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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Clinical Significance of Liver and Spleen Stiffness: Evaluation with Shear Wave Ultrasound Elastography

Karaciğer ve Dalak Sertliğinin Klinik Önemi: Shear Wave Ultrason Elastografi ile Değerlendirme

Zeynep Eskalen[1], Nuray Haliloğlu[2]

[1]Tunceli State Hospital, Clinic of Radiology, Tunceli, Türkiye
[2]Ankara University Faculty of Medicine, Department of Radiology, Ankara, Türkiye

Abstract

Objectives: To investigate clinical significance of liver and spleen stiffness in patients with chronic parenchymal liver disease.

Materials and Methods: Fifty patients with chronic parenchymal liver disease who underwent 2D ultrasound (US) shear wave elastography (SWE) in the Ultrasonography Unit of Ankara University Medical Faculty Hospital between November 2018-June 2021 were enrolled in our prospective study. Liver size, contour, echogenicity, presence of portosystemic collateralls, and ascites were investigated on B-mode examination. Portal vein diameter was measured. Splenic volume was calculated. Liver and spleen stiffness values were measured by 2D SWE. Serum platelet count was noted. Child-Pugh score was calculated for all patients.

Results: Thirty-four patients were grouped as Child-Pugh A, 15 patients were grouped as Child-Pugh B, 1 patient was grouped as Child-Pugh C. Platelet count was between 51-360x10^9/L. The most common conventional US finding was parenchymal heterogeneity. All patients had splenomegaly, the mean portal vein diameter was 12.58 mm, 34 patients had hepatopedal flow. Portosystemic collateralls were detected in 15 patients. Liver and spleen stiffness values were between 4.12 kPa-16.29 kPa, and 9.20 kPa-29.19 kPa, respectively. There was a positive correlation between liver and spleen stiffness (p=0.002). The relationship between splenic volume and spleen/liver stiffness was statistically significant (p=0.0004, p=0.008, respectively). Both liver and spleen stiffness was correlated with Child-Pugh score (p=0.02, p=0.00003, respectively). There was no statistically significant correlation between portal vein diameter and liver/spleen stiffness, and between platelet count and liver stiffness (p>0.05). The correlation between platelet count and spleen stiffness was statistically significant (p=0.002).

Conclusion: SWE can provide information about the clinical status of the patients. Measuring spleen stiffness is as important as measuring liver stiffness.

Key Words: Cirrhosis, portal hypertension, elastography, ultrasound

Öz

Amaç: Kronik karaciğer parankim hastalığı olanlarda karaciğer ve dalak sertliğinin klinik önemini araştırmaktır.

Gereç ve Yöntem: Prospektif çalışmamıza, Kasım 2018-Haziran 2021 tarihleri arasında Ankara Üniversitesi Tıp Fakültesi Hastanesi Ultrasonografi Ünitesi'nde ultrason (US) shear wave elastografi (SWE) ve abdomen US incelemesi yapılan kronik karaciğer parankim hastalığı olan elli hasta dahil edildi. B-mod incelemede karaciğer boyutu, konturu, ekojenitesi, portosistemik kollaterallerin varlığı ve asit araştırıldı. Portal ven çapı ölçüldü. Dalak hacmi hesaplandı. Karaciğer ve dalak sertlik değerleri SWE ile ölçüldü. Serum trombosit sayısı not edildi. Tüm hastalar için Child-Pugh skoru hesaplandı.

Bulgular: Otuz dört hasta Child-Pugh A, 15 hasta Child-Pugh B, 1 hasta Child-Pugh C grubundaydı. Trombosit sayısı 51-360 x10^9/L arasındaydı. En yaygın konvansiyonel US bulgusu parankimal heterojeniteydi. Tüm hastalarda splenomegali vardı, ortalama portal ven çapı 12,58 mm idi, 34 hastada hepatopedal akım vardı. On beş hastada portosistemik kollateraller saptandı. Karaciğer ve dalak sertlik değerleri sırasıyla 4.12 kPa-16.29 kPa ve 9.20

Address for Correspondence/Yazışma Adresi: Zeynep Eskalen, Tunceli State Hospital, Clinic of Radiology, Tunceli, Türkiye
Phone: +90 537 940 83 92 **E-mail:** zeynep_cotaoglu@hotmail.com **ORCID ID:** orcid.org/0000-0001-7671-5131
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kPa-29.19 kPa arasındaydı. Karaciğer ve dalak sertliği arasında pozitif korelasyon vardı (p=0,002). Dalak hacmi ile dalak/karaciğer sertliği arasındaki ilişki istatistiksel olarak anlamlıydı (sırasıyla p=0,0004, p=0,008). Hem karaciğer hem de dalak sertliği Child-Pugh skoru ile koreleydi (sırasıyla p=0,02, p=0,00003). Portal ven çapı ile karaciğer/dalak sertliği arasında ve trombosit sayısı ile karaciğer sertliği arasında istatistiksel olarak anlamlı bir ilişki yoktu (p>0,05). Trombosit sayısı ile dalak sertliği arasındaki korelasyon istatistiksel olarak anlamlıydı (p=0,002).

Sonuç: SWE, hastaların klinik durumu hakkında bilgi sağlayabilir. Dalak sertliğini ölçmek, karaciğer sertliğini ölçmek kadar önemlidir.

Anahtar Kelimeler: Siroz, portal hipertansiyon, elastografi, ultrason

Introduction

Ultrasound (US) is a fast, easy and ionising radiation free technique which is frequently used in the diagnosis and follow-up of patients with cirrhosis. Shear wave elastography (SWE) may be performed easily during the routine US examination, and may provide additional information about the fibrotic process within the liver parenchyma (1). Cirrhosis is also the most common cause of portal hypertension (PHT). Patients with PHT may be asymptomatic, may present with splenomegaly, ascites, and portosystemic collaterals or may present with major complications like variceal bleeding or hepatic encephalopathy (2,3). The gold standart technique to diagnose PHT is measuring the hepatic venous pressure gradient (HVPG) but it is an invasive procedure so non-invasive alternatives like Elastography would be quite valuable (4). It has been suggested that liver and spleen stiffness may help to predict the presence and severity of PHT (3-5). Liver stiffness can be used as a parameter to exclude or predict clinically significant PHT (HVPG >10 mmHg) (6,7). It has also been suggested that with the progression in PHT the correlation between liver stiffness and fibrosis decreases, but spleen stiffness which can be useful to predict clinically significant PHT, may also correlate with liver fibrosis (8-10).

The aim of this study is to demonstrate and compare the liver and spleen stiffness in patients with chronic parenchymal liver disease, and to investigate their clinical significance.

Materials and Methods

This study was approved by the Ankara University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 18-1207-18, date: 12.11.2018) and informed consent was obtained.

Patients

Fifty patients with histopathologically diagnosed chronic parenchymal liver disease who underwent US and SWE in our department between November 2018-June 2021 were enrolled in our prospective study. Patients who could not cooperate, who had portal vein thrombosis, patients with transjugular intrahepatic portosystemic shunt and patients who underwent liver transplantation were not included.

The etiology of chronic parenchymal liver diseases, and the laboratory findings including serum albumin, creatinine, aspartate aminotransferase, alanine aminotransferase, serum bilirubine, prothrombin time, "International normalised ratio" values and platelet count were investigated from the institutional database. Laboratory examinations within 1 month before or after the US examinations were noted. Child-Pugh score was calculated for each patient (Table 1).

US and SWE Examinations

All US and SWE examinations were performed in the same US system (LOGIQ S8 GE Healthcare, Milwaukee, WI, USA) using a 3.5 MHz convex transducer, by the same radiologist with 18 years of experience in abdominal imaging. All patients were fasting for 6-8 hours prior the examination.

Liver contour and echogenicity, segmental atrophy/hypertrophy, presence of portosystemic collateralls, and ascites were investigated on B-mode examination. The diameter of portal vein was measured at the level of portal hilum. The length, width and depth of spleen was measured, and splenic volume was calculated using the standard prolate ellipsoid formula (length × width × depth × 0.52).

Liver stiffness measurements were performed while the patient was in supine position with the right arm elevated over the head. Measurements were made intercostally in the right lobe, and 2 cm deep to the liver capsule during shallow breath-hold. Spleen stiffness measurements were performed in right lateral decubitis position with the left arm elevated over the head. Measurements were made intercostally in the parenchyma as far as possible from the splenic hilum to avoid vessels and 2 cm deep to the splenic capsule during shallow breath-hold. At least 8 measurements in both liver and spleen parenchyma were obtained in each patient.

Table 1: Child-Pugh scoring and classification

Ascites	**No**	**Slight**	**Moderate**
Encephalopathy	No	Mild-Moderate	Severe
Total bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (sec) or INR	1-3 or <1.7	4-6 or 1.7-2.3	>6 or >2.3
Class	**Points**		
Child-Pugh A	5-6		
Child-Pugh B	7-9		
Child-Pugh C	10-15		

Statistical Analysis

Statistical analysis was performed using SSPS 20 software programme. Normalized variables were expressed as mean ± standard deviation, non-normalized variables were expressed as median (minimum-maximum), and categorical variables were expressed as frequency and percentiles (%). Spearman and Pearson correlation test were used for non-normalized and normalized variations, respectively. Student's t-test was used to compare correlation coefficients of dependent variables. P-value less than 0.05 was considered as statistically significant.

Results

There were 30 (60%) female, and 20 (40%) male patients with a mean age of 54 years (age range 18-79 years) (Table 2). The most common cause of chronic parenchymal liver disease was viral hepatitis (44%) (Table 3).

As patient co-operation was utmost important for elastography measurements, none of our patients had hepatic encephalopathy. The mean Child-Pugh score was 6.04 (range 5-10). Thirty-four patients (68%) were categorized as Child-Pugh A, 15 patients (30%) were categorized as Child-Pugh B, and only 1 patient (2%) was categorized as Child-Pugh C.

The most common conventional US finding was parenchymal heterogeneity (90%), and 30 of the 50 patients (70%) had all conventional US findings of chronic parenchymal liver disease including parenchymal heterogeneity, atrophy/hypertrophy complex, and contour nodularity. Three patients (6%) did not have any conventional US findings of chronic parenchymal liver disease.

All patients had splenomegaly, and mean splenic volume was 450.35 cm^3 (range 320-915 cm^3).

The mean portal vein diameter was 12.58 mm (range 7-16 mm). Thirty-four of the 50 patients (68%) had hepatopedal flow. Portosystemic collateralls were detected in 15 of the 50 patients (30%).

Table 2: Demographic characteristics of patients

	Female	Male
Number (rate)	30 (60%)	20 (40%)
Average age	54.16	53.80

Table 3: The etiology of chronic parenchymal liver disease

Etiology	Number of the patients	Rate (%)
Chronic viral hepatitis	22	44
Non-alcoholic steatohepatitis (NASH)	11	22
Primary biliary cholangitis	8	16
Otoimmune hepatitis	6	12
Alcoholic cirrhosis	2	4
Primary sclerosing cholangitis	1	2

Twelve patients (24%) had ascites and ony 2 of them was massive.

Liver stiffness values were between 4.12 kPa-16.29 kPa (mean value 10.77 kPa, median value 11.02 kPa). Spleen stiffness values were between 9.20 kPa-29.19 kPa (mean value 14.16 kPa, median value 14 kPa) (Figure 1A, B). There was a positive correlation between liver and spleen stiffness (p=0.002, rho=0.424). The relationship between splenic volume and spleen and liver stiffness values was statistically significant (p=0.0004, p=0.008, respectively).

Both liver and spleen stiffnes showed positive correlation with Child-Pugh score (p=0.02, rho=0.323; p=0.00003, rho=0.548, respectively) but correlation between spleen stiffness and Child-Pugh score was significantly stronger than that of liver stiffness (p=0.047). Correlation between liver and spleen stiffness and Child-Pugh class (A, B, C) was also statistically significant (p=0.03, p=0.01, respectively) (Table 4). In addition, a statistically significant difference was detected between the patients in the Child-Pugh A and B-C groups in terms of splenic volume, liver and spleen stiffness values (p=0.004, p=0.033, p=0.15 respectively).

Platelet count was between 51-360x10^9/L, and there was no statistically significant correlation between platelet count and liver stiffness (p>0.05). Nevertheless statistical analysis showed

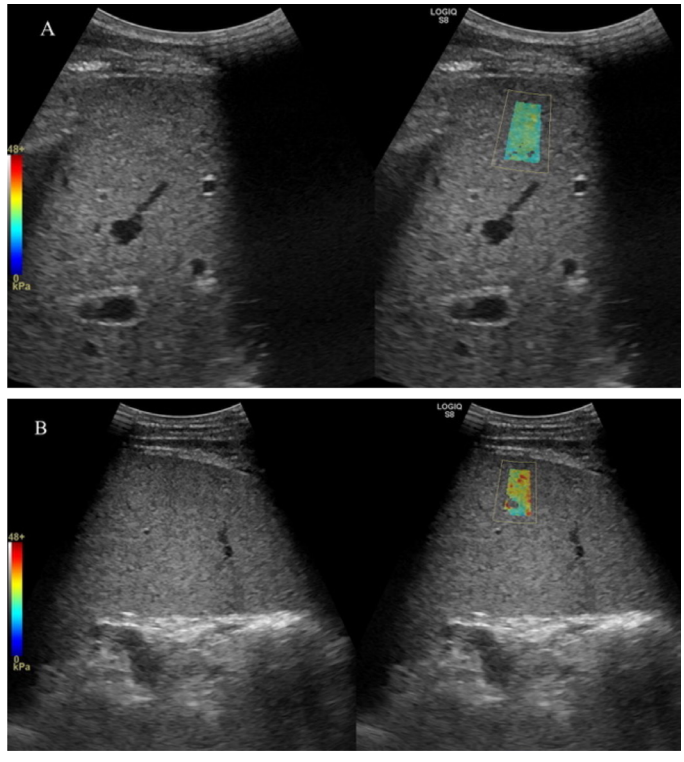

Figure 1A, B: Liver (A) and spleen (B) parenchyma stiffness measurements of a 20-year-old male patient with primary biliary cholangitis. Mean liver stiffness was 10,91 kPa, mean splenic stiffness was 14,87 kPa, Child-Pugh score was 7, and platelet count was 118x10^9/L.

Table 4: Statistical data for values showing significant positive correlation					
	Liver stiffness	Spleen stiffness	Splenic volume	Child-Pugh score	Child-Pugh class (A, B, C)
Liver stiffness	-	p=0.002 rho=0.424	p=0.008 rho=0.367	p=0.02 rho=0.323	p=0.03 rho=0.304
Spleen stiffness	p=0.002 rho=0.424	-	p=0.0004 rho=0.478	p=0.00003 rho=0.548	p=0.01 rho=0.360

significant negative correlation between platelet count and spleen stiffness (p=0.002).

There was no statistically significant correlation between portal vein diameter and neither liver nor spleen stiffness (p>0.05).

Discussion

Patients with chronic parenchymal liver disease should be under follow-up in terms of liver functions and development of hepatocellular carcinoma. Detection and grading of fibrosis within the liver parenchyma is crucial. It is also known that with the increased portal venous pressure risk of hepatic decompansation increases. Therefore it is utmost importance to show the presence and severity of PHT in these patients (11). Both liver biopsy and measurement of HVPG are invasive procedures, and should be saved for certain indications. Child-Pugh scoring is widely used to evaluate the clinical significance of hepatic parenchymal damage, and to predict prognosis. The association between liver stiffness and Child-Pugh score has been shown previously (12). Our results support that there is a statistically significant relationship between Child-Pugh score and both liver and spleen stiffness values, and there is a positive correlation between liver and spleen stiffness, which is also consistent with the literature (13-15). Both liver and spleen stiffness values on SWE may provide information about the clinical status of patients with chronic parenchymal liver disease. As these patients are usually under follow-up with US, measurement of liver and spleen stiffness with SWE would be a complemantary tool in monitoring hepatic functions (16).

It has been suggested that both liver and spleen stiffness has a high sensitivity and specificity in predicting clinically significant PHT (75-91%, and 77-90% for liver stiffness, and 70-96%, and 72-92% for spleen stiffness, respectively) (17,18). We found that the stiffness of both liver and splenic parenchyma is correlated with the splenic size and it is well known that splenomegaly is a sign of PHT.

Platelet count is one of the non-invasive tests to to identify clinically significant PHT. Along with the liver and spleen stiffness measurements, it has been suggested that platelet count ≥150x10^9/L rules out clinically significant PHT (8). Our results support this statement as we found that spleen stiffness is significantly correlated with platelet count.

In consistence with the literature we also found that the association between splenic stiffness and Child-Pugh score is more significant than that of liver stiffness (13). Therefore not just the size but also the stiffness of the spleen should be screened in patients with chronic parenchymal liver disease to estimate prognosis and also PHT.

On the other hand the portal vein diameter is not accepted as an indicator of PHT, and we did not find a correlation between portal vein diameter and hepatic or splenic stiffness. Nevertheless it has been suggested that portal vein diameter combined with splenic stiffness values may help to predict the risk of oesophageal variceal bleeding, and splenic stiffness may be used as a parameter to evaluate hepatic decompansation and risk of mortality (19-22).

Study Limitations

Our study has some limitations. First limitation is the small number of patients, and the heterogeneity in etiology. In addition there was only 1 patient with Child-Pugh C score. HVPG measurement was not performed in most of the patients. Also lack of a control group can be considered as a limitation.

Conclusion

In conclusion; adding SWE on routine US examinations can provide useful information about the clinical status of the patients, and progression of the disease. Liver and spleen stiffness values are correlated and measuring spleen stiffness is as important as measuring liver stiffness.

Ethics

Ethics Committee Approval: This study was approved by the Ankara University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 18-1207-18, date: 12.11.2018).

Informed Consent: Informed consent was obtained.

Authorship Contributions

Concept: Z.E., N.H., Design: Z.E., N.H., Data Collection or Processing: Z.E., N.H., Analysis or Interpretation: Z.E., N.H., Literature Search: Z.E., N.H., Writing: Z.E., N.H.

Conflict of Interest: No potential conflict of interest any financial or non-financial interestwas reported by the authors.

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