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CARDIOVASCULAR IMAGING

ORIGINAL ARTICLE

Liver stiffness value obtained by point shear-wave elastography is significantly related with atrial septal defect size

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PURPOSE
The increase in volume and pressure in the right atrium (RA) and right ventricle (RV) has been shown to increase the liver stiffness (LS). In the literature, there is no information about the changes in LS value in patients with atrial septal defect (ASD). The aim of our study was to investigate the change of LS values obtained by point shear-wave elastography (pSWE) in patients with ASD and the clinical utility of pSWE for this disease.

METHODS
This cross-sectional study included 66 patients with ostium secundum ASD: 21 patients with no indication for ASD closure (Group I), 38 patients who underwent ASD closure (Group II), and 7 patients who had ASD with Eisenmenger syndrome (Group III). All patients underwent echocardiography and pSWE. Increased LS was accepted as ≥7 kPa.

RESULTS
LS values as well as transaminases, clinical signs of heart failure and functional and structural heart abnormalities (increase of RA and RV diastolic dimensions, tricuspid regurgitation pressure gradient [TRPG], ASD size and decrease of ejection fraction, tricuspid annular plane systolic excursion) significantly increased from Group I to Group III ($P < 0.001$ for all comparisons). Mean LS values for Group I, Group II, and Group III were 5.16±1.55 kPa, 7.48±1.99 kPa, and 13.9±2.58 kPa, respectively. In multivariate linear regression analysis, ASD size and TRPG were significantly associated with LS increase. Only ASD size independently predicted abnormal LS increase ≥7 kPa according to multivariate logistic regression. Clinical value of LS increase was comparable to TRPG for detection of Eisenmenger syndrome; in the receiver operating curve analysis, area under the curve was 0.995 for LS ($P < 0.001$) and 0.990 for TRPG ($P < 0.001$). At 10 kPa threshold, LS determined the Eisenmenger syndrome with 100% sensitivity and 91.5% specificity.

CONCLUSION
LS value assessed by pSWE was significantly increased in ASD patients with closure indication and Eisenmenger syndrome compared to patients without ASD closure indication and was comparable with TRPG in regards to Eisenmenger syndrome identification. ASD size significantly associated with LS and independently predicted abnormal LS increase ≥7 kPa.

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Atrial septal defect (ASD) is the most common congenital heart disease (CHD) in adults and constitutes 10% of all patients with CHD (1–3). Initially, pulmonary arterial pressure (PAP) is normal, but increases in the later stages of the disease. Up to 5% of cases may present with Eisenmenger syndrome. These patients are followed by echocardiography in the absence of significant defect. The right atrium (RA) and right ventricle (RV) diameter and function, tricuspid regurgitation and PAP values and pulmonary to systemic flow ratio (Qp/Qs) are followed in echocardiography. Volume and pressure increase are the most important parameters that determine the closure indication of ASD. Transesophageal echocardiography (TEE) is used especially for ASD closure and other accompanying abnormalities, because it gives better and clearer images (1).

Liver ultrasonography (US) is not a routine study in adult patients with CHD, including ASD. Liver US can be performed as part of the abdominal US only in patients with Eisenmenger syndrome or after Fontan surgery who have increased central venous pressure

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(CVP) and peripheral congestion findings (1). Recent studies have shown a significant increase in liver stiffness (LS) with liver elastography in adults and children with CHD, and the LS value was independently associated with CVP in these patients (4–9). Patients with and without ASD and other CHD were enrolled in these studies; one study included 18 patients with ASD and another one included 2 patients with ASD, but specific LS values were not reported for ASD (6, 9).

ASD physiopathology progresses as follows: *i*) An amount of increased blood in the left atrium (LA) passes through the RA; *ii*) RA pressure and volume increases; *iii*) RV and pulmonary artery volume and pressure increases; *iv*) the ratio of total pulmonary blood flow to total systemic blood flow (Qp:Qs) increases; *v*) after a period of time, there is an increase in pressure due to volume increase; *vi*) RV end-diastolic pressure, RA pressure and CVP increase; *vii*) liver has a fibrous-capsule that cannot expand adequately and LS increases due to congestion (Fig. 1). Based on the independent association between LS value and CVP in patients with congenital heart disease (4, 6, 7, 9), we thought that increased volume and pressure of RA and RV in patients with ASD could be determined objectively and noninvasively with LS obtained by liver elastography, without an invasive procedure. In patients with newly diagnosed ASD who require percutaneous or surgical closure of ASD, the evaluation of LS may be of additional benefit to other examinations prior to the procedure. Similar to previous studies, an increase in LS may be an objective finding of congestion and heart failure symptoms and signs in ASD patients. To the best our knowledge in the literature, there is no information about LS change or usage in patients with secundum ASD. The aim of our study was to investigate the change of LS values obtained by point shear-wave elastography (pSWE) in patients with ASD and the clinical utility of pSWE for this disease.

Main points

- Liver stiffness (LS) assessed by pSWE was significantly increased in ASD patients with closure indication and Eisenmenger syndrome, compared to patients without ASD closure indication.
- LS ≥7 kPa can determine an ASD size >15 mm with acceptable sensitivity and specificity.
- LS was comparable with tricuspid regurgitation pressure gradient in regards to Eisenmenger syndrome identification.
- ASD size was significantly associated with LS and independently predicted abnormal LS increase ≥7 kPa.
- LS assessment may be useful in the evaluation of hepatic congestion in cardiac diseases in the future, but multicentric studies involving more patients are needed.

Methods

Study population

This cross-sectional study included 21 patients with no indication for closure of ASD (Group I), 38 patients who underwent ASD closure (Group II), and 7 patients who had ASD with Eisenmenger syndrome (Group III). Patients in group I and II had secundum-type ASD with left-to-right (L-R) shunt. In Group I, RV volume load was not increased (Qp/Qs <1.5), ASD diameter was <10 mm and ASD-related symptoms and signs were not developed, and therefore these patients were not indicated for ASD closure. In Group II, RV volume load was increased (Qp/Qs >1.5), ASD diameter was >10 mm and ASD-related symptoms and signs were developed, and therefore these patients were indicated for ASD closure. Group III patients had very large secundum-type ASD (>30 mm) with no clear L-R passage; a right-to-left shunt was visible, RV volume load and pressure were significantly increased (at least one measurement yielding Qp/Qs <1.0), and ASD-related symptoms and signs were developed. Therefore, the closure of ASD was no longer deemed possible by the Cardiology and Cardiovascular Diseases Clinics Council. End-stage renal disease, other CHD, acute or chronic pulmonary embolism, acute or chronic liver diseases, alcohol consumption (>20 g/day), serious heart valve diseases except functional tricuspid regurgitation, thyroid diseases, cancer and/or pregnancy suspicion and patients unwilling to participate in the study were excluded. The study was conducted according to the recommendations of the Human Subjects Biomedical Research Helsinki Declaration, and the protocol was approved by the institutional ethics committee (decision/protocol number 2018/262). Patients were informed about the study and written consent forms were signed by all patients prior to inclusion in the study .

Detailed medical history was taken and physical examination was performed. Presence of dyspnea, orthopnea, cyanosis, pretibial edema, hepatomegaly and hepatojugular reflux were obtained. Age, gender, presence of diabetes mellitus, hypertension, active smoking, hyperlipidemia, and coronary artery disease were noted. Heart rate and blood pressure was obtained. Body mass index of all patients was measured. Blood urea nitrogen, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured using automated laboratory methods (Abbott Aeroset) and using appropriate commercial kits (Abbott).

Figure 1. Atrial septal defect (ASD) physiopathology. *i)* An amount of increased blood in the left atrium passes through the right atrium (RA); *ii)* RA pressure and volume increases; *iii)* RV and pulmonary artery volume and pressure increases; *iv)* the ratio of the blood amount to the pulmonary system to the systemic circulation (Qp:Qs) increases; *v)* after a period of time, there is an increase in pressure due to volume increase; *vi)* RV end-diastolic diameter, RA and central venous pressure increase; *vii)* liver has a rigid fibrous or non-elastic capsule that cannot expand adequately and tissue stiffness increases due to congestive hepatomegaly.

Liver ultrasonography

All of the patients who participated in the study underwent liver ultrasound (US) screening using a high-resolution US device (Philips EPIQ 7), with a 5–1 MHz high-resolution convex probe. A pSWE technique was used for LS measurements. The patients were in lateral decubitus position. Least possible compression was applied during the liver US assessment. Elastography was performed with breath hold to minimize

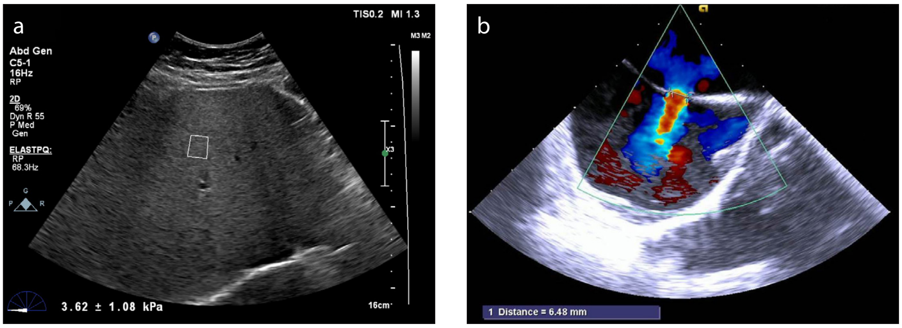

Figure 2. a, b. Small size ASD (<10 mm) with no indication for closure: **(a)**, the normal liver stiffness (LS) value obtained by point shear-wave elastography (pSWE) is 3.62±1.08 kPa; **(b)**, bicaval transesophageal echocardiography (TEE) image in 116 degrees in a patient with small ASD shows that ASD diameter is 6.48 mm and there is left-to-right (L-R) shunt.

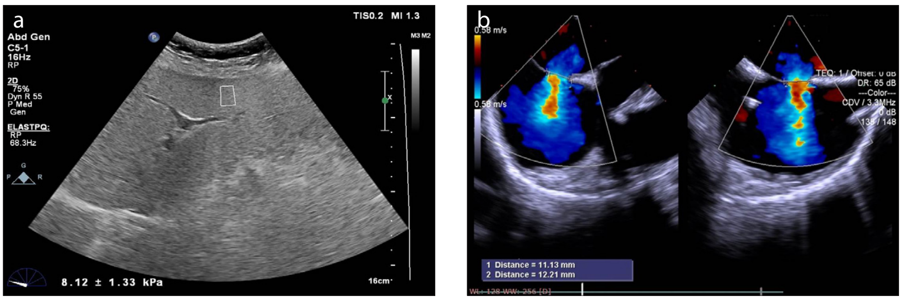

Figure 3. a, b. Medium ASD (10–30 mm) with indication for closure: **(a)**, the elevated LS value obtained by pSWE is 8.12±1.33 kPa; **(b)**, bicaval TEE image in 101 degrees in a patient with medium-size ASD and ASD closure indication shows that ASD diameter is 12.2 mm and there is L-R shunt.

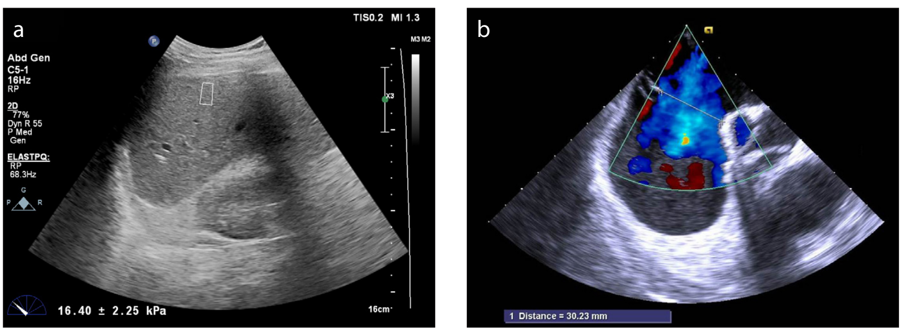

Figure 4. a, b. Large size ASD (>30 mm) and Eisenmenger syndrome: **(a)**, the highly elevated LS value obtained by pSWE is 16.40±2.25 kPa; **(b)**, aortic short axis image of a patient with Eisenmenger syndrome and no ASD closure indication and TEE image at 17 degrees show that ASD diameter is 30.23 mm and there is no L-R shunt.

motion artifacts. First, regular US images were obtained, then the radiologist determined the target area, and the region of interest (ROI) was positioned on the target before measurements (Figs. 2a, 3a, 4a). The radiologist used gray-scale imaging to find an appropriate measurement area, and at least 1 cm depth of the liver capsule was measured. The ROI was placed perpendicular to the liver capsule, perpendicular to a line parenchyma area containing no bile ducts and vascular structures or space occupying lesions. In our study, the maximum ROI target distance was 8 cm, with a constant ROI box dimension of 0.5×1 cm. To avoid mechanical pressure on the liver parenchyma, least possible compression was maintained during the imaging. In each participant, 10 valid measurements from different segments of hepatic parenchymal were obtained and their average was calculated. If the LS measurement was not reliable or there was a patient or operator condition that affected the measurement value, the measurement was accepted as 0.00 kPa and not included in the mean measurement, and another reliable measurement was obtained. Subjects were evaluated by two experienced radiology specialists for regular and pSWE examinations. Specialists had more than 5–6 years of experience and did at least 400–500 pSWE procedures in a year. Whole procedure time was 20–25 minutes. Using the cutoff values reported in two important recent studies, mild increased LS value threshold for the presence of heart failure was adopted as ≥7 kPa (10–13).

Echocardiographic evaluation

Two dimensional and Doppler echocardiography were done with EPIQ 7 (Philips Healthcare). All of the patients were monitored and left-sided; a standard long and parasternal short axis was obtained, as well as apical five, four and two chambers and at least three consecutive cycles (14). All echocardiography procedures were performed by three echocardiographers, who were experienced in TEE. Echocardiographers were selected from physicians who had at least 100 TEE procedures per year and worked in TEE laboratory for at least 5 years. M-mode examination in parasternal long-axis showed left ventricular (LV) diastolic dimension, LV systolic dimension and LA diastolic dimension. Measurement of RA diastolic diameter was performed in the apical 4-chamber position from edge of tricuspid annulus to lateral to septal area. The LV ejection fraction was calculated from apical four and two chambers by the modified Simpson method (14). Tricuspid regurgitation pressure gradient (TRPG) was calculated by the Bernoulli equation over the peak flow rate of tricuspid regurgitation. Tricuspid annular plane systolic excursion (TAPSE) and RV diastolic diameter was measured from a RV focused apical 4-chamber view (15). Finally, Qp/Qs ratio was measured by using two dimensional and Doppler echocardiography. The Qp/Qs ratio vas calculated as the mean of at least six measurements obtained by three echocardiographers, and the mean of at least 12 measurements in patients with atrial fibrillation and/or atrial flutter.

TEE procedure was applied after 8 hours of fasting and the patient was deeply sedated by an anesthesiologist. TEE probe was a multiplane transesophageal transducer. Patients were positioned to left lateral decubitis position. Probe was engaged to the esophageal and gastric entry level. The echocardiographers were blinded to patient details. TEE procedure was well-tolerated in all patients and there was no complication. During the procedure, inter-atrial septum was evaluated in the middle esophageal space with four-chamber

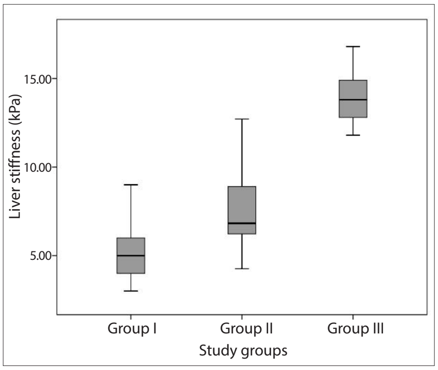

Figure 5. The Boxplot graphic shows increasing liver stiffness values from Group I to Group III. Group I, patients with no indication for closure of ASD; Group II, patients with indication for closure of ASD; and Group III, ASD with Eisenmenger syndrome.

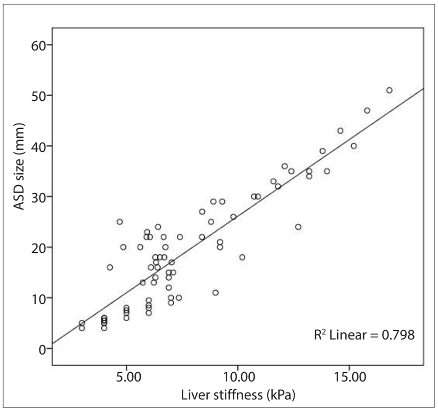

Figure 6. Scatter plot diagram of the relationship of ASD size with liver stiffness.

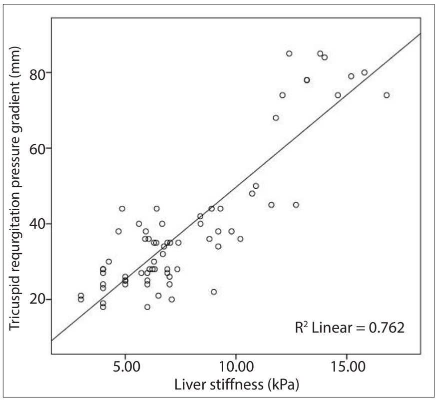

Figure 7. Scatter plot diagram of the relationship of tricuspid regurgitation pressure gradient with liver stiffness.

image at 0 degrees, aortic short axis image at 45 degrees and bicaval image at 120 degrees. Presence of L-R shunt was also evaluated during color Doppler (Figs. 2b, 3b, 4b).

Statistical analysis

All analyses were conducted using SPSS 22.0 (SPSS for Windows 17.0). The Kolmogorov-Smirnov test was used to determine whether the continuous variables were normally distributed. The data are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables and as percentage and number for categorical variables. The normally distributed continuous variables were compared using one-way ANOVA, whereas the Kruskal Wallis test was used for samples without normal distribution. For normally distributed data, Scheffe and Games-Howell tests were used for multiple comparisons of groups with respect to homogeneity of variances. Evaluation of non-normally distributed data, Bonferroni adjusted Mann Whitney U test was used for multiple comparisons of groups. The categorical variables were compared by the chi-square (χ^2) test. The kappa coefficient was used to examine the inter- and intraobserver variability of echocardiographic parameters, and US measurements. Parameters associated with LS were determined using univariate Spearman's or Pearson's correlation analyses. In multivariate linear regression analysis, the parameters that have the closest association with the LS were identified. In univariate analyses, multivariate logistic regression analysis was performed to determine the independent markers among patients with LS ≥7 kPa. A receiver operating curve (ROC) analysis was performed for parameters that independently determined Eisenmenger syndrome and LS ≥7 kPa. We established the points with the minimum difference between sensitivity and specificity as the optimal limit value in the ROC analysis (16).

Results

Echocardiographic parameters and liver elastography measurement were successfully obtained. Cohen kappa values that evaluate the interobserver variability were over 90% for all echocardiographic and liver US measurements (P < 0.001 for all comparisons). The study population was divided into three groups (Group I, II, III) according to the previously stated ASD type and two groups according to LS (≥7 kPa to <7 kPa), and all study data were evaluated separately. LS increased from Group I to Group III with significant difference between the three groups (Fig. 5).

Presence of dyspnea, orthopnea, cyanosis, pretibial edema, hepatomegaly and hepatojugular reflux were higher in Group III. Demographic, clinical and laboratory findings of the study groups were compared. When the demographic and clinical data of all groups were evaluated, all demographic and clinical parameters except AST and ALT were found to be similar between the two groups (Table 1). Serum AST level was higher in Group III than in Group I and Group II, whereas ALT level was higher in Group III than in Group I (Table 1).

LA and RA diastolic dimensions, RV dimension, TRPG, ASD size, liver size, and LS levels increased and LV ejection fraction, TAPSE levels decreased from Group I to Group III (Table 1). LA and RA diastolic dimensions, RV dimension, TRPG, ASD size, liver size, LS, LV ejection fraction, TAPSE levels were statistically different between all three study groups (Table 2). Qp/Qs ratio was higher in Group II compared with Group I and Group III (Table 2).

Correlation analysis was performed between LS and other demographic, clinical, laboratory and echocardiographic parameters (Table 3). Linear regression analysis was performed for the parameters associated with LS significantly in the univariate analysis. As a result of this analysis, ASD size and TRPG, were found to be related to LS (Table 3). The closest relationship between ASD size, TRPG and LS was shown in Figs. 6 and 7.

In the ROC analysis of the LS for the prediction of the patients with Eisenmenger syndrome, the area under the ROC curve (AUC) for the LS value was 0.995 (0.984–1.000) and P < 0.001. LS cutoff set at 10 kPa, predicted the Eisenmenger syndrome with 91.5% specificity and 98.5% sensitivity. The AUC for TRPG was 0.990 (95% confidence interval [CI], 0.978–1.000) and P < 0.001. At TRPG cutoff value of 60 mmHg, Eisenmenger syndrome could be predicted with 98% specificity and 99% sensitivity.

Increased LS was taken as ≥7 kPa. A total of 31 patients (47%) had LS ≥7 kPa and the frequency of having an LS ≥7 kPA increased from Group I to Group III (Table 2). In univariate analyzes, the parameters that differ in ASD patients with LS ≥7 kPa compared to patients with LS <7 kPa are shown in Table 4. Multivariate logistic regression analysis was performed with demographic, clinical, laboratory and echocardiographic parameters associated with LS ≥7 kPa in univariate analysis. In these parameters, only ASD size was independently associated with patients with LS ≥7 kPa (Table 5). In the ROC analysis of the ASD size for the detection of the patients with LS ≥7 kPa, AUC for the ASD size was 0.843

Table 1. Study findings according to patients with and without ASD							
Variable	Group I n=21	Group II n=38	Group III n=7	*P*	*P* (Group I vs. II)	*P* (Group I vs. III)	*P* (Group II vs. III)
Age (year)	38.7±7.8	37.6±10.1	38.5±15.3	0.920	–	–	–
Sex (male/female)	14/7	21/17	4/3	0.293	–	–	–
Dyspnea, n (%)	0 (0)	25 (69)	7 (100)	<0.001	<0.001	<0.001	0.048
Orthopnea, n (%)	1 (5)	10 (26)	6 (85)	<0.001	0.014	<0.001	<0.001
Cyanosis, n (%)	0 (0)	0 (0)	6 (85)	<0.001	0.644	<0.001	<0.001
Pretibial edema, n (%)	0 (0)	10 (26)	5 (71)	<0.001	0.010	0.003	0.041
Hepatomegaly, n (%)	0 (0)	14 (37)	6 (85)	<0.001	0.003	<0.001	0.008
Hepatojugular reflux, n (%)	0 (0)	6 (16)	5 (71)	<0.001	0.042	<0.001	0.003
Hypertension, n (%)	5 (24)	9 (24)	9 (24)	1.000	–	–	–
Diabetes mellitus, n (%)	1 (5)	1 (3)	1 (3)	0.589	–	–	–
Current smoker, n (%)	10 (48)	12 (32)	12 (32)	0.174	–	–	–
Hyperlipidemia, n (%)	1 (5)	4 (11)	4 (11)	0.410	–	–	–
CAD, n (%)	0 (0)	1 (3)	1 (3)	0.644	–	–	–
SBP (mmHg)	129±17	127±15	115±10	0.205	–	–	–
DBP (mmHg)	81±13	82±12	80±12	0.289	–	–	–
Pulse (bpm)	78.1±7.1	76.2±5.7	79.1±12	0.188	–	–	–
Body mass index (kg/m^2)	26.8±5.6	25.9±2.6	23.8±3.0	0.120	–	–	–
Total cholesterol (mg/dL)	176±28	182±39	162±32	0.253	–	–	–
LDL cholesterol (mg/dL)	107±26	120±29	98±27	0.083	–	–	–
HDL cholesterol (mg/dL)	40±8.9	44±12	47±9.1	0.155	–	–	–
Triglycerides (mg/dL)	161 (158)	95 (200)	122 (240)	0.076	–	–	–
AST (u/L)	21 (30)	22 (32)	28 (43)	0.002	0.925	0.003	0.013
ALT (u/L)	16 (30)	20 (33)	23 (40)	0.029	0.823	0.032	0.702
BUN (mg/dL)	28.5±8.8	29.1±7.9	31.1±10.1	0.800	–	–	–
Creatinine (mg/dL)	0.74±0.10	0.70±0.16	0.72±0.15	0.372	–	–	–

The values are presented as mean±standard deviation, median (interquartile range) or n (%). Group I, patients with no indication for closure of ASD; Group II, patients with indication for closure of ASD; Group III, ASD with Eisenmenger syndrome.
CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogren.

(95% CI, 0.754–0.932; $P < 0.001$). When ASD size was taken as 15 mm, LS ≥7 kPa could be predicted with 82.4% sensitivity and 75.2% specificity. Due to the close relationship between LS and TRPG, when the ROC analysis for TRPG was used to identify patients with ≥7 kPa, AUC for the TRPG was 0.808 (95% CI, 0.705–0.911; $P < 0.001$). When TRPG was taken as 30 mmHg, LS ≥7 kPa could be predicted with 79.4% sensitivity and 70.4% specificity.

Discussion

The main finding of our study was that the LS value determined by pSWE was significantly increased in ASD patients with closure indication and in patients with Eisenmenger syndrome. In our study, LS was found to be significantly higher in patients with Eisenmenger syndrome than in patients with ASD alone. LS value was able to detect patients with Eisenmenger syndrome with high specificity and sensitivity when the cutoff value was >10 kPa. Another important finding in our study is that the increased LS value in patients with ASD was closely related to ASD size and TGRP, which has been shown to increase in these patients in later years and show the hemodynamic effect of ASD. In addition, ASD was independently associated with LS ≥7 kPa and determined patients with LV ≥7 kPa with acceptable sensitivity and specificity. For patients with ASD >15 mm, LS value can be used as a new follow-up parameter for monitoring.

Patients with ASD usually do not have symptoms in childhood, but if not treated, can cause symptoms and signs of RV failure, decreased functional capacity, dyspnea, palpitation, paradoxical embolism, and congestion in the fourth decade of life (1, 17, 18). Although patients with ASD may have hepatomegaly as in other patients with heart failure, cardiac cirrhosis has been rarely reported in patients with pulmonary hypertension and Eisenmenger syndrome in advanced period (17–19). L-R shunt volume in patients with ASD depends on RV/LV compliance, defect size, and LA/RA pressure. In simple ASD, RV compliance is higher than LV compliance, so that the patient has L-R shunt and when the ASD defect is ≥10 mm, RV volume load and pulmonary artery over-circulation occur (1). Recent studies have shown that congestion parameters

Table 2. Liver ultrasound and echocardiographic findings according to study groups

Variable	Group I n=21	Group II n=38	Group III n=7	*P*	*P* (Group I vs. II)	*P* (Group I vs. III)	*P* (Group II vs. III)
LVd dimension (mm)	46.1±3.7	46.8±3.1	47.8±5.6	0.388	–	–	–
LVs dimension (mm)	27.9±2.7	29.5±2.9	31.1±5.7	0.052	–	–	–
LVEF (%)	62.3±3.5	58.2±3.8	49.8±3.7	<0.001	<0.001	<0.001	<0.001
LAd dimension (mm)	35.9±4.1	40.6±3.1	44.2±5.1	<0.001	<0.001	<0.001	<0.001
RAd dimension (mm)	35.8±4.0	41.4±4.2	46.2±4.9	<0.001	<0.001	<0.001	<0.001
RVd dimension (mm)	30.9±2.5	40.3±2.9	46.3±2.6	<0.001	<0.001	<0.001	<0.001
TAPSE (mm)	21.1±1.7	20.2±1.6	17.2±1.1	<0.001	0.023	<0.001	<0.001
TRPG (mmHg)	23.9±3.2	35.9±7.0	78.1±9.4	<0.001	<0.001	<0.001	<0.001
Qp/Qs ratio	1.11±0.15	2.20±0.55	0.92±0.81	<0.001	<0.001	0.815	<0.001
ASD size (mm)	7.21±2.1	20.2±7.4	36.8±5.9	<0.001	<0.001	<0.001	<0.001
Liver size (mm)	13.1±1.6	14.1±1.4	15.7±2.1	<0.001	0.045	<0.001	0.001
Liver stiffness (kPa)	5.16±1.55	7.48±1.99	13.9±2.58	<0.001	<0.001	<0.001	<0.001
Liver stiffness ≥7 kPa, n (%)	4 (19)	20 (53)	7 (100)	< 0.001	0.018	<0.001	0.006

The values are presented as mean±standard deviation or n (%).
Group I, patients with no indication for closure of ASD; Group II, patients with indication for closure of ASD; Group III, ASD with Eisenmenger syndrome.
LVd, left ventricular diastolic; LVs, left ventricular systolic; LVEF, left ventricular ejection fraction; LAd, left atrial diastolic; RAd, right atrial diastolic; RVd, right ventricular diastolic; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient; Qp/Qs, pulmonary to systemic flow ratio; ASD, atrial septal defect.

Table 3. The parameters associated with liver stiffness

	Univariate analysis		Multivariate analysis		
	P	r	*P*	β	95% CI
AST (u/L)	0.001	0.377	0.052	0.111	0.016–0.083
LVd dimension (mm)	0.004	0.336	0.222	0.071	0.012–0.132
LVs dimension (mm)	0.046	0.230	0.139	0.091	0.042–0.151
LVEF (%)	<0.001	-0.741	0.158	-0.122	-0.158–0.104
RVd dimension (mm)	<0.001	0.781	0.054	0.102	0.046–0.162
TAPSE (mm)	<0.001	-0.786	0.074	-0.156	-0.626–0.004
TRPG (mmHg)	<0.001	0.873	0.003	0.361	0.023–0.107
ASD size (mm)	<0.001	0.601	<0.001	0.569	0.096–0.314

CI, confidence interval; AST, aspartate aminotransferase; LVd, left ventricular diastolic; LVs, left ventricular systolic; LVEF, left ventricular ejection fraction; RVd, right ventricular diastolic; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient; ASD, atrial septal defect.
R^2Adjusted=0.823 and *P* < 0.001 in multivariate analyses.

such as pretibial edema, hepatomegaly, hepato-jugular reflux and increased central venous pressure are closely associated with LS in acute and chronic heart failure patients; it was also shown that patients with an increased LS value obtained in these patient groups had a worse prognosis (11, 20). In our study, LS increase was also associated with higher frequency of dyspnea, orthopnea, cyanosis, pretibial edema, hepatomegaly, and hepatojugular reflux which increased from Group I to Group III. This supported the association of increased congestion or volume-related symptoms and physical examination findings with the increase in the LS value obtained by liver elastography, as in previous studies (11, 20). In addition, as a result of the data obtained from the previous studies, a LS limit value of 7 kPa was accepted to indicate increased stiffness and the patients were grouped as ≥7 kPa and <7 kPa. Consistent with other studies in the literature, the frequency of dyspnea, orthopnea, cyanosis, pretibial edema, hepatomegaly and hepatojugular reflux was found to be higher in patients with LS ≥7 kPa. In patients with ASD and other CHD, especially in patients with Eisenmenger syndrome, deterioration of liver function tests has been reported due to increased liver congestion (1, 21). Therefore, it is recommended to evaluate liver function tests in these patients. In our study, AST and ALT values increased as clinical significance of ASD increased. In addition, serum AST levels were significantly higher in patients with LS ≥7 kPa. In a recent study similar to ours, the AST level was significantly higher in patients with LS ≥7 kPa, but the ALT level was not significantly higher (11). However, another study found no correlation between LS increase, AST and ALT (20). In our study, from echocardiographic parameters, RV diastolic diameter TRPG, Qp/Qs and ASD size were higher and TAPSE was lower in ASD patients with LS ≥7 kPa. Among these parameters, only ASD was independently associated with LS ≥7 kPa. In addition, there was a very close and significant relationship between LS and ASD size and TRPG. This supported our opinion that the relationship between LS and ASD is very important.

There are no clear data and recommendations for LS measurement and clinical follow-up in the diagnosis and follow-up of ASD in either European and American guidelines on CHD (1, 21, 22). Liver US is not a routine follow-up procedure for patients with ASD. The latest CHD guideline does not recommend liver US (1, 21). Only in patients with ASD-associated liver diseases, the liver US can be performed for evaluating the Eisenmenger syndrome or RV failure (1, 21). LS measurement is mainly performed

Table 4. Study findings according to patients with LS <7 kPa and ≥7 kPa

Variable	LS <7 kPa n=35	LS ≥7 kPa n=31	*P*
Dyspnea, n (%)	11 (10)	25 (32)	<0.001
Orthopnea, n (%)	3 (5)	17 (16)	<0.001
Cyanosis, n (%)	0 (0)	7 (0)	<0.001
Pretibial edema, n (%)	4 (0)	12 (16)	<0.001
Hepatomegaly, n (%)	3 (0)	17 (13)	0.003
Hepatojugular reflux, n (%)	2 (0)	12 (11)	0.002
AST (u/L)	22 (31)	23 (47)	0.030
LVEF (%)	60.4±3.2	55.7±5.3	<0.001
RV diastolic dimension (mm)	35.3±4.5	41.8±5.6	<0.001
TAPSE (mm)	21.0±0.9	18.9±2.1	<0.001
TRPG (mmHg)	29.1±7.2	49.4±21.5	<0.001
Qp/Qs ratio	1.49±0.49	1.84±0.87	0.043
ASD size (mm)	12.9±6.9	26.4±11.2	<0.001

The values are presented as mean±standard deviation or n (%).
LS, liver stiffness; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient; Qp/Qs, pulmonary to systemic flow ratio; ASD, atrial septal defect.

Table 5. Independent parameters for occurrence of LS ≥7 kPa

	OR	95% CI	*P*
Atrial septal defect size (mm)	1.175	1.088–1.268	<0.001

R^2Adjusted=0.466 and $P < 0.001$ in multivariate analyses.
LS, liver stiffness; OR, odds ratio; CI, confidence interval.

in hepatology clinics (23, 24). Studies have also reported increased LS levels in CHD (4–9). Considering the pathophysiology of ASD and increased right heart pressures, right heart volume and pressure should be closely related to LS. With the development of US devices and increased accessibility of liver elastography examination, the LS measurement has been routinely applicable for all patients with CHD, especially ASD. Pretibial edema, hepatomegaly, and increased CVP are subjective parameters of congestion in patients with ASD who have right heart failure; these parameters vary from person to person and over time. For this reason, the LS value, obtained as the mean of at least 10 different liver elastography measurements, can be a new follow-up parameter to indicate the hepatic congestion state.

Although no study evaluated LS in patients with ASD in particular, the increase in RV volume and pressure due to CHD was shown to result in increased LS due to liver congestion (4–9). The first study to evaluate CHD by LS was performed using transient elastography (TE) method in 96 patients in 2015, and 18 ASD patients were included (6). In this study by Jalal et al. (6), the LS assessment proved to be a rapid and acceptable method for the detection of CVP in these patients. They reported that when the LS limit value was taken as 8.8 kPa, CVP >10 mmHg was determined with 96.3% specificity and 91.2% sensitivity (6). In two other studies, it was shown that the increase in CVP in two patient groups with Fontan operation and cavopulmonary window procedures was accompanied by an increase in LS (4, 7). A case report published in 2017 described a patient with constrictive pericarditis, whose LS was initially measured as 21 kPa, decreased to 8.4 kPa postoperatively, increased to 11.4 kPa with development of pulmonary stenosis, decreased to 6.8 kPa with pulmonary valvuloplasty, and increased to 12 kPa with recurrence of pulmonary stenosis (5). This case illustrates that LS can be directly affected by RV-associated diseases and can be used as an easy and non-invasive follow-up parameter for these patients. In a recent study, 10 adult patients with Eisenmenger syndrome underwent LS and fibrosis evaluation with liver elastography (8). In a study by Mebus et al. (8), the number of patients with <7.2 kPa, 7.2–12.5 kPa, 12.5–17.6 kPa and >17.6 kPa was 1, 2, 3 and 4, respectively. In our study, all patients with Eisenmenger syndrome had LS >10 kPa; patients with Eisenmenger syndrome could be determined with acceptable sensitivity and specificity when LS >10 kPa was taken as cutoff. In a recent study by Terashi et al. (9), the relationship between LS value and CVP value was evaluated in patients with CHD who had no liver disease, with only 2 ASD patients included. Similar to other studies, they reported a very close relationship between LS and CVP (9). In our study, when the cutoff value for TRPG was taken as ≥30 mmHg, patients with LS values ≥7 kPa could be determined with acceptable sensitivity and specificity. The relationship of 30 mmHg TRPG, which is an echocardiographically abnormal cutoff value, with 7 kPa LS, which was accepted as an increased LS cutoff value in our study, has once again demonstrated the utility of LS evaluation in assessing increased right heart pressures. This finding supports the studies in the literature showing that there is a relationship between CVP value, right heart pressure and increased LS value. Previous studies demonstrated a close relationship between LS and RV pressure, volume increase and CVP (4–7, 9). In our study, although the relationship between invasively measured RV or CVP and LS was not evaluated, there was a close and independent relationship between LS and TRPG, which was detected objectively in echocardiography. Patients with ASD closure indication had higher LS values than patients without ASD closure indication. In the ASD cases with Eisenmenger syndrome, higher LS values were obtained than the other ASD groups. These findings suggest that the LS obtained by liver elastography can be a new follow-up parameter in addition to routine echocardiography in patients with ASD.

Considering the data obtained from ASD patients in our study and other studies related to clinical and prognostic use of LS increase in acute heart failure and chronic heart failure patients (10, 11, 20), the novel and widely available LS evaluation obtained by the liver elastography method may be an important and objective indicator of increased liver congestion in cardiac diseases.

Our study had some important limitations. Patients with hepatic and renal failure were excluded from this study. There are 4 types of ASD and the most common type is secundum type ASD which was included in our study; therefore, studies including other types of ASD may be required. Previous studies have shown changes in LS value after treatment of CHD (4, 7); however, patients were not followed up in our study. Another important limitation in our study is that the relationship between CVP and LS was not evaluated because CVP measurement was not performed in all patients, since no invasive procedure was performed in patients without ASD closure. However, we found that there is a close relationship between LS and another pressure indicator, TRPG. Since only patients with ASD were included in the study and the ElastPQ technique was used for liver elastography, limit values could not be compared with other studies. There are many methods in the literature for evaluating liver elastography. We performed this study with pSWE, a new high-resolution technique. This exam may not be available at all centers. For this reason, it is necessary for researchers to know that our limit and average values are determined by this device.

In conclusion, our study has important implications for ASD as LS values were found to be increased significantly in all patients with ASD for the first time and a very close positive relationship was demonstrated between ASD size and LS. In particular, the association of LS ≥7 kPa with ASD size >15 mm can be very useful for clinical practice. LS value was significantly higher in patients with Eisenmenger syndrome and LS value >10 kPa may be used to determine these patients. There is a close relationship between increased TRPG and LS in patients with ASD, which is an indicator of increased pressure on the liver with RV and PAP-enhancing effect of increased volume in these patients. The most important indication for closure of defect in patients with ASD is increased volume and pressure in RV. For this reason, LS measurement is thought to be a cheap, simple and noninvasive follow-up parameter that can be used for the routine follow-up of patients with ASD. However, the results obtained in our study should be strengthened by new studies involving multicentric patients, and larger and different patient groups.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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