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ORIGINAL ARTICLE

The Role of Shear Wave Elastography in Predicting Early Stage Liver Fibrosis

Erken Evre Karaciğer Fibrozisini Öngörmede Shear Wave Elastografinin Rolü

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ABSTRACT

Aim: We examined the relationship between shear wave elastography (SWE) values and histopathological results in our study. Thus, we found the sensitivity of SWE in demonstrating early fibrosis.
Materials and Methods: A total of consecutive 70 patients with chronic hepatitis B were prospectively evaluated. The patients included in fibrosis stages (F) 0, 1, 2, 3 and 4 according to Ishak scoring were examined with SWE. SWE measurements of F2, F3 and F4 patients who were found to have early stage fibrosis were compared with those of F0 and F1 patients.
Results: The velocity+SD, and kPa+SD values in the group requiring treatment (F2, F3 and F4) were significantly higher than the group not requiring treatment (F0 and F1)($p < 0.05$). The sensitivity rate of the 1.85 cut-off value for velocity+SD was 53.8%, the positive prediction rate was 80.8%, the specificity rate was 83.3%, and the negative prediction rate was 58.1%. For kPa+SD, the cut-off value of 10.8 had a sensitivity rate of 51.3%, a positive prediction rate of 95.2%, a specificity of 96.7%, and a negative predictive rate of 60.4%. A significant correlation was observed between the fibrosis score and the kPa+SD distribution.
Conclusion: SWE can differentiate the patients requiring treatment (F2, F3 and F4) from the patients not requiring treatment.

Keywords: Sher Wave Elastgraphy, Liver, Fibrosis

ÖZ

Amaç: Çalışmamızda ultrason shear wave elastografi (SWE) değerleri ile histopatolojik sonuçlar arasındaki ilişkiyi inceledik. Böylece, SWE'nin erken fibrozu göstermedeki duyarlılığını değerlendirdik.
Materyal ve Metod: Kronik hepatit B hastalığına sahip ardışık 70 hasta prospektif olarak değerlendirildi. Ishak skorlamasına göre fibroz evreleri (F) 0, 1, 2, 3 ve 4'e dahil edilen hastalar SWE ile incelendi. Erken evre fibroz tespit edilen F2, F3 ve F4 hastalarının SWE ölçümleri, tedavi gerektirmeyen F0 ve F1 hastalarının ölçümleri ile karşılaştırıldı.
Bulgular: Tedavi gerektiren grup (F2, F3 ve F4) içindeki hız+SD ve kPa+SD değerleri, tedavi gerektirmeyen grup (F0 ve F1) içindeki değerlere göre anlamlı şekilde yüksekti ($p < 0.05$). Hız+SD için 1.85 kesme değerinin duyarlılık oranı %53.8, pozitif tahmin oranı %80.8, özgüllük oranı %83.3 ve negatif tahmin oranı %58.1 olarak bulundu. kPa+SD için, 10.8 kesme değeri duyarlılık oranı %51.3, pozitif tahmin oranı %95.2, özgüllük oranı %96.7 ve negatif tahmin oranı %60.4 olarak saptandı. Fibroz skoru ile kPa+SD dağılımı arasında anlamlı bir korelasyon gözlendi.
Sonuç: KDE, tedavi gerektiren hastaları (F2, F3 ve F4) tedavi gerektirmeyen hastalardan ayırt edebilir.

Anahtar Kelimeler: Shear Wave Elastografi, karaciğer, fibrozis

Introduction

Liver fibrosis is usually asymptomatic until it progresses to cirrhosis, and many cirrhotic patients are unaware of the condition until they are decompensated (1). Early liver fibrosis is a reversible condition. Detecting early fibrosis and initiation antiviral treatment may be important in preventing disease progression (2). Fibrosis is a process that can show both progression and regression, and regression of fibrosis is possible with treatment response. Liver biopsy is performed to determine the extent of fibrosis, but biopsy is an invasive method and the tissue examined is limited. Biopsy does not examine large tissue pieces in the liver. False negative results of up to 30% have been reported (3, 4). For this reason, laboratory tests evaluating the whole liver and alternative imaging methods are being investigated (5). Shear wave elastography (SWE) is a recently developed technology that is equivalent to palpation. SWE is a non-invasive and reproducible method that provides quantitative assessments of liver tissue stiffness (6). In denser and harder textures, the propagation velocity of shear waves is higher. In meta-analyses evaluating the liver parenchyma with SWE in patients with hepatitis, it has been found that it can be used as an indirect indicator of hepatic fibrosis (7, 8). High elasticity score has also been reported to correlate with histopathological findings (7, 8). In our study, we examined the relationship between SWE values and histopathological results. Thus, we aimed to demonstrate the success of SWE in determining early fibrosis.

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Material and Method

Study Design and The Patient Cohort

A total of 69 consecutive patients with chronic hepatitis B were prospectively evaluated between the years 2020-2022. Patients with chronically increased HBV-DNA and elevated serum alanine aminotransferase were included the study. HBV-DNA viral load was determined by performing quantitative real-time PCR. In our study, we examined patients in fibrosis stage (F) 0, 1, 2, 3 and 4 according to the Ishak scoring. The SWE measurements of F2, F3 and F4 patients who were found to have early-stage fibrosis and would receive treatment were compared with those of F0 and F1 patients who would not receive treatment. Patients with F5 and F6 Ishak scores were excluded from the study. Patients coinfected with other hepatitis virus, human immune deficiency virus and severe steatosis are removed from the study. Patients with prolongation of prothrombin time for more than 3 seconds, platelet count <80.000 /mm3 and chronic kidney failure are also excluded from the study.

Patients were first evaluated by SWE. After SWE measurements, liver biopsy was performed by the same radiologist. For standardization of the results, SWE measurements and liver biopsy were performed at segment 7-8 localization. SWE measurements were performed with the patients in supine position with their right arm under the head. Then, the patients were asked to hold breath and SWE measurements were taken by intercostal approach at the level of segment 7-8. SWE mode was turned on by finding the appropriate area. After the appropriate waveforms were seen, measurements were taken with elliptical ROI from 5 different locations within this area. In our study, the mean speed and kPa values of these measurements were recorded. After SWE measurements, the patient was placed in the same position and the skin area to be biopsied was cleaned with antiseptic solution. Afterwards, local anesthetic agent was applied from the subcutaneous layer to the liver capsule. Then, liver parenchymal biopsy was performed using a fully automatic Tru-cut biopsy gun with an 18-gauge biopsy needle through an intercostal approach under ultrasound guidance. Special care was taken to choose a location 2 cm away from the capsule and away from vascular structures for tissue samples and elastographic measurements. Histopathological examination was evaluated at the same center and the Ishak scoring system was used to measure necro inflammatoryactivity and fibrosis (9).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval obtained from a local committee (date: 05.03.21 and decision number: 2765). Consent form was obtained from all patients.

SWE technique

Real-time SWE examinations were performed using Toshiba's Aplio 500 ultrasound system. All elastographic measurements were taken using a round the region of interest (ROI) without applying pressure to the convex probe (12-24 MHz). During the evaluation of tissue stiffness with SWE, the pressure force applied by the tissue in kPa and the velocity values in m/s, which indicate the speed of shear waves within the tissue, were measured. (10). The mean and standard deviation were recorded. In the color mapping, the hardest parenchymal tissue was depicted in red, while the softest parenchymal tissue was represented in blue. Tissue stiffness was calculated with the formula available in the device's own software. Tissue stiffness was calculated using the formula provided by the device's software. The formula is represented as E = Pc^2, where 'E' stands for tissue elasticity (kPa), 'P' represents tissue density (kg/m^3), and 'c' is the shear-wave velocity (m/s) (11). All elastographic examinations were performed by a radiologist with 4 years of SWE experience (M.K.).

Histopathological examination

Histological findings obtained from liver biopsy of the patients were evaluated according to Ishak scoring (9). Fibrosis scoring of the patients was performed according to Ishak scoring. Accordingly, 0 was evaluated as no fibrosis, 1-2 mild fibrosis, 3-4 moderate fibrosis, and 5-6 severe fibrosis (9). Periportal or periseptal interphase hepatitis, confluent necrosis, focal necrosis, apoptosis and focal inflammation, portal inflammation, bile duct inflammation and damage, presence of lymphoid follicles, steatosis, hepatocellular dysplasia, iron, copper accumulation and intracytoplasmic inclusions were evaluated.

Statistical Analysis

Statistical evaluation is performed using the tests listed below in the SPSS 28.0 software. Mean, standard deviation, median, minimum, maximum value frequency and percentage were used for descriptive statistics. The distribution of variables was checked with kolmogorov-smirnov test. Mann-Whitney U test was used for the comparison of quantitative data. Kappa test was used for the accuracy analysis. Chi-Square test was used for the comparison of the comparison of qualitative data. ROC analysis was used to show the effect level. Logistic Regression (Forward LR) was used to show the effect level.

Results

A total of 69 patients with a mean age of 41.33 (19-61 years) participated in the study. Forty-one patients were male. The mean velocity +SD value of the patients participating in the study was 1.83m\s (min-max:1.16-2.80m\s). The mean kPa +SD value of the patients participating in the study was 10.19 Pa (min-max: 5.10-18.90m\s). There were 6 patients with F0, 24 with F1, 18 with F2, 13 with F3 and 8 with F4 (Table 1). The age and gender distribution of the patients did not differ significantly between the groups that needed treatment and those who did not (p>0.005). The

velocity+SD and kPa+SD values in the group requiring treatment (F2, F3 and F4) were significantly higher than the group not requiring treatment (p <0.005 and p <0.005) (Table 2). In the univariate model, a significant (p<0.005) efficiency of velocity+SD, kPa+SD value was observed in predicting patients in need of treatment. In the multivariate model, a significant-independent (p<0.005) efficacy of kPa+SD value was observed in predicting patients in need of treatment (Table 3). A significant (Under the curve area 0.713(0.593-0.330)) efficacy of velocity+SD value was observed in predicting patients in need of treatment (Graphic 2). The sensitivity rate of the 1.64 cut-off value for velocity+SD was 74.4%, the positive prediction rate was 59.8%, the specificity rate was 50%, and the negative prediction rate was 66.1%. To predict patients who need treatment; a significant effectiveness of velocity+SD value was observed (Area under the curve 0.784 (0.677-0.891)) (Graphic 3). For kPa+SD, the cut-off value of 8.65 had a sensitivity rate of 79.5%, a positive prediction rate of 68.4%, a specificity of 63.3%, and a negative predictive rate of 75.5%. A significant correlation was observed between the fibrosis score and the kPa+SD distribution (Table 3).

Table-1:

		Min-Max			Median	Mean±sd/n-%		
Age		19.00	-	61.00	41.00	41.33	±	9.75
Gender	Female					28		40.6%
	Male					41		59.4%
Fibrosis Score	0					6		8.7%
	I					24		34.8%
	II					18		26.1%
	III					13		18.8%
	V					8		11.6%
Speed+SD		1.16	-	2.80	1.75	1.83	±	0.38
KPA+ SD		5.10	-	18.90	9.40	10.19	±	3.17
KPA+SD	<7					11		15.9%
	7-8.9					18		26.1%
	9-10.9					19		27.5%
	11-12.9					6		8.7%
	≥ 13					14		20.3%

Table-2: General SWE measurements data of the patients

		Treatment Need (-)				Treatment Need (+)				p	
		Mean±SD/n-%			Median	Mean±SD/n-%			Median		
Age		40.17	±	9.77	40.00	42.23	±	9.77	43.00	0.326	m
Sex	Female	15		50.0%		13		33.3%		0.162	X^2
	Male	15		50.0%		26		66.7%			
Velocity+SD		1.67	±	0.24	1.65	1.95	±	0.41	1.87	0.003	m
kPA+ SD		8.42	±	1.77	8.25	11.56	±	3.35	11.00	0.000	m
kPA+SD	<7	9		30.0%		2		5.1%		0.000	X^2
	7-8.9	10		33.3%		8		20.5%			
	9-10.9	10		33.3%		9		23.1%			
	11-12.9	0		0.0%		6		15.4%			
	≥ 13	1		3.3%		13		33.3%			

[m] Mann-Whitney U test / [X²] Chi-square test, Treatment Need (-):Patients with F0 and F1 Ishak score ,Treatment Need (+):Patients with F1, F2, F3 and F4 Ishak score

Table-3

	Univariate Model				p	Multivariate Model				p
	OR	%95 CI				OR	%95 CI			
Speed+SD	13.808	2.317	-	82.302	0.004					
KPA+SD	1.591	1.230	-	2.059	0.000	1.591	1.230	-	2.059	0.000
Logistic Regression (Forward LR)										

Treatment Need (-): Patients with F0 and F1 Ishak score

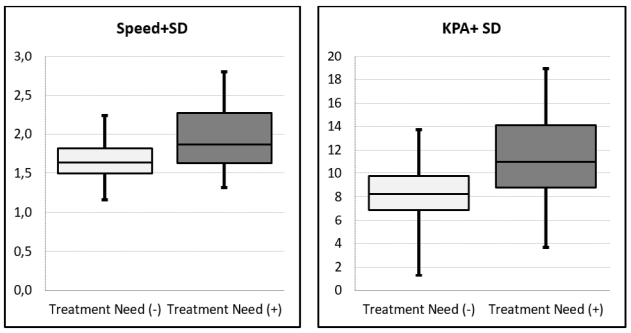
Treatment Need (+): Patients with F2, F3 and F4 Ishak score

Table-4

0		Fibrosis Score					Kappa	p
		I	II	III	IV			
kPa+SD	<7	5	4	2	0	0	0.359	0.000
	7-8.9	0	10	6	2	0		
	9-10.9	1	9	7	2	0		
	11-12.9	0	0	1	5	0		
	≥ 13	0	1	2	4	8		

Kappa Compliance Analysis,
Treatment Need (-): Patients with F0 and F1 Ishak score
Treatment Need (+): Patients with F2, F3 and F4 Ishak score

Graphic 1: The univariate analysis which predict the necessity of treatment

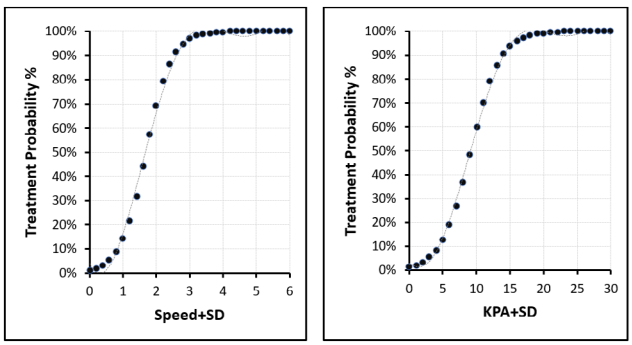


Treatment Need (-): Patients with F0 and F1 Ishak score

Treatment Need (+): Patients with F2, F3 and F4 Ishak score

*In the univariate model, a significant (p<0.05) efficiency of velocity+SD, kPa+SD value was observed in predicting patients in need of treatment.

Graphic 2:



Treatment Need (-): Patients with F0 and F1 Ishak score

Treatment Need (+): Patients with F2, F3 and F4 Ishak score

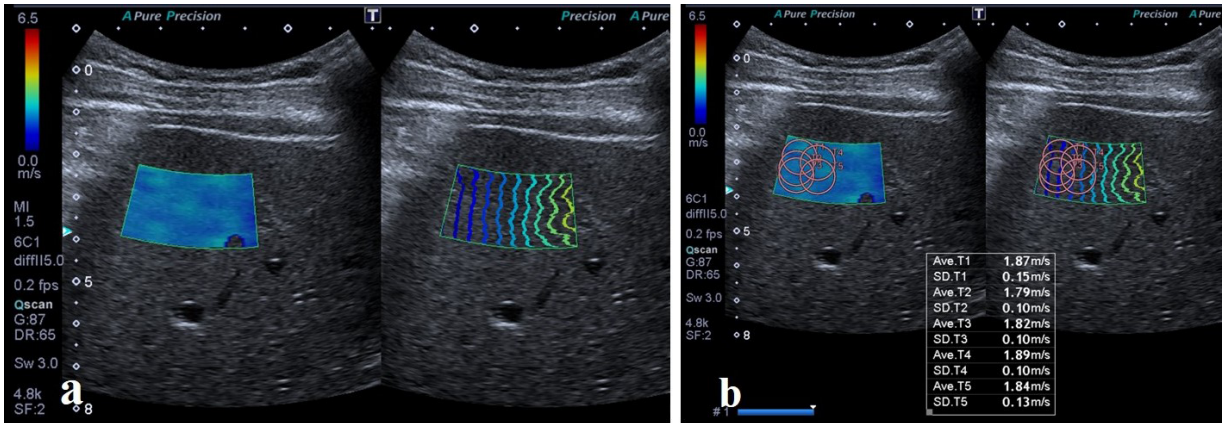
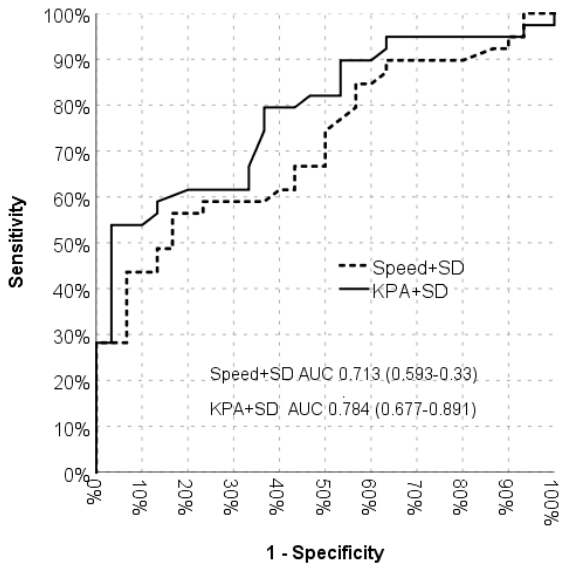


Figure1:

A 37-year-old male patient was being followed up with the diagnosis of chronic hepatitis B. In the SWE examination **(a)** the speed was measured as 1.84m/sec and **(b)** elasticity was 10.1 kPa before the liver biopsy. The Ishak score was reported as 1 in the histopathological examination.

Graphic 3:



Treatment Need (-): Patients with F0 and F1 Ishak score

Treatment Need (+): Patients with F2, F3 and F4 Ishak score

* A significant (Under the curve area 0.713(0.593-0.330)) efficacy of velocity+SD value was observed in predicting patients in need of treatment. To predict patients who need treatment; a significant effectiveness of velocity+SD value was observed (Area under the curve 0.784 (0.677-0.891))

Discussion

In the treatment of chronic hepatitis B, very serious complications such as cirrhosis, portal hypertension and hepatocellular carcinoma that may occur with fibrosis progression can be prevented (12). Due to the high costs of new drugs and treatments used in the treatment of fibrosis, it is important to identify the patients who will primarily benefit (12). The accurate recognition and staging of hepatic fibrosis is extremely important in terms of clinical management. According to Ishak scoring, grades 2, 3 and 4 benefit from drug therapy, grade 3-4 reflects advanced fibrosis, while grade 5-6 means cirrhosis (13, 14).

In our study, SWE has shown that it can distinguish F0-1 from F2, 3, 4 with higher sensitivity. Thus, with SWE, early-stage fibrosis was distinguished from advanced fibrosis with high specifity in a larger parenchyma area compared to biopsy. Since it is a non-invasive method, SWE will also provide convenience in following the regression of fibrosis during medical treatment. Ferraioli et al. (15) reported that SWE is successful in demonstrating significant fibrosis (≥ stage 2). Guibal et al. (16) conducted a study to evaluate the correlation of SWE with histopathological results. They found that SWE sensitivity and specificity were respectively 85.1% and 82.7% (≥ stage 2), 88.9% and 90.3% (≥ stage 3), 93.3% and 98.3% (stage 4). In our study, the sensitivity of 8.65 cut-off value for kPa+SD was, 79.5%, the positive prediction rate, 68.4%, the specificity rate, 63.3%, and the negative prediction rate was, 75.5%. In another study, different hepatic acquisition sites for staging liver fibrosis in SWE examination were assessed (17). They reported that right upper lobe was the most suitable acquisition area for SWE measurements. Measurements from the right upper lobe most accurately reflected the severity of liver fibrosis.

Tutar et al. (11) evaluated the effectiveness of SWE in the staging of liver fibrosis in children with chronic liver disease. In their study, while SWE could accurately diagnose liver fibrosis, it failed to differentiate fibrosis stages. The most important reason was that steatosis significantly increased the mean SWE values in elastography. In our study, we included only patients with chronic hepatitis B infection and excluded those with additional parenchymal diseases to minimize the

impact of factors that can increase liver stiffness such as steatosis. Another study reported that determining disease-specific cutoff values for assessment of fibrosis stage is required (10). Thus, we will know the limit values in terms of velocity and kPa for the increase in stiffness in the liver parenchyma due to different causes such as severe steatosis. Sporea et al. (18) reported that SWE measurements for assessing liver stiffness can be influenced by factors such as obesity and advanced age. They also reported that the most suitable cut-off values for determining the different stages of liver fibrosis were F≥1:>7.1kPa; F≥2:>7.8 kPa; F≥3: >8 kPa and for F=4:>11.5kPa (18).

In a study on staging liver fibrosis among chronic hepatitis B patients, Ma et al. (19), on the other hand, reported that other factors had no impact on SWE measurements. This result is somewhat unexpected and contrasts with findings from other studies. In our study, we included only chronic HBV patients in order to evaluate the increase in parenchymal stiffness due to older age, steatosis, and other storage diseases. Ma et al. (19) found kPa values for F1(5.60±2.55kPa) and F2 (7.44±3.43kPa) (P=0.001<0.005), and F3 (8.71±3.14kPa) and F4 (10.87±5.25kPa) (P=0.001<0.005). In another study, fibrosis stages were defined according to its kPa values, the median values for F0 were 3.5 kPa, 6.4 kPA for F1, 9.5 kPa for F2, 11.4 kPa for F3, and 15.4 kPa for F4 in patients with chronic hepatitis B infection (20). In our study, kPa+ SD was notably higher in the treatment-requiring group (F2, F3, and F4) compared to the non-treatment group (F0-1) (p <0.005).

There are studies reporting that the kPa and velocity values obtained by SWE measurements are not only predictive of the fibrosis stage, but are also indicators that can predict the development of fibrosis in 5-year follow-ups (21, 22). Chon et al. (24) reported that low kPa and value (<12.0kPA) at baseline was a significant predictor for development of fibrosis during 5-year follow-up. In addition, a decrease was observed in the kPa values of the patients with antiviral treatment in the follow-ups, indicating improvement and good treatment response. Vergniol et al. (22) conducted a study which aimed to evaluate the prognostic value of 3-year liver stiffness measurement in chronic hepatitis. They found that patients with an increase in ≥14 kPa in liver stiffness had the worst prognosis. As a noninvasive measure of liver fibrosis, SWE has a strong prognostic value in liver stiffness (22).

Chronic progressive liver fibrosis requires accurate diagnosis and interval monitoring (26). Since SWE is a promising tool for both diagnosing liver fibrosis and monitoring treatment responses, it is necessary to determine reference values (23).

Our study has some limitations, first the steatosis was evaluated subjectively on US and patients who were found to have steatosis in the parenchyma were excluded from the study. Elastographic measurements were always captured from the same location, and stiffness was not evaluated in different areas of the liver. The different trademarks of US devices were not employed.

Conclusion

SWE can differentiate the patients requiring treatment (F2, F3 and F4) from the patients not requiring treatment. It can also accurately show the severity of fibrosis. SWE is promising in the diagnosis and follow-up of parenchymal fibrosis in chronic HBV patients.

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