with the portal vein diameter and velocity, splenic vein diameter, and spleen size; however, they did not detect any relationship between PVF and fibrosis. The most important difference between these previous studies and our study is that we did not include cirrhotic patients in our sample. In other studies in the literature that did not evaluate cirrhotic patients, Rocha et al. (15) and Bernatik et al. (24) showed no relationship between the degree of fibrosis and portal vein velocity and flow, but the sample sizes of both studies were much lower than the previously mentioned works. In contrast, we found a statistically significant negative correlation between PVF and liver fibrosis in our study. We calculated the cut-off value of PVF as 480 mL/min in differentiating between patients with mild and significant fibrosis. The extent to which and the order in which fibrosis, inflammation, and steatosis

can alter arterial and venous hepatic vascular patterns before cirrhosis remain controversial (15). Therefore, we consider that this decrease in PVF, which we detected in our sample that did not include cirrhotic patients, can be used as a non-invasive evaluation method in the differentiation between mild and significant fibrosis. However, this recommendation should be supported by studies conducted with larger case series. Nevertheless, none of the threshold parameters obtained by non-invasive laboratory or imaging methods has good diagnostic performance. In the literature, it has been stated that using at least two of these non-invasive laboratory tests simultaneously are useful in the evaluation and follow-up of the fibrosis degrees of CHB patients. Thus, the use of markers obtained by Doppler US, especially PVF together with laboratory markers can provide significant contributions. Further studies with a high number of patients evaluating both laboratory and imaging markers together will be important in terms of elucidating this situation.

Study Limitations

Our study also had certain limitations: first, the number of patients was relatively small, and second, all measurements were undertaken by a single person only once. Therefore, we did not evaluate intraobserver and interobserver agreement. Considering the user-dependent nature of this process, it is inevitable that there would be differences between the measurements of different radiologists, and even between those performed by the same radiologist at different times.

Conclusion

There is a consistent and growing need for easily reproducible tests for the effective diagnosis of significant hepatic fibrosis. Studies comparing the efficacy of liver biopsy and non-invasive tests guide the development and implementation of new techniques. This study concludes that Doppler US can help identify CHB patients with significant fibrosis.

Ethics

Ethics committee approval: This study was conducted with the approval of the Clinical Research Ethics Committee of our university (approval number: 9/15, date: 18.06.2020).

Informed Consent: All patients provided written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.K., Ş.Ö.D., T.P., Concept: U.K., Ş.Ö.D., T.P., Design: U.K., Ş.Ö.D., T.P., Data Collection or Processing: U.K., Ş.Ö.D., T.P., Analysis or Interpretation: U.K., Ş.Ö.D., T.P., Literature Search: U.K., Ş.Ö.D., T.P., Writing: U.K., Ş.Ö.D., T.P.

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