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The Relationship of Liver Stiffness with Liver Size, Age, Gender, and Body Mass Index in Child and Adult Age Groups by 2-D Shear Wave Elastography

Çocuk ve Erişkin Yaş Gruplarında Karaciğer Elastisitesinin Karaciğer Boyutu, Yaş, Cinsiyet ve Beden Kitle İndeksi ile İlişkisinin 2-D Shear Wave Elastografi ile Değerlendirilmesi

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ABSTRACT

Aim: The study aimed to evaluate the normal liver stiffness value (LSV) with shear wave elastography (SWE) in children and adults, and reveal the relationship between LSV and age, gender, body mass index (BMI), and liver size.
Material and Methods: A total of 173 healthy volunteers, 92 female and 81 male, aged between 4 and 50 years were included in this study. LSV measurements were performed in the supine position during normal breathing and from the right intercostal space where the acoustic window is best. The mean of the five valid measurements was accepted as the mean LSV. The relationship between the mean LSV and age, gender, liver size, and BMI was evaluated.
Results: There was a moderate positive correlation between LSV and age ($p<0.001$, $r=0.609$), LSV and BMI ($p<0.001$, $r=0.512$), and LSV and liver size ($p<0.001$, $r=0.485$). However, the multivariate linear regression analysis revealed that the effects of liver size and gender on LSV were not significant ($p=0.091$, and $p=0.759$, respectively), while the effects of age and BMI were significant ($p<0.001$, and $p=0.019$, respectively).
Conclusion: 2-D SWE is an effective imaging method to evaluate LSV both in children and adults. LSV increases with increasing age and BMI, however, it is not affected by gender and liver size. The normal LSV obtained in the present study can be used as reference values in the evaluation of various liver diseases with 2-D SWE.
Keywords: Liver; shear wave elastography; ultrasonography.

ÖZ

Amaç: Bu çalışma çocuklarda ve erişkinlerde normal karaciğer elastisite değerinin (liver stiffness value, LSV) shear wave elastografi (SWE) ile değerlendirilmesini ve LSV ile yaş, cinsiyet, beden kitle indeksi (BKİ) ve karaciğer boyutu arasındaki ilişkinin ortaya koyulmasını amaçlamaktadır.
Gereç ve Yöntemler: Bu çalışmaya yaşları 4 ve 50 yıl arasında olan, 92 kadın ve 81 erkek olmak üzere toplam 173 sağlıklı gönüllü dahil edilmiştir. LSV ölçümleri supin pozisyonda, normal nefes alma esnasında sağ interkostal aralıktan, akustik pencerenin en iyi olduğu aralıktan yapıldı. Beş güvenli ölçümün ortalaması ortalama LSV değeri olarak kabul edildi. Ortalama LSV ile yaş, cinsiyet, karaciğer boyutu ve BKİ arasındaki ilişki değerlendirildi.
Bulgular: LSV ile yaş arasında ($p<0,001$; $r=0,609$), LSV ile BKİ arasında ($p<0.001$; $r=0,512$) ve LSV ile karaciğer boyutu arasında ($p<0,001$; $r=0,485$) pozitif yönlü orta dereceli bir ilişki saptanmıştır. Ancak multivariate lineer regresyon analizi karaciğer boyutunun ve cinsiyetin LSV üzerine etkisinin anlamlı olmadığını (sırasıyla $p=0,091$ ve $p=0,759$), yaş ve BKİ'nin etkisinin ise anlamlı olduğunu ortaya çıkarmıştır (sırasıyla $p<0,001$ ve $p=0,019$).
Sonuç: 2-D SWE hem çocuklarda hem de erişkinlerde LSV'nin değerlendirilmesinde etkili bir görüntüleme yöntemidir. LSV yaş ve BKİ arttıkça artış göstermekte, bununla birlikte, cinsiyet ve karaciğer boyutundan etkilenmemektedir. Mevcut çalışmada elde edilen normal LSV çeşitli karaciğer hastalıklarının 2-D SWE ile değerlendirilmesinde referans değerler olarak kullanılabilir.
Anahtar kelimeler: Karaciğer; shear wave elastografi; ultrasonografi.

INTRODUCTION

Shear wave elastography (SWE) is an ultrasound (US) based non-invasive imaging method used in clinical practice to detect and grade liver fibrosis resulting from various etiological factors. The introduction of SWE into clinical use has led to a significant decrease in the rate of liver biopsies performed to evaluate liver fibrosis (1). There are several ultrasound-based elastography methods to assess liver fibrosis. These include transient elastography (TE), and acoustic radiation force impulse (ARFI). Two ARFI techniques are clinically available: point SWE (p-SWE) and 2-D SWE (2).

2-D SWE is an imaging method that quantifies the elasticity of tissue by measuring the speed of shear waves induced in the tissue by acoustic push pulses, generating 2-D quantitative images of shear wave speed. 2-D SWE displays 2-D color images of shear wave speed in a region of interest (ROI). The ROI can be adjusted in size and position, and the tissue stiffness can be obtained at any location within the ROI, as shear wave speed (m/s), or converted to Young's modulus (kPa) (3).

Although the reliability is high due to high inter- and intra-observer agreement in SWE, recent studies have reported high intersystem variability and overlapping in reference values (1,4-8).

Despite the abundance of studies on the evaluation of liver parenchymal pathologies with SWE (1,2,9,10), the literature involves fewer studies examining the normal liver stiffness value (LSV) in both adult and child age groups (3,11-14). However, determining the normal LSV reference values for each new elastography technique is crucial to increasing the diagnostic efficiency of SWE in various liver diseases (14,15). In addition, the high intersystem variability makes it necessary to determine the normal reference values well and therefore requires more studies involving different devices and SWE techniques that evaluate normal parenchyma. To the best of our knowledge, there is no study in the literature evaluating LSV both in children and adults together in the same study, examining at the same time the relationship between liver size and LSV. For all these reasons, this study aimed to evaluate the normal LSV with 2-D SWE in children and adults to determine the normal reference values and reveal the relationship between LSV and age, gender, body mass index (BMI), and liver size.

MATERIAL AND METHODS

Study Group

The study was approved by the Clinical Researches Ethics Committee of Tokat Gaziosmanpaşa University Faculty of Medicine (06.02.2020/20-KAEK-019). The participants were selected among the patients who were referred to the Radiology Department of Tokat Gaziosmanpaşa University Hospital from March 2020 to July 2021 for routine Abdominal US examination. It included healthy volunteers, without any history or suspicion of chronic liver disease, liver fibrosis, liver congestion, acute hepatitis and infiltrative liver diseases, hepatic and splenic inflammation, those with elevated liver enzymes, hepatomegaly, hepatosteatosis, viral hepatitis, portal hypertension, portal vein or bile duct dilatation, autoimmune or metabolic disease, focal liver lesion, or another disease. The participants consisted of those with normal values as defined by the World Health Organization criteria. The relationship of LSV with age, gender, BMI, and liver size was investigated.

2-D SWE Measurements

SWE measurements were performed by a radiologist with Logiq E9 XDclear, GE Healthcare, Milwaukee; WI ultrasonography device using C1-6-D XDclear 1-6 MHz convex probe. SWE measurements were performed in the supine position, during normal breathing, while the right arm was at maximum abduction, and from the right intercostal space at the location of the best acoustical window. The transducer was perpendicular to the liver capsule. The rectangular box was placed 1.5 to 2.0 cm below the liver capsule to avoid reverberation artifacts, and it did not contain vessels and bile ducts. The SWE images were obtained in the form of homogeneous color-coding filling inside the rectangle (16). LSV was calculated in kPa by placing an ROI drawn in the largest possible diameter into the rectangular box (Figure 1). Five valid measurements were conducted. Median LSV, interquartile range (IQR), and IQR/median ratio were calculated for each patient based on the five valid measurements. The average of these five values was determined as the mean LSV. In addition, the IQR/median value of the five values was calculated and patients with an IQR/median ratio of over 30% were not included in the study. The liver size measurements were performed in the supine position with the right arm at maximum abduction, and the patient deeply breathing, from the right midclavicular line, extending from the hepatic dome to the lower hepatic margin as a sonographic measurement parameter (17). All measurements were recorded to the nearest millimeter.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation, and categorical variables were expressed as frequency and percentage. Independent sample t-test and one-way analysis of variance were used to compare the normal-distribution continuous data between/among groups. For post hoc comparisons between the pair-wise groups, the Tukey HSD test was used. The chi-square test was used to compare the categorical data between/among groups. Pearson's correlation coefficient was used for correlation between variables. A multivariate linear regression model was implemented to determine the relationships between age, gender, BMI and liver size, and LSV. A p-value of <0.05 was considered significant. Statistical analyses were performed using IBM SPSS v.20 statistical package.

RESULTS

The study involved a total of 173 volunteers. They were divided into two groups: those <18 and ≥18 years of age, which formed the first classification of age groups. They were further split into five groups: those aged 4-9 years, 10-18 years, 19-28 years, 29-38 years, and 39-50 years, and this classification constituted the second classification of age groups. We investigated whether there was a difference in LSV between the groups. In both classifications, there was no significant difference in gender between the groups ($p=0.730$, and $p=0.261$, respectively). Characteristics of the study group were presented in Table 1.

When LSV was evaluated in the general study group in terms of gender, the mean LSV was 5.49±0.87 kPa in females and 5.33±0.89 kPa in males, and there was no statistically significant difference in LSV in terms of gender (p=0.238, Table 2).

Table 3 demonstrates the comparison of the age groups by the first classification of age into two groups, as <18 and ≥18 years of age. Accordingly, LSV was 4.95±0.73 kPa in the group aged <18 years and 5.70±0.85 kPa in the group aged ≥18 years, and the difference between the groups was statistically significant (p<0.001). The differences between the two groups both in BMI (p<0.001) and in liver size (p<0.001) were also statistically significant.

Table 4 presents the comparison of BMI, liver size, and LSV in the age groups by the second classification of age into five groups, as 4-9, 10-18, 19-28, 29-38, and 39-50 years of age. Accordingly, the general comparison revealed that the difference in LSV between all age groups was statistically significant (p<0.001). When the age groups by the second classification were compared among themselves, the differences between the following age groups were significant according to the post hoc test results: 4-9 years and 10-18 years, 29-38 years, and 39-50 years; 10-18 years and 4-9 years, 29-38 years, and 39-50 years; 19-28 years and 29-38 years and 39-50 years; 29-38 years and all age groups; 39-50 years and all age groups; and LSV increased with age. The differences between the five groups were also significant in BMI (both p<0.001) and liver size (p<0.001).

According to Pearson's correlation coefficient, there was a moderate positive correlation between LSV and age (p<0.001, r=0.609), LSV and BMI (p<0.001, r=0.512), and LSV and liver size (p<0.001, r=0.485) in the general group. In the group aged <18 years, there was a weak positive correlation between LSV and age (p=0.002, r=0.380), and LSV and BMI (p=0.003, r=0.362), as well as a moderate positive correlation between LSV and liver size (p=0.001, r=0.405). In the group ≥18 years of age, we found a moderate positive correlation between LSV and age (p<0.001, r=0.613) and LSV and BMI (p<0.001, r=0.491), and a weak positive correlation between LSV and liver size (p=0.003, r=0.287).

The multivariate linear regression analysis revealed that the effects of gender (p=0.759) and liver size (p=0.091) on LSV were not statistically significant while the effects of age (p<0.001) and BMI (p=0.019) were statistically significant. A one-unit increase in age causes an increase of 0.029 units in LSV, and a one-unit increase in BMI causes an increase of 0.052 units in LSV, both statistically significant (p<0.001, and p=0.019, respectively). Age is the variable that contributed to the model the most (Beta=0.412, p<0.001). The results of multivariate linear regression analysis were presented in Table 5.

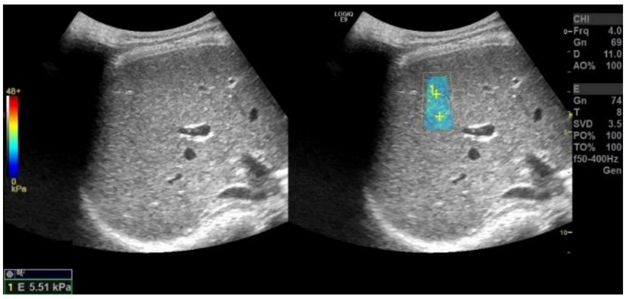

Figure 1. Measurement of normal liver parenchyma with 2-D SWE obtained from a 36-year-old female patient

Table 1. Characteristics of the study group

Characteristics	(n=173)
Gender, n (%)	
Female	92 (53.2)
Male	81 (46.8)
Age Groups, n (%)	
4-17	66 (38.2)
18-50	107 (61.8)
Age Groups, n (%)	
4-9	26 (15.0)
10-18	41 (23.7)
19-28	33 (19.1)
29-38	51 (29.5)
39-50	22 (12.7)
Age (year)	24.51±12.47 (4-50)
BMI (kg/m^2)	21.28±3.11 (14.10-26.40)
Liver Size (mm)	133.55±18.99 (86-160)
LSV (kPa)	5.41±0.88 (3.29-7.10)

BMI: body mass index, LSV: liver stiffness value, descriptive statistics of the continuous variables were expressed as mean±standard deviation (min-max)

Table 2. Comparison of the study group by gender

	Female (n=92)	Male (n=81)	p
Age (year)	25.76±12.37	23.10±12.51	0.162
BMI (kg/m^2)	21.64±2.81	20.88±3.39	0.110
Liver Size (mm)	134.26±18.14	132.75±20.00	0.604
LSV (kPa)	5.49±0.87	5.33±0.89	0.238

BMI: body mass index, LSV: liver stiffness value, descriptive statistics of the continuous variables were expressed as mean±standard deviation (min-max)

Table 3. Comparison of the age groups by first classification

	4-17 (n=66)	18-50 (n=107)	p
BMI (kg/m^2)	19.33±3.71	22.48±1.85	**<0.001**
Liver Size (mm)	119.12±15.28	142.46±15.24	**<0.001**
LSV (kPa)	4.95±0.73	5.70±0.85	**<0.001**

BMI: body mass index, LSV: liver stiffness value, descriptive statistics of the continuous variables were expressed as mean±standard deviation (min-max)

Table 4. Comparison of the age groups by second classification

	4-9 (n=26)	10-18 (n=41)	19-28 (n=33)	29-38 (n=51)	39-50 (n=22)	p
BMI (kg/m^2)	15.7±1.16^{a}	21.78±2.76^{bc}	21.58±2.04^{c}	22.88±1.64^{b}	22.8±1.54^{bc}	**<0.001**
Liver Size (mm)	107.85±11.65^{a}	126.78±12.75^{b}	139.97±16.14^{c}	142.53±15.99^{c}	146.14±11.95^{c}	**<0.001**
LSV (kPa)	4.65±0.79^{a}	5.17±0.62^{b}	5.11±0.88^{ab}	5.78±0.67^{c}	6.38±0.58^{d}	**<0.001**

BMI: body mass index, LSV: liver stiffness value, descriptive statistics of the continuous variables were expressed as mean±standard deviation (min-max), different superscripts (a, b, c, d) in the same row indicate a statistically significant difference between the groups

Table 5. Results of multivariate linear regression analysis

Model	Unstandardized Coefficients		Standardized Coefficients	p
	B	SE	Beta	
Age (year)	0.029	0.006	0.412	**<0.001**
BMI (kg/m^2)	0.052	0.022	0.185	**0.019**
Liver Size (mm)	0.006	0.004	0.132	0.091
Gender	-0.032	0.105	-0.018	0.759

Dependent variable: liver stiffness value, BMI: body mass index, SE: standard error

DISCUSSION

To the best of our knowledge, the present study is the first study evaluating adult and child groups together with the same technical equipment and method, comparing LSV in children and adult groups and examining the relationship between liver size and liver stiffness.

Normal LSVs vary according to the elastography method used in both children and adults (3,14). Mulabecirovic et al. (14) adopted TE as a reference and used 2-D SWE and p-SWE techniques in healthy individuals aged 20-70 years. They reported that the mean LSV was 4.5±0.8 kPa with 2-D SWE, 4.2±1.1 kPa with TE, and 4.1±0.8 kPa with p-SWE. They stated that the values were higher with 2-D SWE than that with TE. Bende et al. (3) revealed that the average LSV was 5.9±1.2 kPa in males and 4.7±1.2 kPa in females with 2-D SWE, and the values were lower compared with those obtained with TE in the study. In our study, the values obtained in the adult age group are similar to that of other 2-D SWE techniques mentioned in the literature and similarly higher than the values obtained with TE (3,14).

In the childhood age group, Yang et al. (11) found the normal LSV to be 6.3±1.1 kPa and 6.2±1.1 kPa in segments V and VI, respectively, in their study with 2-D SWE in school children. Eiler et al. (18) reported the mean LSV as 1.16±0.14 m/sec with point SWE in healthy children aged 0-17 years. In the study by Lewindon et al. (12) in children aged 0-18 years, they found LSV with TE 3.5±0.5 kPa in the 0-2 year-old group, 3.8±0.3 kPa in the 3-5 year-old group, 4.1±0.2 kPa in the 6-11 year-old group, and 4.5±0.2 kPa in the 12-18 year-old-group. Tokuhara et al. (13) divided children aged 1-18 years into three groups; 1-5 years, 6-11 years, and 12-18 years of age. The LSV they found with TE was 3.4 (2.3-4.6) kPa in the pre-school group, 3.8 (2.5-6.1) kPa in the primary school age group, and 4.1 (3.3-7.9) kPa in the adolescent group. In the child age group, the closest technique to that in our study is that in the study of Yang et al. (11) and the values obtained in both studies are similar.

There are several studies examining the relationship of LSV with age and gender in the child age group. Similar to ours, most of them found an increase between age and LSV (12,13); however, one study reported no relationship between age and LSV (18). Another one stated that LSV increased between the ages of 6-9 years and plateaued between the ages of 10-15 years (11).

There was no relationship between childhood gender and LSV in most studies similar to our study (11-13,19). However, one study reported the values to be lower in females (18).

Some studies examining the relationship between age and LSV in adult patients found the effect of age on LSV to be not significant (14,20), while some others reported that LSV increased with age (3,21). We found a positive correlation between age and LSV in the adult group, and the effect of age on LSV was significant in the multiple regression analysis. In addition, LSVs were higher in the adult age group compared to the child group. To our knowledge, the present study is the first that compared LSV in child and adult age groups.

The relationship between gender and LSV in adult patients is controversial. While some researchers claim that there are higher values in males (14,21,22), some studies report the difference between genders to be not significant, similar to ours (3,20,23).

A meta-analysis of large series conducted with TE examined the relationship between BMI and LSV and investigated the normal and fibrosis-related LSV and the factors affecting it. The study found the mean, lower, and upper limit values of the normal LSV to be 4.61 (4.51-4.71) kPa in those with BMI <30 kg/m^2, and 4.46 (3.96-4.96) kPa in those with BMI>30 kg/m^2, respectively (20). A study not involving obese patients in the adult age group found the difference not significant in the comparison of the groups with a BMI of 18.0-25.0 kg/m^2 and a BMI of 25-30 kg/m^2, and suggested that BMI did not affect LSV (14). A study targeting the childhood age group reported no relationship between BMI and LSV in children with normal BMI (19). However, we found a positive correlation between BMI and LSV both in the general group and the groups aged <18 and ≥18 years. We also found the effect of BMI on LSV significant in the multiple regression analysis.

We believe that the current study is the first that shows the relationship between liver size and LSV. Although we found a moderate positive correlation between liver size and LSV in both the general group and the groups aged <18 and ≥18 years, the effect of liver size on LSV was not significant in the multiple regression analysis.

Our study has some limitations worth mentioning. Firstly, the measurements were made by a single radiologist. However, the values included five measurements obtained following the validation criteria specified in the materials and method section. In addition, patients with an IQR/median ratio of over 30% were not included in the study. Many studies show that intra- and inter-observer compatibility is remarkable in 2-D SWE (14,24). Secondly, the number of patients is relatively small. Studies involving a higher number of patients can be conducted in the upcoming period.

CONCLUSION

2-D SWE is an effective imaging method to evaluate LSV in both child and adult age groups. Normal LSV presented in this study can be used as reference values in the evaluation of various liver diseases with 2-D SWE. While there is a positive correlation between LSV and age, and BMI, there is no significant correlation between LSV and gender and liver size.

Ethics Committee Approval: The study was approved by the Clinical Researches Ethics Committee of Tokat Gaziosmanpaşa University (06.02.2020, 019).

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