ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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EVALUATION OF LIVER ELASTICITY USING pSWE AND 2D-SWE TECHNIQUES IN HEALTHY CHILDREN

SAĞLIKLI ÇOCUKLARDA KARACİĞER ELASTİKİYETİNİN pSWE VE 2D-SWE TEKNİKLERİ İLE DEĞERLENDİRİLMESİ

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Öz

Amaç

Share wave elastografi (SWE), karaciğer sertliğini non-invaziv olarak değerlendirebilen yeni bir ultrasonografi tekniğidir. Yetişkinlerde SWE'nin etkinliği çok sayıda çalışmayla gösterilmiştir, ancak pediatrik gruplarda çok az SWE çalışması vardır. Karaciğer sertliği değerleri (KSD), cihaza ve kullanılan SWE yöntemine göre değişiklik gösterdiğinden, standart referans değerleri henüz oluşturulmamıştır. Bu çalışmanın amacı, iki farklı SWE yöntemine göre, sağlıklı çocuklarda normal karaciğerin referans sertlik değerlerini belirlemekti.

Gereç ve Yöntem

Karaciğer sertliği değerleri, 8-18 yaş arası 107 sağlıklı çocukta, iki farklı SWE yöntemi olan point SWE (pSWE) ve 2-dimentional SWE (2D-SWE) ile ölçüldü. pSWE (EPQ) ve 2D-SWE (EQI) ölçümleri aynı cihaz (Philips Epiq Elite) ile, tek seansta ve en az 4 saat aç kaldıktan sonra alındı. Cinsiyet, yaş, vücut kitle indeksi (VKİ), bazı biyokimyasal belirteçler ((açlık kan şekeri, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), albümin, trombosit, INR gibi)) ve karaciğer boyutunun, KSD'ye etkisi araştırıldı.

Bulgular

Ortalama KSD, pSWE ile 4,04±0,84kPa ((%95 güven aralığı (CI):3,67-4,42)) ve 2D-SWE ile 4,41±0,71kPa (%95 CI:4,09-4,72) bulundu. Üst sınır KSD'ler sırasıyla 4,42kPa ve 4,72kPa idi. 2D-SWE'de ölçülen KSD'ler, pSWE'den daha yüksekti ((sırasıyla medyan; min-maks, 4,34kPa; 2,82-6kPa ve 3,86kPa; 2,55–5,78, (r=0,59, p<0,001)). KSD ile yaş arasında düşük düzeyde anlamlı pozitif korelasyon saptandı (r=0,267; p=0,006). Fakat karaciğer büyüklüğü, cinsiyet, VKİ ve biyokimyasal belirteçler ile KDS arasında anlamlı ilişki saptanmadı.

Sonuç

8-18 yaş arası sağlıklı çocuklarda ortalama karaciğer sertliği referans değerleri, Philips Epiq Elite ultrason cihazı ile yapılan ölçümlerde, pSWE yöntemi ile 4,04±0,84kPa ve 2D-SWE yöntemi ile 4,41±0,71kPa olarak bulundu. Bu referans değerleri, kronik karaciğer hastalıklarında karaciğer parankiminin değerlendirilmesinde SWE yönteminin daha etkin kullanılmasına yardımcı olacaktır.

Anahtar Kelimeler: Çocuk, İki boyutlu-shear wave elastografi, Karaciğer sertliği, Shear wave elastografi, Ultrason

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Abstract

Objective

Shear wave elastography (SWE) is a new ultrasonography technique that can non-invasively evaluate liver stiffness. The efficacy of SWE in adults has been demonstrated by numerous studies, but there are few SWE studies of pediatric groups. Since the liver stiffness values (LSV) vary according to the device and the SWE method used, standard reference values have not been established as yet. The aim of this study was to establish the reference values of normal liver stiffness in healthy children according to the two SWE methods.

Materials and Method

Liver stiffness values were measured using the two different SWE methods of point SWE (pSWE) and 2-dimensional SWE (2D-SWE) in 107 healthy children aged 8-18 years with no liver disease. The pSWE (EPQ) and 2D-SWE (EQI) measurements were taken in one session on the same device (Philips Epiq Elite) and after at least 4 hours of fasting. The effects on liver elasticity values were investigated of gender, age, body mass index (BMI), some biochemical markers (such as fasting blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, platelet, INR) and liver size.

Results

The mean LSV was 4.04±0.84kPa ((95% confidence interval (CI):3.67-4.42)) on pSWE and 4.41±0.71kPa (95% CI:4.09-4.72) on 2D-SWE. The upper limit LSVs were found to be 4.42kPa and 4.72kPa, respectively. The LSVs measured on 2D-SWE were found to be higher than on pSWE ((median; min-max, 4.34kPa; 2.82-6kPa and 3.86kPa; 2.55–5.78, respectively, ($r=0.59$, $p<0.001$)). A low-level significant positive correlation was determined between LSV and age ($r=0.267$; $p=0.006$). No significant association was determined between LSV and hepatic size, gender, BMI and biochemical markers.

Conclusion

In healthy children aged 8-18 years, the mean liver stiffness reference values obtained on the Philips Epiq Elite ultrasound device were 4.04±0.84kPa using the pSWE method and 4.41±0.71kPa using the 2D-SWE method.These reference values will help the SWE method to be used more effectively in the evaluation of liver parenchyma in chronic liver diseases.

Keywords: Children, Liver stiffness, Shear wave elastography, Two-dimensional shear wave imaging, Ultrasound

Introduction

Ultrasonographic elastography is a new diagnostic imaging modality that finds use in the diagnosis and follow-up of chronic liver disease. Hepatic inflammation, edema, cell damage and the development of extracellular fibrosis represent the histopathological process of chronic liver disease (CLD), which may occur due to different etiological causes. In direct proportion to fibrosis, the tissue hardens and the intraparenchymal pressure increases, potentially resulting in portal hypertension, liver failure (cirrhosis) and associated complications. Even hepatocellular cancer may develop in some cases of CLD. Therefore, knowing the degree of fibrosis in the parenchyma is very important for predicting the prognosis, treatment planning and follow-up of CLD (1, 2). The gold standard method for evaluating liver fibrosis is biopsy. However, the search for non-invasive methods continues due to the disadvantages of vulnerability to complications because of its invasive nature, representing only 1/50,000 of the entire parenchyma, and requiring special training and equipment (3).

Sonographic elastography is a non-invasive imaging method, the effectiveness of which in the evaluation of liver stiffness (LS) has been investigated for approximately 20 years and the development process continues. There are basically two types of sonoelastography techniques. In Strain Elastography (SE), which is the first used elastography method, external pressure is applied to the liver several times (with the push-pull method) with the probe, and the shape change created in the tissue is evaluated qualitatively. The harder the tissue, the less deformation there will be. This technique can be applied in superficial tissues such as thyroid and breast where probe pressure can be applied easily. Information about tissue stiffness is evaluated visually on gray scale or color maps. Semi-quantitative measurements can be made by calculating the strain index as a proportion of the adjacent normal tissue color map. Tissue deformation can also be achieved with strong collimated sound waves (ARFI: Acoustic Radiation Force Impulse) produced by special probes (4, 5).

Another elastography method is the shear wave elastography (SWE) technique. In this method, the propagation velocity of sound waves caused by the force applied perpendicular to the tissue to propagate in the transverse plane (shear wave) in the parenchyma is measured. The oldest of the shear wave (SW) generation methods is Transient Elastography (TE), in which external mechanical pressure is applied to the liver with a special probe with a spring-piston mechanism. Another way to generate SW is with powerful collimated one/multiple ARFI packages created with special probes. There are different SW methods (pSWE, 2D-SWE and 3D-SWE) created with ARFI. In the point SWE (pSWE) method, the velocity of the shear waves created in a small area (1 cm) is measured with a single collimated and reinforced ARFI package. There is no color map in this method, and unlike TE, measurements are made with gray-beard imaging. In the 2D-SWE method, unlike pSWE, multiple parallel cylindrical ARFI packets are sent to the tissue in real time, enabling more than 1000 measurements per second from a larger area (5-7 cm). The obtained velocity values are evaluated both qualitatively with the color map and quantitative measurements are obtained with the region of interest (ROI) placed in the colored area. Thus, by avoiding large vascular structures and the gall bladder, it is possible to obtain a homogeneous color map, and measurement inconsistencies due to respiration are minimized due to the large number of measurements taken within milliseconds. These advantages provide significant convenience in the evaluation of LS, especially in children (6–8). 3D-SWE provides the opportunity to perform quantitative measurement in real time (9). The rate of SW propagation generated in the tissue is obtained quantitatively in kilo Pacal (kPa) or m/s (5, 9).

The degree of tissue hardening (ie., fibrosis) can be evaluated according to the flexibility of the tissues and the propagation speed of sound waves in the parenchyma using elastography (5). However, the variability of liver stiffness values (LSV) from device to device limits the routine use of these methods Therefore, in order to interpret liver fibrosis, each center should establish normal LS reference values according to its own device. LS reference values have been established for some methods and devices in healthy adult groups. However, there have not been enough studies conducted on healthy children in this respect. Although reference values for TE in children have been determined, reference values have not yet been established for p-SWE/2D-SWE, which is faster, easier for routine use, and for which results equivalent to TE have been reported in experimental studies (10–15).

The aim of this study was to determine the liver stiffness reference values for pSWE and 2D-SWE of the devices used in our center in the healthy pediatric age group. Thus it was aimed to contribute to the more effective use of non-invasive SWE techniques in the detection, follow-up and evaluation of treatment response in cases of chronic liver disease.

Material and Method

This case-control study was conducted in accordance with the ethical guidelines of the Helsinki Declaration and Institutional Ethics Committee approval was obtained. In keeping with the policies for a retrospective review, the informed consent requirement was waived.

Study Population

In order to determine normal LSVs in the pediatric age group, the study initially included a total of 128 patients who presented at the pediatric gastroenterology clinic of Suleyman Demirel University Medical Faculty with cold, non-specific abdominal pain or similar mild ailments between February 2021 and December 2022 and were considered generally healthy. The clinical, laboratory and ultrasound (US) examination data of the patients were obtained from picture archiving and communication system (PACS). The results of the biochemical tests (fasting blood glucose (FBG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, platelet, INR) and demographic data (gender, age, weight, height and BMI) performed within a week before the US examination were recorded. The subjects were selected from non-obese children with normal biochemical-microbiological test results (viral hepatitis markers, liver function tests, total bilirubin, serum albumin concentrations, complete blood count) and B-mode ultrasound examination findings.

Children were excluded from the study if they were aged >18 years or <8 years,or had any liver disease (eg., NAFLD, acute/chronic hepatitis, cholestatic chronic hepatitis, HBV/HCV infection), cardiopulmonary disease, chronic inflammatory disease, autoimmune disease, anti-inflammatory drug use, rapid weight loss, known endocrinological diseases, or any kidney disease determined in standard clinical and laboratory evaluations according to the PACS data. After the further exclusion of 6 children with normal laboratory findings but BMI>2SD, 12 with BMI<-2SD, and 3 without US images and/or measurements in PACS or with missing demographic data, a final total of 107 subjects were included in the study.

Ultrasound Examination

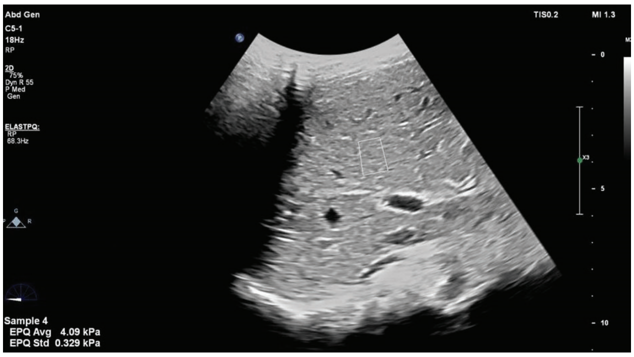
All US examinations were performed by single radiologist (H.A. who is an experienced ultrasound doctor with 25 years in clinical practice) using a Philips Epiq Elite machine (Philips Healthcare-Bothell, Washington, USA) with a 1-5MHz convex broadband transducer. The examinations were performed in the supine position, with both arms at maximum abduction, after at least 4 hours of fasting and at least 15 minutes of rest (16). The liver parenchyma was evaluated with subcostal and intercostal approaches in terms of parenchymal echo and space-occupying lesions with gray scale US. After general gray-scale examination, elastographic measurements were obtained in the right liver lobe in the last/second-last right intercostal space, 1–2cm under the liver capsule, avoiding areas with large vessels, without applying excessive pressure to the probe. Liver stiffness was evaluated in the same examination with two elastographic methods: pSWE (EPQ) and 2D-SWE (EQI).

pSWE (EPQ) Measurement

The area 1cm in diameter to be measured was determined with the moving track-ball and then by pressing the "up-date" button, the image was recorded for a total of 5 seconds (Fig.1). This procedure was performed at least 5 times from the same region to obtain an accurate stiffness average (17). If the measurement process is not suitable, the device does not give the measurement result. Measurements with a result >1kPa were considered successful. Finally, the median value of the measurements was calculated, and liver stiffness measurements (LSM) were recorded using the automatic calculation feature of the machine. As a result of 5 measurements, those with an IQR/median value of ≤30%, used as a reliability indicator, were considered successful. Participants with an IQR/median ratio of >30% of the average stiffness value were excluded from the study.

2D-SWE (EQI) Measurement

For 2D-SWE measurement, a colored map box was placed in a 5cm wide area free from large vessels in the region where the pSWE measurement was performed (Fig.2). When the color map was observed to be filled completely homogeneously, the recording was made for 5 seconds by the subject holding the breath at the end of the expiration. This recording process was repeated three times (13,18,19). When little or no color signal was obtained in the SWE box, the examination was considered inadequate and these subjects were excluded from the study. At the end of the examination, a single measurement was made by placing an ROI with a diameter of 10mm on the recorded image, to be in the central and homogeneous colorised area as far as possible (5). The mean LSM was then noted on the



A

Abdominal: Measurements and Calculations

ElastPQ Stiffness Measurements

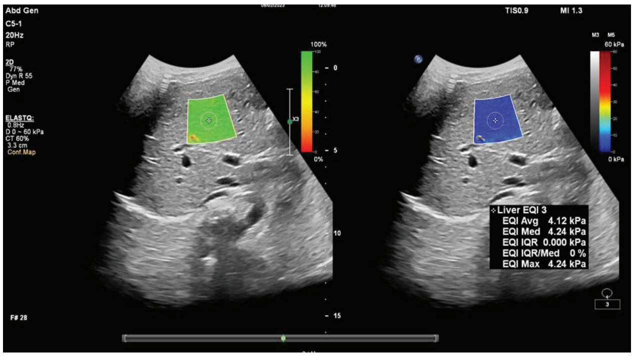
Sample 1		
EPQ Avg	3.53 kPa	
EPQ Avg Vel	1.09 m/s	
Sample 2		
EPQ Avg	3.73 kPa	
EPQ Avg Vel	1.12 m/s	
Sample 3		
EPQ Avg	3.67 kPa	
EPQ Avg Vel	1.11 m/s	
Sample 4		
EPQ Avg	4.09 kPa	
EPQ Avg Vel	1.17 m/s	
Sample 5		
EPQ Avg	3.01 kPa	
EPQ Avg Vel	1.00 m/s	

ElastPQ Stiffness Calculations

EPQ Avg	3.61 kPa
EPQ Std	0.35 kPa
EPQ Med	3.67 kPa
EPQ IQR	0.64 kPa
EPQ IQR/Med	17 %
EPQ Avg Vel	1.10 m/s
EPQ Std Vel	0.06 m/s

B

Figure 1:
Liver stiffness measurement with pSWE (A) and automatic hardness values of the device at the end of 5 measurements are shown (B).



A

EQI Liver Stiffness Calculations

Liver EQI Avg	4.41 kPa
Liver EQI Med	4.52 kPa
Liver EQI IQR/Med	10 %
Liver EQI IQR	0.46 kPa
Liver EQI Std	0.20 kPa
Liver EQI Avg Vel	1.21 m/s
Liver EQI Med Vel	1.23 m/s
Liver EQI IQR/Med Vel	5 %
Liver EQI IQR Vel	0.06 m/s
Liver EQI Std Vel	0.03 m/s

B

Figure 2:
Liver stiffness measurement with 2D-SWE (A) and automatic hardness values of the device at the end of 5 measurements are shown (B).

report page, which includes the automatic calculations of the device (5).

The results of LSM using pSWE and 2D-SWE can be expressed in kPa or m/s. The units of kPa were preferred in this study(5).

Power Analysis

The power analysis of the study was performed using GPower 3.1.9.2. software (Universitaet Kiel, Germany). The study was designed to be conducted on healthy children to determine the normal reference values of the pSWE (EPQ) and 2D-SWE (EQI) methods of assessing the elasticity of the liver. In the pilot study, the EPQ-median and EQI-median values were calculated with the information obtained from 10 children, and it was decided to select the sample group from the population by a simple random sampling method. The effect size was determined as d=0.526 and n=46 for the EPQ-median measurements, and d=0.358 and n=96 for the EQI-median measurements. By considering the largest sample value, it was decided to complete the study with a minimum of 96 healthy children. The study was completed a total of 107 children.

Statistical Analysis

The statistical analyses of the study were performed using SPSS vn. 20.0 software (IBM Inc, Chicago, IL, USA). Descriptive statistics were calculated as mean±standard deviation values, 5% trimmed mean, and 95% confidence interval around the mean, median, minimum, maximum, and percentiles (5, 10, 25, 50, 75, 90, 95). The normality assumption was analyzed using both Kolmogorov-Smirnov and Shapiro-Wilk tests for all measurements. With the exception of the BMI-SD scores, the distribution of all the other measurements was found to be normal. The comparisons of all the measurement values between the genders was performed using the Independent Samples t-test, and One-Way Analysis of Variance with the Tukey HSD post-hoc test was used in comparisons according to age groups. The relationships between EPQ- and EQI-median values and other laboratory data (FBG, AST, ALT, albumin, platelet and INR) were analyzed with Pearson correlation analysis. A value of $p<0.05$ was considered statistically significant in the analyses.

Results

The characteristics of the subjects included in the study are presented in Table 1. The total 107 children comprised 66 (61.7%) females and 41 males with a mean age of 13.4±2.77 years, mean weight of 43.05±12.87 kg, mean height of 152.36±15.36 cm, and mean BMI of 18.14±2.86kg/m2.

The mean median values of the EPQ and EIQ measurements were 4.04±0.84kPa (EPQ-IQR:0.87± 0.3, EPQ-IQR/median:21.41±7.61), and 4.41±0.71kPa (EQI-IQR:0.76±0.57, EQI-IQR/median: 17.16±10.64), respectively. A moderate and significant correlation was observed between the median values of EPQ and EQI ($r=0.590$; $p<0.001$). 95% confidence intervals were calculated with 5% trimmed mean values for all measurements (Table 2). The 5% trimmed mean is the

Table 1 Baseline characteristics of all the study participants

Male/Female (n)	41/66
	Mean±SD
Age (years)	13.4±2.77
BMI (kg/m^2)	18.14±2.86
BMI-SD	-0.82±1.00
FBG (mg/dL)	94.59±16.27
Albumin (g/dL)	4.57±0.25
Aspartate aminotransferase (AST) (IU/L)	27.73±16.69
Alanine aminotransferase (ALT) (IU/L)	19.95±11.78
Platelet ($10^{3/\mu L}$)	287.09±71.14
INR	1.07±0.09

BMI: body mass index, FBG: fasting blood glucose, SD: standard deviation

Table 2 The liver stiffness values measured with pSWE and 2D-SWE in healthy children aged 8 to 18 years

	Mean±SD (kPa)	**5% Trimmed mean** (kPa)	**95% CI of mean** (kPa)	**Median (min-max)** (kPa)
pSWE (EPQ)				
median	4.04±0.84	4.03	3.67 - 4.42	3.86; 2.55 -5.78
IQR	0.87±0.3	0.85	0.73 - 0.99	0.83; 0.43-1.56
IQR/medianian	21.41±7.61	21.01	18.04 - 24.78	21.5; 9 - 42
2D-SWE (EPQ)				
median	4.41±0.71	4.41	4.09 - 4.72	4.34; 2.82 -6
IQR	0.76±0.57	0.69	0.51 - 1.01	0.67; 0.13- 2.59
IQR/medianian	17.16±10.64	16.42	12.44 - 21.88	14.5; 3- 45
Right lobe size (mm)	123.09±19.88	121.24	114.27 - 131.90	118; 100 -180

CI: confidence interval, 2D-SWE: 2 dimensional shear wave elastography, EPQ: name of the pSWE method on the Philips Epiq Elite ultrasound device, EQI: name of the 2D-SWE method on the Philips Epiq Elite ultrasound device, IQR: interquartile range, pSWE: point shear wave elastography.

Table 3 Percentage values of measurements of liver stiffness using 2D-SWE and pSWE in healthy children aged 8-18 years.

	(%)	**5**	**10**	**25**	**50**	**75**	**90**	**95**
pSWE (EPQ) (kPa)								
median		2.64	3.13	3.39	3.88	4.74	5.26	5.71
IQR		0.44	0.49	0.65	0.83	1.03	1.35	1.53
IQR/medianian		9.30	11.30	15.75	21.50	25.25	29.70	40.20
2D-SWE (EPQ) (kPa)								
median		2.91	3.47	4.09	4.34	4.76	5.57	5.97
IQR		0.14	0.25	0.35	0.67	0.90	1.69	2.47
IQR/medianian		3.30	5.90	8.75	14.50	24.25	35.00	43.95

2D-SWE: 2 dimensional shear wave elastography, EPQ: name of the pSWE method on the Philips Epiq Elite ultrasound device, EQI: name of the 2D-SWE method on the Philips Epiq Elite ultrasound device, IQR: interquartile range, pSWE: point shear wave elastography.

mean value obtained as a result of subtracting the 5% extreme values in the distribution of the variable. When the measurement mean values and the trimmed mean values were examined, they were seen to be quite close to each other. Accordingly, it was observed that there were no extreme values in the measurements of the variables and that the distributions were not skewed. A similar situation was encountered when the median values were analyzed. Significant percentiles of all the measurement values were also calculated (Table 3).

The correlation between the EPQ and EQI-median values was examined. The LSVs of EIQ were found to be moderately significantly higher than EPQ (med; min-max:4.34kPa; 2.82 - 6 and 3.86kPa; 2.55 – 5.78, respectively) ($r=0.59$, $p<0.001$). The correlations between LSVs and patient descriptive information (age, height, weight, BMI) and laboratory findings (FBG, AST, ALT, albumin, platelet, INR) were analyzed. A very low-level positive correlation was observed between the age of the children and the median pSWE value ($r=0.267$; $p=0.006$). No significant correlation was found between other measurements and the median values of EPQ and EQI.

Since there was a low correlation between the EPQ-median value and age, the subjects were divided into three age groups; 96-132 months (Group A), 133-180 months (Group B), and 180+ months (Group C). The EPQ and EQI measurements were compared according to these groups (Table 4). The EPQ-median measurement results differed significantly according to age groups: median values were 3.75±0.70kPa in Group A, 3.96±0.90kPa in Group B and 4.23±0.76kPa in Group C ($p=0.045$). In the median EQI values, a significant difference was observed in the age groups: 4.24±0.75kPa in Group A, 4.23±0.75kPa in Group B, and 4.66±1kPa in Group C ($p=0.051$). The EPQ-IQR, EPQ-IQR/median, EQI-IQR and EQI-IQR/median measurement results did not differ significantly according to age groups.

The measurement results of the study group were compared according to gender in one-way analysis of variance. All the EPQ and EQI values were slightly higher in girls, but not at a statistically significant level. In girls, the EPQ-median values were close to each other in groups A and B, but significantly higher in group C ($p=0.040$). The LSVs of EQI in girls were not significantly different according to age groups ($p=0.137$). In boys, the LSVs of both methods were not significantly different ($p=0.255$). There was no significant difference between height, weight and BMI measurements according to gender. The fasting blood glucose levels were significantly higher in boys than in girls ($p=0.003$), however FBG levels were within normal reference limits.

Discussion

The results of this study demonstrated normal LSM reference values in healthy children aged 8-18 years with two different SWE methods (pSWE and 2D-SWE). The mean LSVs in all children were 4.04±0.84kPa (95% CI:3.67-4.42kPa) for pSWE and 4.41±0.71kPa (95% CI:4.09-4.72kPa) for 2D-SWE. The 2D-SWE LSVs were higher than the pSWE values. While LSVs had a low level of significant positive correlation with increasing age, no significant difference was found according to gender.

To the best of our knowledge, few studies have been conducted with the SWE method to determine the normal stiffness reference values of the liver in healthy children (13–15,20–22). In these studies, different results were reported in liver parenchymal stiffness values due to the difference in the devices used, different sample sizes, and different age groups. Mjelle et al. reported that the median stiffness of the liver in children aged 4-17 years was 4.1kPa (IQR:3.6–4.7) for pSWE (Samsung) and 3.3kPa (IQR:2.7-4.39) for 2D-SWE (General Electric (GE))(21). Marginean et al. reported LSV 3.72±0.48kPa for 2D-SWE (GE) in children aged 3-18 years (20), and Galina et al. determined values of 4.29±0.59kPa for 2D-SWE (GE) in the 0-16 years age group (15). Franchi-Abella et al. reported 6.58±1.46kPa for 2D-SWE (Aixplorer, Supersonic Imaging) and Shin et al. reported 5.5±1.3kPa for 2D-SWE (Aixplorer, Supersonic Imaging) in the 0-18 years age group (13,14).

Keeping the age group high in the current study (8-18 years old) may have affected the higher LS values than in other studies, because a positive correlation has been shown between the increase in age and elasticity values in children (20,21,23–25). In the present study, a low level of significant positive correlation was observed with the increase in age in the pSWE method in LS values ($r=0.267$; $p=0.006$). In the 2D-SWE method, there was a significant increase in LS values, especially in the 180+ month group ($p=0.051$). However, there are also studies reporting that age does not affect LSVs (26,27).

In this study, gender was not found to affect LSM values. Conflicting results have been reported in the literature regarding the effect of gender on LSM values. It has been suggested that LSM values may be lower in girls due to the anti-fibrotic effect of estrogen (15,20,25,28,29). In the present study, the fact that the EPQ-median values in girls were close to each other in the A and B age groups, but significantly higher in the C group may support this idea ($p=0.040$). However, the EQI-median values in girls did not differ significantly between age groups. ($p=0.137$). However, there are a few studies in literature reporting that gender has no effect on LSVs (24,30–33).

In the current study, there was no significant relationship between LS median values, liver size and BMI, and this finding was consistent with the literature (15,21,27,34).

In the current study, the LS values were found to be higher in 2D-SWE than in pSWE (4.04±0.84/4.41±0.71, $p<0.001$). There are very few studies comparing both methods. Mjelle et al. reported median LS values as 3.3kPa (IQR: 2.7–4.3) for 2D-SWE (GE) and 4.1kPa (IQR: 3.6–4.7) for pSWE (Samsung) in a study of a healthy 4-17 years age group (21). These results contradict the results of the present study, which could be attributed to the difference between the study groups and the devices used. Therefore, a reliable comparison cannot be made. In a study conducted by Mulabecirovic et al., the 2D-SWE method of two different devices (GE and Samsung) was compared and significantly higher LSVs were determined with the GE device (4.5±0.8 kPa and 4.1±0.8kPa, respectively, $p<0.001$). The 2D-SWE LS values of the current study are similar to the values obtained from the GE device in the study by Mulabecirovic et al. However, such a comparison may not be accurate, as the aforementioned study was conducted on an adult healthy group.

This study had some limitations. Although biopsy is the gold standard method for liver disease detection, healthy children could not be biopsied due to its invasive nature and for ethical reasons. Therefore, it cannot be said with 100% certainty that the participants did not have liver disease. However, we minimized this limitation by including individuals who were completely normal in terms of anamnesis, laboratory findings and US reports. Second, the intra-observer reliability of the measurements could not be tested because the measurements were taken in one session. As it is difficult to apply in clinical practice, the subjects were not called for remeasurement. However, the 25 years of US experience of the examining physician may partially compensate for this limitation. In addition, intra-observer reliability could not be tested because the measurements were made by a single physician.

In conclussion, LS normal reference values were determined for two different SWE methods in the same session in healthy children aged 8-18 years, in this study. The LS median values were found to be higher in the 2D-SWE method compared to pSWE. The LSVs showed a weak positive correlation with increasing age, but no significant correlation was found with gender, BMI, liver size, and biochemical markers. These reference values created for healthy children will help the SWE method to be used more effectively in the evaluation of hepatic parenchyma in chronic liver diseases.

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Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
We adhered to the Declaration of Helsinki principles. Ethical approval was attained from the Local Clinical Research Ethics Committee (Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee, Date and decision number: 31.01.2023/14).

Consent to Participate and Publish
In keeping with the policies for a retrospective review, the informed consent requirement was waived.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
HA: Planning the study; Methodology; Resources; Data curation; Formal analysis; Writing-original draft; Writing-review; Validation; Visualization;

FİI: Data curation; Investigation; Validation; Supervision; & editing.

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