ORIGINAL ARTICLE

Liver stiffness value obtained with ElastPQ ultrasound increases with NYHA class in chronic heart failure patients and reduced ejection fraction

Düşük ejeksiyon fraksiyonu olan kronik kalp yetersizliği hastalarında ElastPQ ultrasonografi ile elde edilen karaciğer sertlik değeri NYHA evresi ile artar

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ABSTRACT

Objective: Liver stiffness (LS) values are known to be associated with increased right ventricle (RV) pressure in patients with heart failure (HF). The aim of this study was to determine the changes in LS in patients of different New York Heart Association (NYHA) classes and the parameters related to increased LS in HF patients with reduced ejection fraction (HFrEF).

Methods: A total of 181 patients with HFrEF were included in the study. Routine anamnesis, physical examination, laboratory examinations and echocardiography were performed. The LS measurement was performed using the ElastPQ technique. The patients were grouped by NYHA class I-IV.

Results: The LS values were significantly different between NYHA class groups, increasing significantly from NYHA class I to IV. The number of patients with LS >7 kPa or >10.6 kPa was significantly greater among the class III-IV patients. The RV myocardial performance index, tricuspid regurgitation pressure gradient, N-terminal pro b-type natriuretic peptide, and aspartate aminotransferase levels were found to be independently associated with LS. It was also observed that LS independently determined III-IV classification and that an increase of 1 kPa increased the risk of being class III-IV by 94.4%. Receiver operating characteristic analysis with a cut-off value of 7 kPa for LS identified patients with class III-IV disease with 82.8% sensitivity and 81.8% specificity.

Conclusion: In HFrEF, the LS value increased with NYHA class and independently determined patients with class III-IV disease. A higher LS value independently determined increased RV pressure and systolic functions.

ÖZET

Amaç: Karaciğer sertliği (LS) değerlerinin kalp yetersizliği (HF) hastalarında artmış sağ kalp basıncı ile ilişkili olduğu bilinmektedir. Çalışmamızda düşük ejeksiyon fraksiyonu HF (HFrEF) hastalarında NYHA (New York Heart Association) evresi ile LS değişimini ve artmış LS ile ilişkili parametrelerin tespit edilmesi amaçlandı.

Yöntemler: Bu çalışmaya HFrEF olan 181 hasta alındı. Rutine anamnez, fizik muayene ekokardiyografi ve laboratuvar incelemeleri yapıldı. Ek olarak ElastPQ tekniği ile LS ölçümü yapıldı. Hastalar NYHA evresine ayrılarak gruplandırıldı.

Bulgular: Tüm NYHA evreleri arasında LS değeri olarak anlamlı olarak farklıydı. LS değeri NYHA evre I'den evre IV'e doğru anlamlı olarak arttığı ve en yüksek LS değerinin evre IV hastalarında olduğu bulundu. Benzer şekilde LS >7 kPa ve >10.6 kPa olan hasta sayısı evre III-IV hastalarda anlamlı olarak yüksekti. Sağ ventrikül miyokart performans indeks, triküspit yetersizliği basınç gradiyenti, NT-proBNP ve AST düzeyinin bağımsız olarak LS ile ilişkili olduğu bulundu. LS değerinin evre III-IV varlığını bağımsız olarak belirlediği ve her 1 kPa artışı kişinin evre III-IV olma riskini %94.4 artırdığı tespit edildi. ROC analizinde LS için 7 kPa sınır değer olarak alındığında %82.8 duyarlılık ve %81.8 özgüllük ile evre III-IV olan hastaları belirlediği saptandı.

Sonuç: HFrEF de artan NYHA evresi ile LS değeri artar ve evre III-IV hastaları bağımsız olarak belirler. Artan LS değeri ile artmış RV basıncı ve sistolik fonksiyonlarını bağımsız olarak belirler.

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Heart failure with reduced ejection fraction (HFrEF) is a disease with a poor prognosis. It is defined as having a left ventricular (LV) ejection fraction (EF) of <40% in the latest heart failure (HF) guideline.[1] Anamnesis, physical examination, posteroanterior chest X-ray, electrocardiography, echocardiography, and biochemical parameters, including natriuretic peptide (NT-proBNP), are used in the follow-up and treatment of patients with HF.[1] All of the congestive findings that occur in patients with HF are subjective; an objective parameter is needed to determine congestion. Liver function test measurements of bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT) are recommended as routine examinations.

In patients with HF, liver disease occurs in the advanced classes due to liver congestion and is known as cardiac hepatopathy.[2] This condition is associated with increased central venous pressure (CVP) and worsening in liver function tests, and is an indicator of poor prognosis.[3–7] The causes of congestive cardiac hepatopathy are isolated right ventricular (RV) failure, biventricular failure, pulmonary arterial hypertension (HT), severe tricuspid regurgitation, constrictive pericarditis, and congestive HF.[8] In congestive cardiac hepatopathy patients, CVP, filling pressure, and RV diastolic pressure are increased.[9]

The liver is surrounded by a membrane and increased liver congestion leads to an increase in LS. Liver elastography (LE) is a newly developed ultrasound (US) technique that can quantitatively and noninvasively measure liver tissue stiffness and the development of fibrosis. Congestion in the liver due to HF causes hepatomegaly and right upper quadrant pain. This congestion occurs due to the fact that the liver, which has a hard capsule, is not elastic, and increases the stiffness of the tissue.[10] Therefore, a liver stiffness (LS) value obtained with LE in HF patients can be used to assess liver congestion and increased right atrium (RA) pressure.[11] Considering this physiopathology, especially in studies conducted in the last year, the LS measurements obtained with LE have been shown to be associated with RV pressure, poor prognosis, and decreased functional capacity in different HF etiologies.[10–14] An LS value can be obtained for almost all patients and provide a more objective measurement with the recently developed acoustic radiation force impulse or ElastPQ (Philips Healthcare, Inc., Andover, MA, USA) techniques.[15,16]

One of the most important goals in the treatment of HF is the correction of RV and LV systolic functions and functional capacity. These 2 parameters are the most important prognostic indicators for HF. The relevance of LS to these parameters has been assessed in different groups of patients in various studies.[10–14,17,18] However, changes in the LS value in HFrEF in each New York Heart Association (NYHA) class, and the clinical and laboratory HF parameters associated with LS are still unclear. It was hypothesized that this increased pressure physiopathology due to increased volume and increased LS value may be closely related to NYHA class and LV and RV functions in HFrEF patients.

The objective of this research was to determine the LS change according to NYHA class and the LS-related parameters observed in HFrEF patients.

Abbreviations:

AF	*Atrial fibrillation*
ALT	*Alanine aminotransferase*
AST	*Aspartate aminotransferase*
CI	*Confidence interval*
CVP	*Central venous pressure*
EF	*Ejection fraction*
ET	*Ejection time*
GGT	*Gamma-glutamyl transpeptidase*
HF	*Heart failure*
HFrEF	*HF with reduced ejection fraction*
HT	*Hypertension*
ICT	*Isovolumetric contraction time*
IRT	*Isovolumetric relaxation time*
IVC	*Inferior vena cava*
LAd	*Left atrial diastolic*
LE	*Liver elastography*
LF	*Liver failure*
LS	*Liver stiffness*
LSm	*Liver stiffness measurement*
LV	*Left ventricle*
LVd	*LV diastolic*
LVEF	*LV ejection fraction*
LVs	*LV systolic*
MPI	*Myocardial performance index*
MRI	*Magnetic resonance imaging*
NT-proBNP	*Natriuretic peptide*
NYHA	*New York Heart Association*
OR	*Odds ratio*
RA	*Right atrium*
RAP	*Right atrial pressure*
ROI	*Range of imaging*
RV	*Right ventricle*
SWE	*Shear wave elastography*
TAPSE	*Tricuspid annular plane systolic excursion*
TRPG	*Tricuspid regurgitation pressure gradient*
US	*Ultrasound*

METHODS

Study population

This study included 181 patients who were referred to the cardiology clinic (111 males, 70 females; mean age: 64.3±9.1 years) with HFrEF (EF ≤40%) and receiving medical treatment according to HF stage. All of the patients included in the study had chronic HF.

NYHA classification was performed by 2 cardiologists before the patients were included in the study. Another cardiologist's opinion was obtained when necessary to confirm categorization. The patients were divided into 4 groups according to NYHA class I-IV. Patients with known acute or chronic hepatic disease, severe renal failure (estimated glomerular filtration rate [eGFR] <0 mL/kg/1.73 m^2), presence of hepatitis B or C, regular alcohol use (>20 g/day) or alcohol addiction, severe valvular heart disease, portal HT, inflammatory disease, hematological disease, active thyroid disease, cancer, and/or suspected pregnancy, and patients who declined to participate were excluded. The study was conducted according to the recommendations of the Declaration of Helsinki regarding biomedical research involving human subjects and the protocol was approved by the institutional ethics committee (Approval date: 28-Feb-2018, Approval number: 12-171). The study was explained to the patients in detail and written consent was provided by the participants. A detailed anamnesis was obtained from all of the patients and a detailed physical examination was performed. Subsequently, the baseline characteristics of all of the groups were recorded: age, gender, active smoking, and the presence of ischemic etiology for HF, HT, diabetes mellitus, atrial fibrillation (AF), or hyperlipidemia. The patients' pulse rate, systolic blood pressure, and diastolic blood pressure were recorded. Body mass index was calculated by measuring weight and height. The eGFR was calculated using the Modification of Diet in Renal Disease Study Group formula 3: eGFR (mL/min/1.73 m^2) = 186 × (serum creatinine) – 1.154 × (age) – 0.203 (0.742 for female patients).[19]

Echocardiographic evaluation

Echocardiography examinations were performed using the EPIQ 7 device (Philips Healthcare, Inc., Andover MA, USA). Images were taken according to the guidelines of the American Echocardiography Society. Standard parasternal long and short axis view images were obtained, as well as in the apical 5^{th}, 4^{th}, and 2^{nd} space windows for at least 3 consecutive cycles while the patient was in the left lateral decubitus position.[20] Parasternal long-axis M-mode examination revealed LV diastolic and systolic dimensions (LVd and LVs) and left atrial diastolic (LAd) dimensions. The LVEF was calculated using the modified Simpson method from the apical 4^{th} and 2^{nd} space windows.[21] Tricuspid regurgitation pressure gradient (TRPG) was calculated using the Bernoulli equation over the peak flow rate of tricuspid regurgitation. RV diastolic diameter and tricuspid annular plane systolic excursion (TAPSE) were measured from a RV focused apical 4-chamber view. RV isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), and ejection time (ET) were measured 5 times with pulse wave Doppler to obtain the RV-myocardial performance index (MPI) value. RV-MPI was calculated with the formula of (ICT + IRT) / ET after the mean values of 5 measurements were obtained.[22]

Biochemical parameters

Blood samples were taken from an antecubital vein after the patients had rested for 20 minutes in the supine position. Blood samples were collected in tubes containing ethylenediaminetetraacetic acid. A complete blood count was performed. The samples were spun at 3000 rpm for 10 minutes at 0°C. Upon study inclusion, blood urea nitrogen, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured using standard automated laboratory methods (Aeroset; Abbott Laboratories, Lake Bluff, IL, USA) with the appropriate commercial kits. Serum albumin, AST, ALT, GGT, direct bilirubin, uric acid, high-sensitivity C-reactive protein, and NT-proBNP levels were also measured using the Abbott Aeroset automated chemistry analyzer with the appropriate commercial kits.

Liver ultrasound

All of the patients underwent liver US screening using the EPIQ 7 high resolution US device and a 1-5 MHz high-resolution convex probe (Philips Healthcare, Inc., Andover MA, USA). The liver US was performed after a minimum fasting period of 8 hours initially using B-mode gray scale imaging to assess the diameter of the inferior vena cava (IVC) on the long axis and measured within 3 cm of the IVC–RA junction during passive respiration. LS measurements were performed using the ElastPQ technique, which is a point shear wave elastography assessment, with the patient in the lateral decubitus position. During hepatic US, the least possible compression was applied with the probe, which was maintained in a constant position, to avoid mechanical pressure on the liver. During the procedure, the participants were asked to pause breathing for a few seconds to minimize hepatic movement occurring

with respiration. After traditional hepatic US images were obtained, the target area was determined and the measurements were performed after the range of imaging (ROI) was positioned on the target (Figs. 1a-d). The ROI was positioned perpendicular to an area containing no vascular structures or space-occupying lesions. The maximum ROI target distance was 8 cm in this study, with a constant ROI box dimension of 1 cm-0.5 cm. In each patient, 10 valid measurements from different hepatic parenchymal segments were obtained and the average was calculated. The results were expressed in terms of kPa; when the reliability of the measurement was low, the image would have a kPa of 0.00. The study participants were stratified into 2 groups: those with or without liver failure (LF), based on the liver stiffness measurement (LSm). Using the cut-off values reported in 4 important recent studies, the threshold values adopted for mild and severely increased LSm to determine the presence of HF were >7 kPa and >10.6 kPa.[11–14]

Statistical analyses

IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used for all of the statistical analysis. Normal distribution of continuous variables was tested using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean±SD, while categorical variables were expressed as numbers and percentages. Continuous variables that demonstrated normal distribution were compared using Student's t-test and analysis of variance, whereas the Mann-Whitney U test and Kruskal-Wallis test were used for samples without normal distribution. The data for each group and the statistical comparisons are provided in the accompanying tables. A chi-square test was used to compare categorical variables. In univariate analyses, logistic regression analysis was performed to determine the independent markers among patients with an LS >7 kpa and >10.6 kPa. Parameters associated with LS were determined using univariate

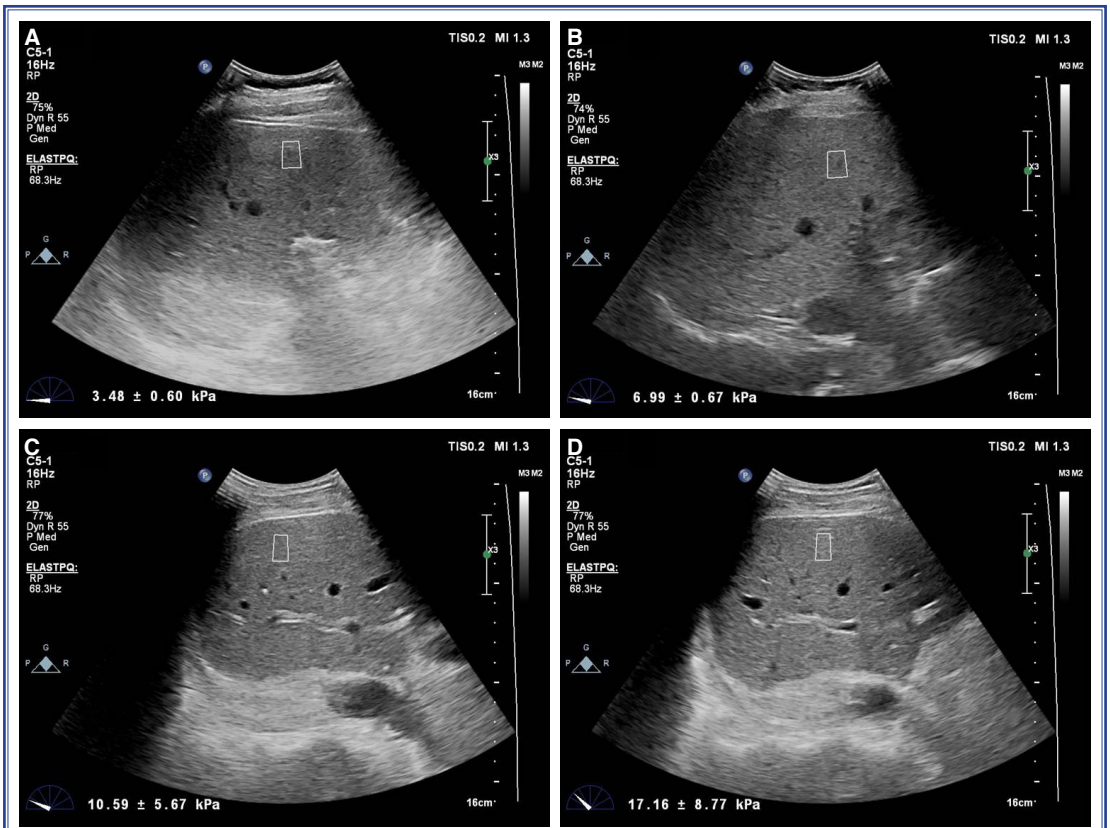

Figure 1. Liver stiffness (LS) measurement by liver elastography in patients with New York Heart Association (NYHA) classification I-IV. **(A)** A NYHA class I patient with a normal LS measurement of 3.48±0.60 kPa; **(B)** A NYHA class II patient with a normal-mild increased LS measurement of 6.99±0.67 kPa; **(C)** A NYHA class III patient with a moderately increased LS measurement of 10.59±5.67 kPa; **(D)** A NYHA class IV patient with a severely increased LS measurement of 17.16±8.77 kPa.

Pearson's and Spearman's correlation analyses. Statistically significant parameters were included in a linear regression analysis, and the parameters with the closest association to LS were identified. ROC curve analysis was performed for LS values to determine the patients with class III-IV HF. From these analyses, limit value determination was conducted to ascertain the best sensitivity and specificity in the determination presence of class III-IV HF. A p level of <0.05 was considered statistically significant.

RESULTS

The mean, median, and minimum and maximum LSm values in HFrEF patients were 7.77±3.07 kPa, 7.20 kPa, and 3.50 kPa and 18.7 kPa, respectively. Successful LS measurements were obtained from all of the patients in the study. The study data were divided into 4 groups according to NYHA class: class I, II, III, and IV patients. In addition, parameters that independently determined the patients with LS values >7 kPa and >10.6 kPa were determined.

Demographic, clinical, and laboratory data according to NYHA class

When the demographic data were compared according to the patients' NYHA class, age, and gender were found to be similar in all NYHA class groups. It was determined that while the presence of AF increased with NYHA class, other demographic and clinical parameters were similar (Table 1). The presence of pretibial edema, hepatomegaly, and hepatojugular reflux were higher in NYHA class III-IV patients. NT-proBNP, ALP, and GGT levels were significantly higher with an increasing level of NYHA classification, and were highest in the NYHA class IV patient group (Table 1). The eGFR value, serum albumin, total cholesterol, and triglyceride levels were significantly lower with each increase in NYHA class, and the values measured were lowest in the NYHA class IV patient group. Other laboratory data were similar in all NYHA classes.

Echocardiography data according to NYHA class

When the echocardiographic parameters of the patients were compared according to NYHA class, it was observed that the LVd and LVs diameters were greater with an increasing NYHA class, and were highest in the NYHA class IV patient group (Table 2). LVEF values decreased with a higher NYHA classification, and were lowest in the NYHA class IV patient group (Table 2). RVd and LAd diameters, and TRPG and RV-MPI values were significantly different between class groups, increased with NYHA classification, and were highest in the NYHA class IV group (Table 2). TAPSE was similarly significantly different between classes, but decreased with a higher NYHA class, and was found to be lowest in the NYHA class IV patient group (Table 2).

Liver ultrasonography data according to NYHA class

In a comparison of liver US findings according to NYHA class, the LS values and the inspiration and expiration IVC diameters were determined to be significantly different between class groups, increasing with the NYHA class, and were highest in the NYHA class IV patient group (Table 2 and Fig. 2). Similarly, a measurement of LS >7 kPa or >10.6 kPa increased with NYHA classification and was found to be highest in the NYHA class IV patient group (Table 2).

Relationship between NYHA class III-IV and liver stiffness

When patients with HFrEF were separated into advanced class HF (NYHA class III-IV) and non-advanced class HF (NYHA class I-II), the LS values measured by LE were found to be 5.85±1.98kPa and 9.59±2.82 kPa, respectively (p<0.001). Logistic regression analysis revealed that LS independently determined the presence of having class III-IV disease (odds ratio [OR]: 1.944, 95% confidence interval [CI]: 1.609-2.348; p<0.001). According to this analysis, the increase of 1 kPa in-

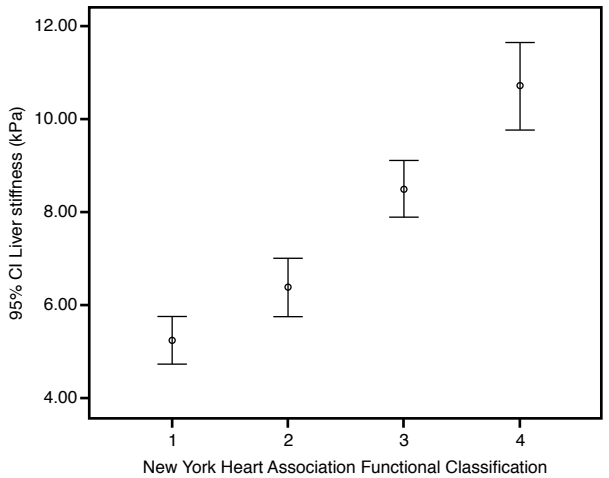

Figure 2. Liver stiffness values according to New York Heart Association class study group.

Table 1. Clinical, demographic, laboratory, and medical treatment findings according to NYHA class

Variable	NYHA I (n=40)	NYHA II (n=47)	NYHA III (n=50)	NYHA IV (n=44)	*p*
Age (years)	63.4±9.0	62.8±11.2	64.8±8.8	65.9±6.4	0.358
Sex (male/female)	26/29	23/32	26/29	26/29	0.855
Hypertension, n (%)	25 (63)	26 (55)	30 (60)	23 (52)	0.465
Diabetes mellitus, n (%)	15 (38)	21 (45)	23 (46)	21 (48)	0.364
Current smoker, n (%)	5 (13)	11 (23)	6 (12)	4 (9)	0.304
Hyperlipidemia, n (%)	12 (21)	13 (24)	17 (31)	17 (31)	0.277
Atrial fibrillation, n (%)	3 (8)	10 (21)	17 (34)	16 (36)	0.001
Pretibial edema, n (%)	3 (8)	21 (45)	36 (72)	44 (100)	<0.001
Hepatomegaly, n (%)	0 (0)	2 (4)	20 (40)	38 (86)	<0.001
Hepatojugular reflux, n (%)	0 (8)	2 (4)	14 (28)	31 (71)	<0.001
Systolic blood pressure (mm Hg)	123±18	120±11	122±17	120±16	0.808
Diastolic blood pressure (mm Hg)	76±13	77±10	77±11	76±9.0	0.871
Pulse (bpm)	76±11	77±11	79±12	80±13	0.783
Body mass index (kg/m^2)	27.2±3.3	26.5±3.2	26.6±3.4	26.0±3.9	0.402
Ischemic HF, n (%)	27 (68)	30 (64)	25 (50)	23 (54)	0.074
Hemoglobin (g/dL)	13.3±1.5	12.9±1.6	12.8±1.8	12.3±1.8	0.067
White blood cell (x10^3/μL)	8.3±1.9	7.9±2.1	8.6±2.7	8.1±2.6	0.426
Total cholesterol (mg/dL)	183±47$^{\alpha}$	175±46	170±50	155±33	0.021
Low-density lipoprotein cholesterol (mg/dL)	117± 39	112±39	103±32	100±28	0.101
High density lipoprotein cholesterol (mg/dL)	42±10	41±16	39±12	35±15	0.146
Triglycerides (mg/dL)	177±93$^{\alpha}$	172±115	154±86	124±74	0.035
Albumin (g/dL)	4.24±0.28$^{\alpha,\beta}$	4.1±0.32$^{¥}$	3.98±0.39**	3.57±0.32	<0.001
Aspartate aminotransferase (u/L)	28.6±7.1	30.9±7.0	31.5±8.9	32.0±7.4	0.194
Alanine aminotransferase (u/L)	32.9±7.9	35.9±8.6	35.1±9.9	35.3±9.5	0.454
Alkaline phosphatase (IU/L)	88.1±21.4$^{\alpha}$	89.5±24.4$^{¥}$	98.8±23.7**	112.6±27.5	<0.001
Gamma-glutamyl transpeptidase (U/L)	37.7±5.2$^{\alpha}$	40.9±6.6$^{¥}$	42.2±7.11**	45.6±8.5	<0.001
Blood urea nitrogen (mg/dL)	46.4±30.4	46.9±21.7	56.3±38.9	58.2±31.5	0.164
Creatinine (mg/dL)	1.17±0.69	1.10±0.98	1.29±1.05	1.40±1.02	0.542
Uric acid	6.41±1.87	6.67±2.32	7.18±2.49	7.32±1.89	0.173
High-sensitivity C-reactive protein (mg/dL)	1.56±2.11	2.17±2.10	2.84±2.95	2.98±3.59	0.054
NT-proBNP (pg/mL)	281±263$^{\alpha}$	537±1487$^{¥}$	685±1102**	2841±7083	0.004
eGFR (mL/min/1.73 m^2)	70.4±33.6$^{\alpha}$	70.7±25.9$^{¥}$	62.2±21.1	55.4±23.7	0.004
Angiotensin converting enzyme inhibitor, n (%)	25 (63)	28 (60)	35 (70)	30 (68)	0.889
Angiotensin receptor blocker, n (%)	11 (28)	9 (19)	8 (16)	7 (16)	0.174
Beta-blocker, n (%)	37 (93)	44 (94)	46 (92)	41 (93)	0.995
Diuretic, n (%)	19 (48)	39 (83)	46 (92)	44 (100)	0.045
Spironolactone, n (%)	22 (55)	25 (53)	40 (80)	29 (66)	0.058

eGFR: Estimated glomerular filtration rate; NYHA: New York Heart Association.
α = the significant association between the NYHA I group and the NYHA IV group (p<0.05); β = the significant association between the NYHA I group and the NYHA III group (p<0.05); * = the significant association between the NYHA I group and the NYHA II group (p<0.05); ¥ = the significant association between the NYHA II group and the NYHA IV group (p<0.05); μ = the significant association between the NYHA II group and the NYHA III group (p<0.05); ** = the significant association between the NYHA III group and the NYHA IV group (p<0.05).

Table 2. Liver ultrasound and echocardiographic findings according to NYHA class

Variable	NYHA I (n=40)	NYHA II (n=47)	NYHA III (n=50)	NYHA IV (n=44)	*p*
Left ventricular diastolic dimension (mm)	57.1±9.2$^{\alpha,*}$	58.5±10.6	61.4±8.3	62.6±11.1	0.038
Left ventricular systolic dimension (mm)	48.3±8.8$^{\alpha,*}$	50.0±10.6	54.7±10.6	54.9±11.5	0.005
Left ventricular ejection fraction (%)	28.2±4.6$^{\alpha,*}$	25.2±6.0	23.8±6.6	24.0±5.2	0.002
Left atrium diastolic dimension (mm)	39.4±2.71$^{\alpha,\beta,*}$	41.5±3.66$^{¥,\mu}$	44.7±5.20**	47.6±5.18	<0.001
Right ventricular diastolic dimension (mm)	26.6±3.74$^{\alpha,\beta,*}$	31.6±4.20$^{¥,\mu}$	35.9±3.83**	40.1±4.42	<0.001
TAPSE (mm)	18.5±1.48$^{\alpha,\beta,*}$	17.3±1.38$^{¥,\mu}$	15.2±1.61**	13.6±1.54	<0.001
TRPG (mm Hg)	24.2±4.73$^{\alpha,\beta,*}$	28.9±5.64$^{¥,\mu}$	38.7±7.4**	49.4±10.2	<0.001
RV-MPI	0.32±0.08$^{\alpha,\beta,*}$	0.33±0.07$^{¥,\mu}$	0.35±0.09**	0.37±0.08	<0.001
Exp-IVC diameter (mm)	14.1±2.72$^{\alpha,\beta,*}$	15.0±3.89$^{¥,\mu}$	17.4±3.61**	18.9±4.77	<0.001
Ins-IVC diameter (mm)	8.01±2.12$^{\alpha,\beta,*}$	9.86±2.55$^{¥,\mu}$	12.8±2.51**	15.1±3.18	<0.001
Liver stiffness (kPa)	5.25±1.51$^{\alpha,\beta,*}$	6.39±2.15$^{¥,\mu}$	8.50±2.14**	10.7±3.10	<0.001
Liver stiffness ≥7 kPa, n (%)	5 (13)	12 (26)	36 (72)	40 (91)	<0.001
Liver stiffness ≥10.6 kPa, n (%)	1 (3)	4 (9)	13 (26)	25 (57)	< 0.001

Exp-IVC: Inferior vena cava expirium; Ins-IVC: Inferior vena cava inspirium; NYHA: New York Heart Association; RV-MPI: Right ventricular-myocardial performance index; TAPSE: Tricuspid annular plane systolic excursion; TRPG: Tricuspid regurgitation pressure gradient.

creased the risk of being class III-IV by 94.4%. A similar analysis was performed with a ROC curve and found that the area under the ROC curve was 0.878 (95% CI 0.825-930; p<0.001; Fig. 3). The analysis indicated that when the cut-off value for LS was 7 kPa, patients with class III-IV disease could be determined with 82.8% sensitivity and 81.8% specificity.

The parameters associated with liver stiffness measurements

The demographic, clinical, laboratory, echocardiographic, and US parameters associated with LS in the univariate analysis are summarized in Table 3. Linear regression analysis was performed with the parameters significantly related to LS (Table 3). LS values were found to be closely related to TRPG, RV-MPI, TAPSE, and NT-proBNP levels (Table 3, Fig. 4a-d).

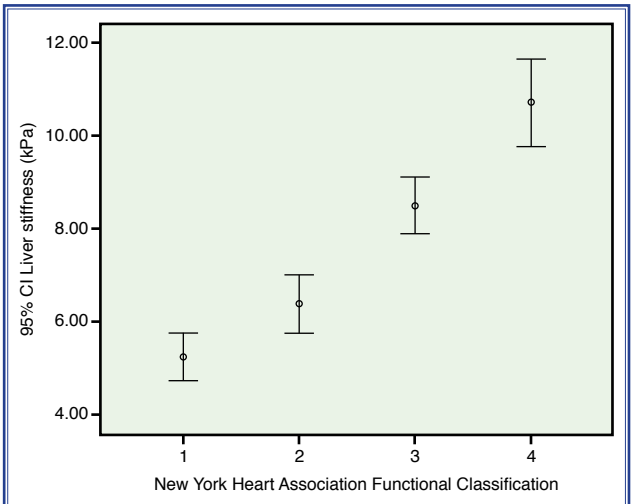

Figure 2. Liver stiffness values according to New York Heart Association class study group.

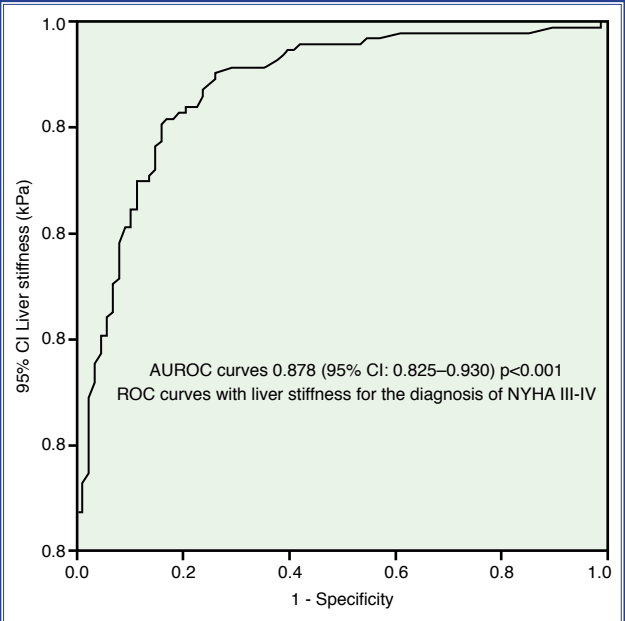

Figure 3. Receiver operating characteristic curves of liver stiffness for the diagnosis of New York Heart Association NYHA class III-IV patients.

Table 3. The parameters associated with liver stiffness measurements

	Univariate analysis		Multivariate analysis	
	p	r	*p*	β
Total cholesterol (mg/dL)	0.025	-0.167	0.970	0.003
Low-density lipoprotein cholesterol (mg/dL)	0.039	-0.153	0.300	0.005
High-density lipoprotein cholesterol (mg/dL)	0.022	-0.170	0.945	0.081
Triglycerides (mg/dL)	0.012	-0.186	0.913	0.009
NT-proBNP (pg/mL)	<0.001	0.695	0.025	0.183
Aspartate aminotransferase (u/L)	<0.001	0.269	0.001	0.210
Alanine aminotransferase (u/L)	0.003	0.221	0.824	0.017
Alkaline phosphatase (IU/L)	<0.001	0.479	0.606	0.040
Albumin (g/dL)	<0.001	-0.365	0.097	0.090
Gamma-glutamyl transpeptidase (U/L)	<0.001	0.458	0.455	0.058
Estimated glomerular filtration rate (mL/min/1.73 m^2)	0.013	-0.187	0.886	0.005
Left ventricular diastolic dimension (mm)	0.027	0.164	0.493	0.054
Left ventricular systolic dimension (mm)	0.010	0.190	0.449	0.059
Left ventricular ejection fraction (%)	0.017	-0.178	0.065	0.113
Left atrium diastolic dimension (mm)	<0.001	0532	0.501	0.053
Right ventricular diastolic dimension (mm)	<0.001	0.636	0.615	0.025
Tricuspid annular plane systolic excursion (mm)	<0.001	-0.839	0.130	0.105
Tricuspid regurgitation pressure gradient (mm Hg)	<0.001	0.892	<0.001	0.616
Right ventricular-myocardial performance index	0.022	0.867	<0.001	0.290
Inferior vena cava expirium diameter (mm)	<0.001	0.814	0.822	0.018
Inferior vena cava inspirium diameter (mm)	<0.001	0.832	0.496	0.053

$R^2_{Adjusted}$=0.738 in multivariate analysis.

Table 4. Independent parameters for the occurrence of LS >7 kPa and >10.6 kPa

	Odds ratio	95% Confidence interval	*p*
For >7 kPa			
Tricuspid annular plane systolic excursion (mm)	2.782	1.201–6.447	0.017
Left atrium diastolic dimension (mm)	7.164	2.215–23.172	0.001
Aspartate aminotransferase (u/L)	1.077	1.032–1.123	0.001
For >10.6 kPa			
Right ventricular-myocardial performance index (each 0.01)	2.184	1.548–3.081	<0.001
Natriuretic peptide (100 pg/mL)	1.114	1.008–1.231	0.035
Alanine aminotransferase (u/L)	1.066	1.009–1.126	0.023

Parameters associated with mild and severely increased liver stiffness values (>7 kPa and >10.6 kPa)

Increased LS was defined as >7 kPa. Multivariate logistic regression analysis was performed with demographic, clinical, laboratory, echocardiographic, and US parameters associated with slightly elevated LS in univariate analysis. TAPSE, AST, and LAd were independently associated with patients with LS >7 kPa (Table 4). The same analyses were performed to identify patients with greater LS. RV-MPI, NT-proBNP, and ALT levels were indepen-

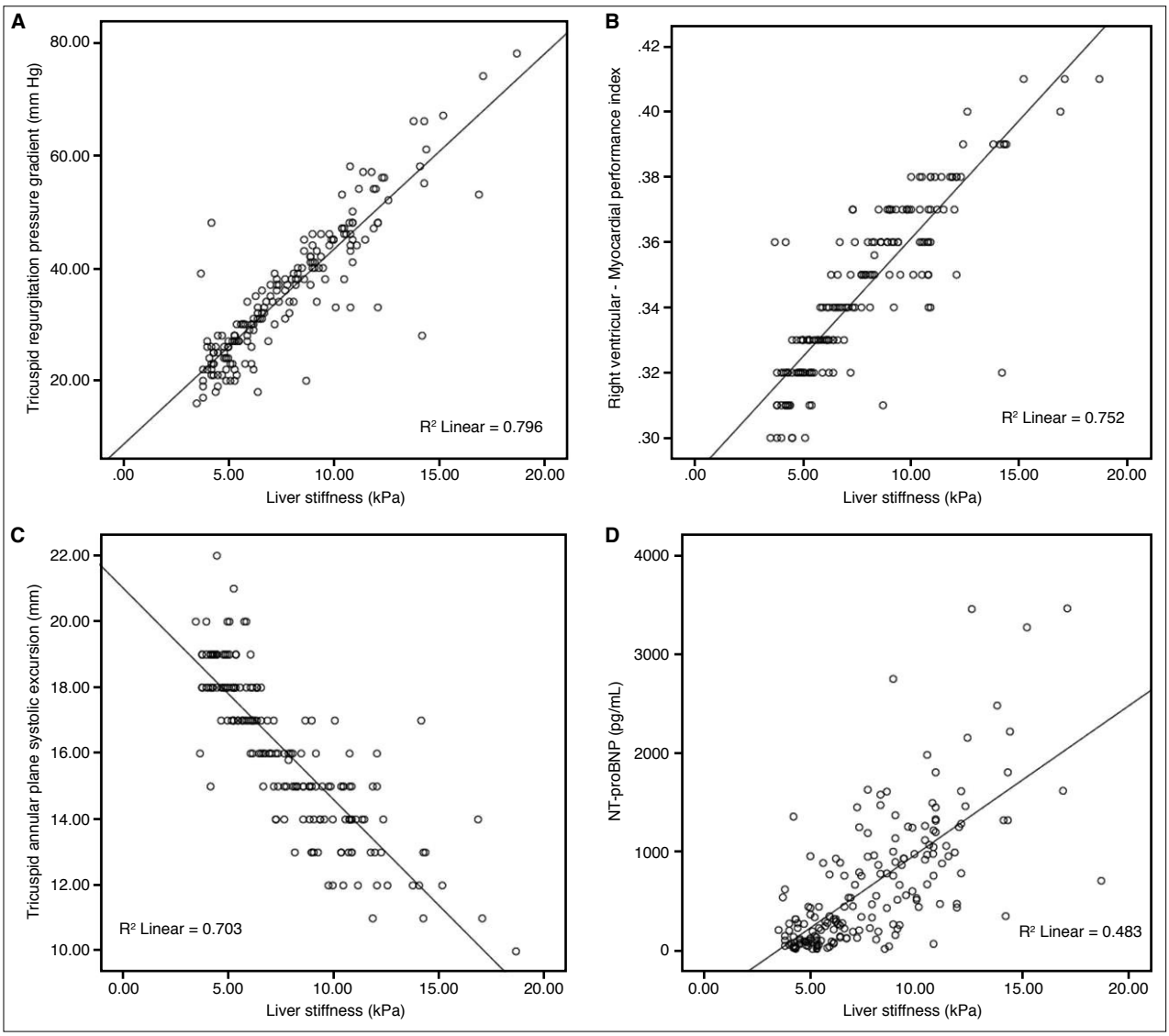

Figure 4. There is significant correlation between liver stiffness and **(A)** tricuspid regurgitation pressure gradient (TRPG) **(B)** Right ventricular-myocardial performance index (RV-MPI) **(C)** tricuspid annular plane systolic excursion (TAPSE) (D) NT-proBNP scatter/dot graphics for **(A)** TRPG **(B)** RV-MPI **(C)** TAPSE **(D)** NT-proBNP.

dently associated with patients with LS >10.6 kPa (Table 4).

DISCUSSION

This study has 3 main findings. The first of these was that the LS value was significantly greater with a higher NYHA classification in HFrEF patients and independently determined the presence of NYHA class III-IV HF. A measurement of >7 kPa was an important LS threshold value in HF, and it also objectively determined patients with advanced class HF. Secondly, LS in patients with HFrEF was closely related to the RV systolic function parameters of TAPSE and RV-MPI. Another important finding was that, as shown in previous HF studies, there was a close association between LS and NT-proBNP, AST, and ALT values calculated in the liver function tests of HFrEF patients. Our study differs from previous studies in terms of using a new LE method, ElastPQ, in isolated HFrEF patients.

LS measurement obtained by LE is primarily used in hepatology clinics and is closely related to LF.[23,24] With evolving technology and LE methods, as well as greater accessibility to US devices, LS measurement

has become feasible for HF patients. Our research revealed that a number of important studies, mostly in 2018, have been conducted on LE evaluation in HF patients without chronic liver disease, and an increase in LS has been reported.[10–14,17,18] As a result of these studies, the conclusion has been reached that LS can be used in the follow-up and treatment of HF patients without chronic liver disease. A study of LS measurement for HF patients was first conducted by Millonig et al.[10] on animal subjects and was reported to be closely related to an increase in central venous pressure. In the evaluation of congestive cardiac hepatopathy since 2010, an LS assessment obtained with LE has critical importance and provides clearer and more objective information. The objective relationship between LS and right atrial pressure (RAP) was clearly shown in an invasive and objective study involving only a small number of patients.[11] The initial LS examination technique was transient elastography[11–13] and developed into shear wave elastography (SWE),[24] and point SWE.[18] All of these studies have demonstrated a greater LS value in HF patients. It has been shown that there is very close correlation between the LS value and right-sided filling pressure in LE studies.[10–13] Taniguchi et al.[11] investigated the correlation between LS obtained with TE and RAP (mmHg) and reported a calculation of -5.8 + 6.1 x ln [LS (kPa)]. We did not use this formula because new kPa values were obtained with new model devices. In addition, a FibroScan device (Echosens SAS, Paris, France) was used in this invasive study and the probability of successful measurement was reported to be <60%.[11] In our study, we used a high-end US device and the ElastPQ technique, described in one of the point SWE studies using state-of-the-art technology. The LS value was successfully obtained for all patients. The most important feature of the ElastPQ technique used in the present study, along with the different LE measurement methods, is ease of use, a high rate of measurement possibility, and high power to predict liver pathology.[15,16]

Different limit values have been used to define increased LS as a result of different devices, methods, and groups of patients (HFrEF or HFpEF). Ten measurements are made in each case and the average is reported in units of kPa as an LS value. In acute decompensated HF patients, LS was high and the increased LS limit value has been defined as 8.8 kPa.[12,26,27] In 2 recent studies and in some previous studies, the LF limit value used was ≥7 kPa.[13, 14] In another study conducted by Taniguchi et al.,[13] the average kPa value was reported to be 5.6 kPa, but when the patients were divided into 3 groups, ≥7 kPa was used to define the high limit for HF severity, increased right-side filling pressure, and poor prognosis. Patients in our study were not divided into 2 or 3 groups according to kPa values as in previous studies for data analysis. Isolated HFrEF and ElastPQ methods were used for the first time in this study and we elected not to use the limit values obtained from previous studies. We found increased LS (LS >7 kPa) in our study at a rate of 13%, 26%, 72%, and 91% in NYHA class I, II, III and IV patients, respectively. In another study by Taniguchi et al.,[11] the authors reported that there was a close relationship between invasively measured RAP and LS obtained with TE. The LS value has been reported to better detect elevated RAP (>10 mm Hg) with a vena cava inferior diameter >21 mm and/or <50% reduction in the diameter with inspiration.[11] In the same study, it was reported that when the LS limit value was 10.6 kPa, it was useful to determine the presence of RAP >10 mm Hg with 85% sensitivity and 93% specificity.[11] However, in this invasive study, HF patients with all EF values were included. LS was observed in patients of NYHA class I, II, III, and IV at a rate of 3%, 9%, 26%, and 57%, respectively, when LS ≥10.6 kPa was used, a level determined in previous studies to identify patients with severe RAP elevation (>10 mm Hg).[11] This result in our study is a separate proposition in terms of results obtained from only patients with HFrEF and using the ElastPQ method.

The increase in LS that occurs in patients with HF is mainly related to clinical, biochemical, and echocardiographic parameters in HF patients.[11,13] Research has revealed that increased liver congestion leads to an increase in cholestasis parameters (AST, ALT, GGT, total protein),[5,11,12,28–30] as well as a decrease in parameters showing synthesis in liver, such as cholesterol and albumin[11,12,31–33] in HF patients. Taniguchi et al.[11] found that increased total bilirubin, GGT, and ALP levels were closely related to LS in patients with HF. In this important study, no significant results were obtained in the regression analysis due to a small study population. In our study, there was a close and independent relationship between NT-proBNP, AST, and ALT levels and LS.

TAPSE measurement from echocardiographic parameters is an important parameter for reduced TV function. A recent study by Saito et al.[12] found a close and negative relationship between TAPSE and LS. Similar results were supported by another recent study.[13] However, the close relationship between TAPSE and LS obtained in both studies was not seen between LS and LVEF.[12,13] The most important reason is that there are different HF groups according to EF. Our study also found that LS was independently associated with RV function parameters TAPSE and RV-MPI, consistent with previous studies. In addition, in our study, although there was a relationship between LVEF and LS values in univariate analysis, there was no independent relationship between LS values and LVEF, also consistent with previous studies. Among the other echocardiographic parameters, LAd diameter and TRPG were closely and independently related to LS. The most important difference between our study and previous studies is that the data in our study was obtained from HFrEF patients with only one type of HF. Echocardiography is still an important study in HF diagnosis and follow-up. The LS value obtained by simple measurement with LE can be a helpful review, especially to illustrate if RV functions have been affected.

NT-proBNP is an important and objective laboratory parameter used for diagnosis, follow-up, treatment and prognosis in HF patients.[1,34,35] One of the non-cardiac causes of NT-proBNP increase is liver dysfunction. Studies have shown a close relationship between NT-proBNP and LS.[13] In our study, the NT-proBNP level was found to independently determine patients with LS >7 kPa.

HF is a major problem in the modern world. The most important problem in HF patients is a poor prognosis and impaired quality of life. It is very important that patients with HF are well classified according to the NYHA system and that patients with low functional capacity are identified. It is important to obtain objective parameters for functional capacity determination. Previous studies have reported that NT-proBNP, low EF, and large heart cavities are associated with decreased functional capacity.[1,34,35] However, in patients with isolated HFrEF, the relationship between NYHA functional class and LS is not clear, and there is no information about LS values in the NYHA classification system. ROC analysis was performed to determine class III-IV patients with advanced HF, and it was determined that when the cut-off value for LS was 7 kPa, the presence of advanced HF was determined independently. Similar to this finding of our study, 2 studies by Taniguchi et al.[11,13] reported a close association between the LS value and the severity of HF. However, in these studies, no regression analysis was performed and the patients were in different HF etiologies.[11,13] In another important study evaluating the association between acute HF and LS, there was no close association between LS value and NYHA class.[12] Our results indicated that the LS value independently determined the NYHA functional class. It was found that LS independently determined the presence of class III-IV and that the increase of 1 kPa increased the risk of being class III-IV by 94.4%. Earlier studies have demonstrated a positive and close relationship between LS value and NYHA class, but this relationship was not independent. In our study, it was also found in the multivariate analysis that the LS value and the NYHA class were independently correlated. We also found that LS independently detected patients with class III-IV HF with advanced class HF for the first time. In HFrEF patients; the median kPa values in patients with NYHA class I, II, III, and IV were observed for the first time as 5.25±1.51 kPa, 6.39±2.15 kPa, 8.50±2.14 kPa and 10.7±3.10 kPa, respectively.

Study limitations

One of the most important limitations of this study is that our study data were not confirmed with a liver biopsy. A liver biopsy and magnetic resonance imaging (MRI) were not performed due to the invasive nature and expense. If this additional research data were available, more objective results could be obtained. However, performing a liver biopsy in patients with HF would be unethical. Based on the results of previous studies, only patients with HF were included and these patients were compared according to their NYHA class. If a healthy control group without active HF were included, different results might be obtained. All of the patients in this study were receiving optimal treatment according to their clinical findings and NYHA class. For this reason, the effect of the current treatment on LS was not evaluated. Medical, and in some diseases, surgical treatment, has been shown to decrease LS.[17,25,36] There is a very close relationship between invasively measured RAP and LS.[11] The LS value may have been even more significant if our present findings included RAP measurements. Pa-

tients with severely kidney and liver failure were not included in the study. These conditions are common in HF patients; however, our data cannot be used for this patient group. Because of the patient selection of isolated HFrEF and the use of the ElastPQ technique, no limit value comparison can be made with another study. LS measurement in HF patients is also both a congestion parameter and a prognosis parameter, but our patients were not followed in terms of prognosis. MRI is a noninvasive modality to detect LS; however, MRI is an expensive imaging method with limited availability.[37] On the other hand, liver US is a noninvasive, inexpensive, and widely available imaging modality that can be used for the same purpose.

Conclusion

An increased LS value in patients with HFrEF is closely related to the progression of NYHA classification, and it's closely and independently related to liver function tests, NT-proBNP, RV systolic function and pressure, and determines advanced class HF presence. LS measurement obtained by LE is a noninvasive, reproducible, objective, inexpensive US study that can be performed in as little as <5 minutes, and can be used in HF cases. As in patients with HF with acute and variable etiology, having HFrEF also increases the LS value, which can be used in the clinical follow-up of patients with measured LS values. Patients with LS >7 kPa should be closely followed and treated. LS measured by LE in HF patients may be added in the coming years as a routine follow-up parameter to the recommended liver function tests routinely performed by the guidelines; however, we concluded that our results should be strengthened by new studies of patients with different and more HF patients, possibly in multicenter studies.

Ethics Committee Approval: Permission was obtained from Local Ethics Commitee of Adana Health Practices and Research Center (Approval date: 28-Feb-2018, Approval number: 12-171).

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Keywords: Functional capacity; heart failure with reduced ejection fraction; liver stiffness; ventricular systolic function.

Anahtar sözcükler: Fonksiyonel kapasite; düşük ejeksiyon fraksiyonlu kalp yetersizliği; karaciğer sertliği; ventrikül sistolik fonksiyonu.