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Liver Stiffness Reflecting Right-Sided Filling Pressure Can Predict Adverse Outcomes in Patients With Heart Failure

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ABSTRACT

OBJECTIVES This study sought to investigate whether elevated liver stiffness (LS) values at discharge reflect residual liver congestion and are associated with worse outcomes in patients with heart failure (HF).

BACKGROUND Transient elastography is a newly developed, noninvasive method for assessing LS, which can be highly reflective of right-sided filling pressure associated with passive liver congestion in patients with HF.

METHODS LS values were determined for 171 hospitalized patients with HF before discharge using a Fibroscan device.

RESULTS The median LS value was 5.6 kPa (interquartile range: 4.4 to 8.1; range 2.4 to 39.7) and that of right-sided filling pressure, which was estimated based on LS, was 5.7 mm Hg (interquartile range: 4.1 to 8.2 mm Hg; range 0.1 to 18.9 mm Hg). The patients in the highest LS tertile (>6.9 kPa, corresponding to an estimated right-sided filling pressure of >7.1 mm Hg) had advanced New York Heart Association functional class, high prevalence of jugular venous distention and moderate/severe tricuspid regurgitation, large inferior vena cava (IVC) diameter, low hemoglobin and hematocrit levels, high serum direct bilirubin level, and a similar left ventricular ejection fraction compared with the lower tertiles. During follow-up periods (median: 203 days), 8 (5%) deaths and 33 (19%) hospitalizations for HF were observed. The patients in the highest LS group had a significantly higher mortality rate and HF rehospitalization (hazard ratio: 3.57; 95% confidence interval: 1.93 to 6.83; $p < 0.001$) compared with the other tertiles. Although LS correlated with IVC diameter and serum direct bilirubin and brain natriuretic peptide levels, LS values were predictive of worse outcomes, even after adjustment for these indices.

CONCLUSIONS These data suggest that LS is a useful index for assessing systemic volume status and predicting the severity of HF, and that the presence of liver congestion at discharge is associated with worse outcomes in patients with HF. (J Am Coll Cardiol Img 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

High rates of mortality and hospital readmission due to heart failure (HF) remain a major burden to health care systems despite advances in the management of HF. Among patients hospitalized with HF, persistent high left ventricular filling pressure at discharge is associated with high mortality and rehospitalization rates (1). To date, considerable attention has been directed toward left-sided filling pressure as a prognostic indicator in patients with HF, whereas the potential importance of right-sided filling pressure has been relatively poorly investigated. Elevated right-sided filling pressure can result in systemic venous congestion, which is considered to be a major driving factor of organ injury and death (2). A common organ manifestation of such congestion is passive liver congestion, which is clinically diagnosed by evidence of increased central venous pressure (CVP) accompanied by abnormal liver

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CI = confidence interval

CVP = central venous pressure

E = peak early diastolic transmitral flow velocity

e′ = mitral annular velocity

GGT = gamma-glutamyl transpeptidase

HF = heart failure

HR = hazard ratio

IVC = inferior vena cava

IQR = interquartile range

LFT = liver function test

ln = natural log-transformation

LS = liver stiffness

NYHA = New York Heart Association

RAP = right atrial pressure

ROC = receiver operating characteristic

function test (LFT) results. Supporting this, previous studies have reported that both high CVP and abnormal LFT portend poor prognosis in HF (3,4).

The noninvasive evaluation of chronic liver disease based on liver stiffness (LS) assessed by transient elastography has attracted growing interest in the field of clinical hepatology (5). LS is calculated based on the sheer wave velocity measurements and is used as a noninvasive method to assess liver fibrosis. LS may also have prognostic potential in various hepatic diseases without HF (6); however, we and other researchers have shown that LS is highly reflective of right-sided filling pressure in patients with HF without chronic liver diseases (7,8). Although these findings indicate the potential clinical usefulness of LS for HF management, the association of LS with clinical outcomes in patients with HF remains unclear.

In the present study, we hypothesized that elevated LS at discharge can reflect subclinical residual liver congestion, which indicates persistent hemodynamic congestion from severe HF or insufficient decongestion therapy during hospitalization, and can be predictive of adverse cardiac events related to HF. To this end, we investigated the prognostic value of LS at discharge for future cardiac events in patients hospitalized with HF.

METHODS

STUDY POPULATION. This single-center, prospective cohort study was approved by our local institutional ethics committee. We prospectively screened 226 consecutive hospitalized HF patients without scheduled surgical treatment between March 2012 and October 2014 at Osaka University Hospital. The diagnosis of HF was based on typical signs and symptoms, particularly dyspnea, on exertion and signs of pulmonary and/or peripheral congestion, and attending physicians provided case-specific optimized therapy to the patients and decided discharge according to established guidelines (9,10). Patients with invalid LS measurements, as described later, were excluded. We also excluded patients with a history or signs of liver disease, previous diagnosis of chronic liver disease, history of alcohol abuse (≥30 g/day for men, ≥20 g/day for women), hepatic ultrasound data showing liver surface nodularity as a sign of severe fibrosis or ascites, positive for anti-hepatitis C antibody, or with hepatitis B surface antigen reactivity. Of the 226 patients screened, 18 (8%) had invalid LS measurements and 37 met the other exclusion criteria, leaving a total of 171 patients available for this study (**Figure 1**). The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and all patients provided written informed consent to participate.

LS ASSESSMENT AND ESTIMATION OF RIGHT-SIDED FILLING PRESSURE. LS measurements were performed by a single experienced examiner (T.T.) before discharge, who was blinded to all clinical data, using a Fibroscan device (Echosens, Paris, France) according to the manufacturer's instructions and as described elsewhere (7). Briefly, the tip of the probe transducer was placed on the skin of the patient between the rib bones and at the level of the right lobe of the liver (Online Figure 1, Online Video). The details are described in the Online Appendix. Right-sided filling pressure was estimated using the following prediction model based on the results of the relationship between invasively measured right-sided filling pressure and LS (7):

$$\text{Estimated right-sided filling pressure (mm Hg)} = -5.8 + 6.7 \times ln\,(\text{LS [kPa]})$$

ln indicates natural log-transformation.

LABORATORY TESTS AND ECHOCARDIOGRAPHY. Routine laboratory data, including serum B-type natriuretic peptide (BNP) and type IV collagen 7S domain, were collected from patients in a stable condition before discharge. Echocardiography was performed before discharge using a Vivid 9E device (GE Healthcare, Milwaukee, Wisconsin), as previously described (11), by experienced sonographers who were blinded to other clinical data. Further details are provided in the Online Appendix.

FOLLOW-UP AND ENDPOINTS. Patients were followed by clinical visits or by telephone interviews. Data of mortality and morbidity were obtained in a blinded fashion by the collection of all available medical records. The LS results were blinded to the primary physicians caring for the patient; frequency of follow-up visits was left to their discretion. The prespecified primary endpoint was the composite of cardiac death or rehospitalization for the treatment of HF. For patients that experienced 2 or more cardiovascular events, only the first event was considered in the analysis.

STATISTICAL ANALYSIS. Categorical variables are presented as numbers (percentages), and continuous variables are shown as the mean ± SD if symmetrically distributed or as the median (interquartile range [IQR]) if asymmetrically distributed. Associations between LS tertiles and relevant clinical variables

were assessed by 1-way analysis of variance and Kruskal-Wallis tests for continuous variables, and using chi-square tests for categorical variables, followed by the Tukey-Kramer test, Steel-Dwass test, or chi-square test with Bonferroni correction as appropriate. BNP *ln* was used to satisfy the model assumptions. Kaplan-Meier curves were constructed to examine the time to an event and were compared using a log-rank test. Cox proportional hazards regression analysis was performed to adjust for differences in baseline characteristics or pertinent covariates on outcomes. Multivariable Cox proportional hazards regression analyses were performed using forced inclusion models involving age, sex, and pertinent covariates. To further evaluate the impact of LS on outcomes, relationships between LS and overall survival were analyzed using a piecewise linear Cox regression model (Online Appendix).

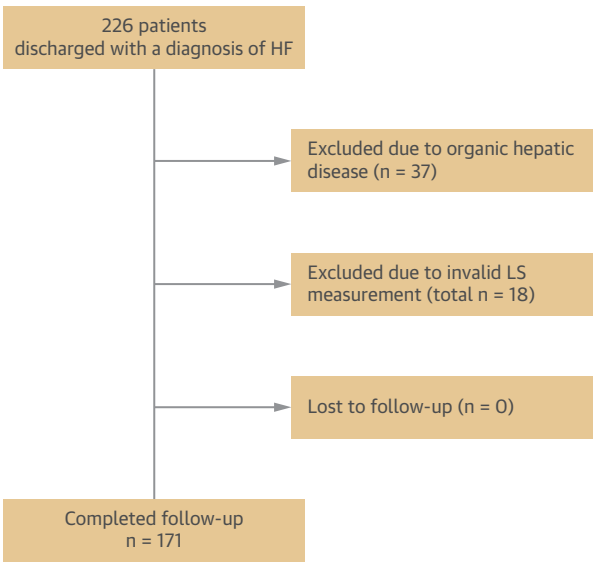
Univariate and multivariate Cox proportional hazard models, including age, sex, estimated glomerular filtration rate, and *ln* (BNP), were constructed for each LFT; thereafter, LS was entered into the models. For comparison of the incremental benefit between LS and the LFTs, sequential Cox models were used with the incremental prognostic value defined by a significant increase in global chi-square value. The incremental effect of adding LS to clinical variables for predicting future cardiovascular events was evaluated using a net reclassification index, as previously described (12). Proportional hazards assumption was verified using the Schoenfeld global test. To further evaluate the usefulness of LS as a predictor of short-term risk, the power of LS to identify patients at a risk of cardiac events within 90 days from discharge was assessed using receiver operating characteristic (ROC) curve analyses with the Youden method. Confidence intervals for the area under the ROC curve were determined from 10,000 bootstrapped samples; the areas under the ROC curve were then compared based on the method of Delong (13).

A p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using the R Statistics version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and JMP version 10.0 (SAS Institute Inc., Cary, North Carolina) software packages.

RESULTS

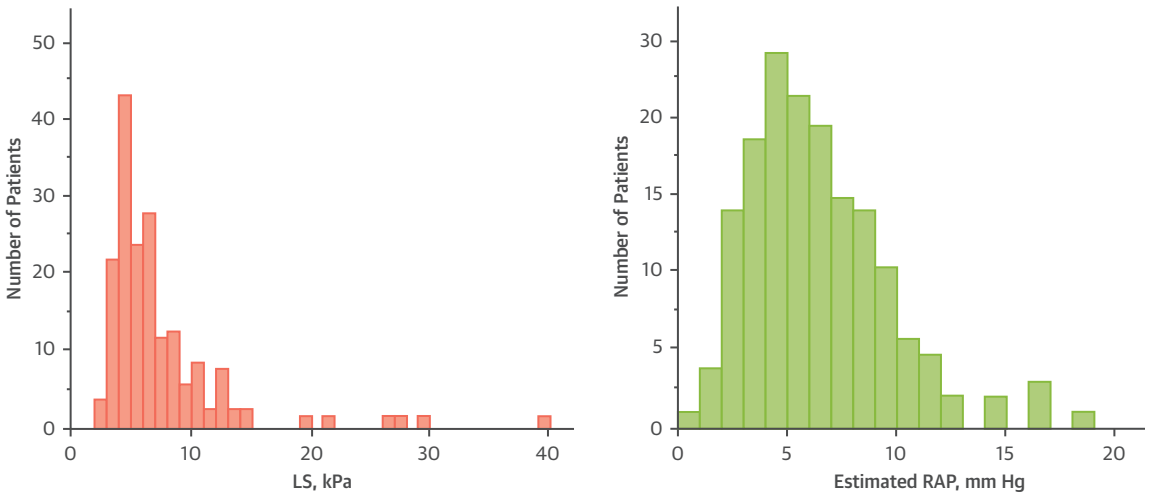
STUDY POPULATION. The distribution of LS values and estimated right-sided filling pressure among the study patients are illustrated in **Figure 2**. The median LS value was 5.6 kPa (IQR: 4.4 to 8.1 kPa; range 2.4 to 39.7 kPa); that of right-sided filling pressure, which was estimated based on LS, was 5.7 mm Hg (IQR: 4.1 to 8.2 mm Hg; range 0.1 to 18.9 mm Hg). The cutoff LS values between the tertiles were 4.7 and 6.9 kPa, which corresponded to estimated right-sided filling pressures of 4.6 and 7.1 mm Hg, respectively. The patients in the highest LS tertile had advanced New York Heart Association (NYHA) functional class, high prevalence of jugular venous distention, anemia and moderate/severe tricuspid regurgitation, low hemoglobin and hematocrit levels, high levels of serum direct bilirubin and type IV collagen 7S domain, and large inferior vena cava (IVC) diameter compared with the lower 2 tertiles (**Table 1**). Although the presence of leg edema was correlated with continuous LS values, the frequency was not high (7%) and was not statistically different among the tertiles. Several echocardiographic indices, including peak early diastolic transmitral flow velocity (E), E/mitral annular velocity (e′) ratio, left atrial diameter, right ventricular diameter, tricuspid annular plane systolic excursion, and tricuspid regurgitation gradient, were correlated with LS, whereas left ventricular dimensions and ejection fraction showed no correlation. Some patients had a disease etiology that often causes right ventricular dysfunction (Online Table). Although the levels of transaminases and bilirubin were not elevated in most patients, aspartate aminotransferase, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, and direct bilirubin were correlated with LS.

FIGURE 1 Study Flowchart



The diagram describes the protocol used for the enrollment of patients with HF in the present study. Details of LS measurement is in Online Figure 1 and Online Video 1. HF = heart failure; LS = liver stiffness.

FIGURE 2 **The Distribution of LS and Estimated Right-Sided Filling Pressure**



Right-sided filling pressure was estimated using the following equation (7): Estimated right-sided filling pressure (mm Hg) = −5.8 + 6.7 × *ln* (LS [kPa]). *ln* = natural log-transformation; LS = liver stiffness; RAP = right atrial pressure.

PREDICTIVE ABILITY OF LS FOR CARDIAC EVENTS. The median follow-up duration was 203 days (IQR: 67 to 429 days), and there were 8 (5%) deaths and 33 (19%) hospitalizations for HF. Kaplan-Meier curves showed that patients in the highest LS group had a significantly higher probability of cardiovascular events compared with those in the other 2 groups (log-rank test: $p < 0.001$, $p = 0.002$, and $p = 0.478$ for first vs. third, second vs. third, and first vs. second tertiles, respectively) (Figure 3). LS showed a significant predictive value in univariate Cox regression analysis with a hazard ratio (HR) per 1-kPa increase of 1.13 (95% confidence interval [CI]: 1.09 to 1.17; $p < 0.001$) for cardiac events, whereas estimated right-sided filling pressure had a HR per 1-mm Hg increase of 1.30 (95% CI: 1.19 to 1.41; $p < 0.001$). The use of the Schoenfeld global test confirmed that the proportional hazards assumptions were appropriate ($p = 0.839$). The identified associations remained significant in multivariate analysis, even after adjusting for other previously reported prognosticators related to left and right ventricular function, volume status, severity of HF, and systemic organ functions (Table 2). LS showed a good predictive value for worse outcomes in patients regardless of severity of diastolic dysfunction (Online Figure 2). Notably, IVC diameter was also associated with the incidence of cardiac events; however, this parameter did not show significant predictive ability in the model that included both LS and IVC ($p = 0.087$).

ASSESSMENT OF LS WITH BNP FOR RISK PREDICTION. Plasma levels of BNP, which is 1 of the established predictors for outcomes in patients with HF, also showed a significant predictive value for cardiac events in the present study (HR: 2.11 per 1 log-unit; 95% CI: 1.50 to 3.01; $p < 0.001$). Although LS and BNP were poorly correlated ($r = 0.181$; $p = 0.019$), higher LS remained associated with higher prevalence of cardiac events even after adjustment for *ln* (BNP) (HR: 1.12 per 1 kPa; 95% CI: 1.07 to 1.16; $p < 0.001$). To evaluate the incremental prognostic value of LS and BNP, the patients were stratified into 4 groups using the second hinge of the LS tertile (6.9 kPa) as the cutoff for high and low LS and the median serum BNP level (199 pg/ml) for high and low BNP. The combined LS and BNP subgroups had significantly different probabilities of cardiovascular events (Figure 4) (log-rank test: $p < 0.001$). In both the low and high BNP groups, the high LS group had a significantly higher rate of cardiac events than the low LS group (log-rank test: $p = 0.038$ and $p = 0.005$, respectively).

COMPARISON OF PREDICTIVE VALUE BETWEEN LS AND LFT. Among the LFTs, univariate analyses revealed that GGT, alkaline phosphatase, and direct bilirubin levels were significant predictors of cardiac events (Table 3). Even after adjustment for clinical variables, including age, sex, estimated glomerular filtration rate, and *ln* (BNP), all of the LFTs remained associated with the risk of cardiac events. When LS was included in the models, however, none of the

TABLE 1 Clinical Characteristics of the Study Population

		LS Tertile				Correlation With LS	
	Overall (n = 171)	First LS ≤4.7 kPa (n = 55)	Second 4.7 < LS ≤ 6.9 kPa (n = 59)	Third LS >6.9 kPa (n = 57)	ANOVA p Value	Correlation Coefficient	p Value
Clinical characteristics							
Age, yrs	65 (52-75)	60 (47-72)	70 (56-79)	66 (55-78)	0.069	0.207	0.007
Male	116 (68)	34 (60)	44 (75)	38 (69)	0.221	0.043	0.581
BMI, kg/m^2	20.5 (18.4-23.2)	20.2 (18.7-24.0)	20.9 (18.7-23.7)	20.2 (18.2-23.1)	0.388	−0.101	0.191
NYHA functional class III or IV	26 (15)	3 (5)	5 (8)	18 (33)*†	<0.001	0.358	<0.001
Systolic BP, mm Hg	104 (96-115)	110 (96-122)	104 (96-110)	102 (90-111)	0.061	−0.161	0.036
Diastolic BP, mm Hg	58 (50-62)	60 (53-67)	60 (52-62)	56 (50-62)	0.167	−0.145	0.058
Heart rate, beats/min	73 ± 11	72 ± 10	72 ± 11	75 ± 10	0.373	0.134	0.080
Jugular venous distention, n = 145	31 (21)	3 (5)	5 (10)	23 (58)*†	<0.001	0.507	<0.001
Leg edema	12 (7)	2 (4)	3 (5)	7 (13)	0.108	0.251	0.001
HF duration, days	922 (51-3,670)	232 (44-2,586)	857 (32-3,296)	2,013 (213-5,174)*†	<0.001	0.272	<0.001
Comorbidities							
CAD	49 (29)	12 (21)	21 (36)	16 (29)	0.223	0.057	0.463
AF	74 (44)	9 (16)	32 (54)*	33 (61)*	<0.001	0.277	<0.001
Hypertension	77 (45)	28 (49)	27 (46)	22 (41)	0.672	−0.078	0.313
Dyslipidemia	105 (61)	33 (58)	42 (71)	30 (55)	0.152	−0.833	0.279
Diabetes mellitus	46 (27)	12 (21)	13 (22)	21 (38)	0.072	0.093	0.228
COPD	8 (5)	1 (2)	3 (5)	4 (7)	0.378	0.009	0.910
Laboratory parameters							
Hemoglobin, g/dl	12.5 ± 2.3	13.0 ± 1.8	12.9 ± 2.4	11.5 ± 2.3*†	<0.001	−0.348	<0.001
Hematocrit, %	38.5 ± 6.4	39.9 ± 4.7	39.6 ± 6.9	35.8 ± 6.6*†	<0.001	−0.334	<0.001
Anemia	62 (36)	14 (25)	18 (31)	30 (55)*†	0.002	0.250	0.001
Platelet count, 10^4/ml	19.4 (15.2-23.7)	20.8 (16.5-24.4)	19.4 (15.0-23.6)	18.0 (13.4-22.4)*	0.037	−0.273	<0.001
Serum Na, mEq/l	137 (134-139)	138 (135-139)	138 (136-139)	136 (132-139)	0.055	−0.191	0.012
eGFR, ml/min/1.73 m^2	52 ± 24	59 ± 27	49 ± 24	48 ± 20*	0.021	−0.263	0.001
BNP, pg/ml	199 (91-356)	126 (47-298)	203 (88-392)	241 (119-367)*	0.034	0.181	0.019
AST, IU/l	23 (17-30)	19 (16-25)	23 (18-28)*	25 (20-35)*	0.003	0.271	<0.001
ALT, IU/l	17 (12-28)	17 (11-27)	17 (12-33)	18 (12-28)	0.614	0.055	0.480
GGT, IU/l	39 (25-76)	28 (21-40)	41 (27-85)*	53 (34-108)*	<0.001	0.413	<0.001
Alkaline phosphatase, IU/l	229 (186-296)	213 (163-294)	240 (191-268)	268 (203-353)*	0.019	0.237	0.002
Total bilirubin, mg/dl	0.6 (0.4-0.8)	0.6 (0.4-0.7)	0.5 (0.4-0.8)	0.6 (0.5-0.8)	0.267	0.135	0.078
Direct bilirubin, mg/dl	0.2 (0.2-0.3)	0.2 (0.1-0.3)	0.2 (0.2-0.3)	0.3 (0.2-0.4)*†	0.007	0.276	<0.001
Indirect bilirubin, mg/dl	0.3 (0.3-0.5)	0.4 (0.3-0.5)	0.3 (0.3-0.5)	0.3 (0.2-0.5)	0.921	−0.024	0.762
Type IV collagen 7S, ng/ml	5.1 ± 1.3	4.3 ± 0.9	5.1 ± 1.2*	5.9 ± 1.4*†	<0.001	0.518	<0.001
Echocardiographic parameters							
LVEDD, mm	57 (49-68)	61 (51-68)	55 (49-67)	57 (48-69)	0.534	−0.071	0.359
LVESD, mm	45 (35-59)	52 (41-61)	44 (32-58)	45 (35-58)	0.454	−0.083	0.279
LVEF, %	36 (25-58)	35 (25-53)	40 (27-59)	35 (25-59)	0.523	0.049	0.527
≥50%	57 (34)	19 (35)	21 (36)	17 (31)	0.784	0.074	0.336
E, m/s	0.73 (0.56-0.94)	0.62 (0.50-0.80)	0.78 (0.61-0.98)*	0.84 (0.70-1.08)*	0.001	0.337	<0.001
e′ velocity, cm/s	4.7 (3.8-6.2)	4.6 (3.6-6.2)	5.1 (4.0-6.5)	4.3 (3.6-6.0)	0.353	−0.047	0.585
E/e′ ratio	14.1 (10.3-18.8)	11.4 (8.0-17.1)	14.9 (10.7-19.5)	15.5 (11.7-20.6)*	0.023	0.269	0.002
Left atrial diameter, mm	45 ± 10	42 ± 9	46 ± 9	47 ± 10*	0.009	0.271	<0.001
Moderate/severe MR	36 (21)	12 (21)	10 (17)	14 (25)	0.538	0.047	0.540
Moderate/severe TR	31 (18)	4 (7)	7 (12)	20 (36)*†	<0.001	0.374	<0.001
IVC diameter, mm	15 ± 5	12 ± 4	14 ± 4*	17 ± 4*†	<0.001	0.442	<0.001
Right ventricular diameter, mm	36 ± 9	34 ± 6	36 ± 9	38 ± 10*	0.041	0.192	0.014
TAPSE, mm	15.2 ± 4.8	16.1 ± 4.9	15.8 ± 4.9	13.8 ± 4.3*	0.021	−0.187	0.017
TR gradient, mm Hg	24 (18-31)	21 (18-28)	23 (18-32)	26 (20-37)	0.071	0.202	0.014

Continued on the next page

LFT remained associated with cardiac event rate. In the Cox regression analyses of cardiac events, the effects of clinical variables (age, sex, estimated glomerular filtration rate, *ln* [BNP]) were augmented by LS (chi-square = 41.67; $p < 0.001$) as compared with GGT (chi-square = 26.43; $p < 0.001$), alkaline phosphatase (chi-square = 27.07; $p < 0.001$), and direct bilirubin (chi-square = 28.93; $p < 0.001$).

TABLE 1 Continued

	Overall (n = 171)	LS Tertile: First LS ≤4.7 kPa (n = 55)	LS Tertile: Second 4.7 < LS ≤ 6.9 kPa (n = 59)	LS Tertile: Third LS >6.9 kPa (n = 57)	ANOVA p Value	Correlation With LS: Correlation Coefficient	Correlation With LS: p Value
Medications							
Beta blockers	132 (77)	48 (84)	45 (76)	39 (71)	0.240	−0.128	0.095
ACEIs or ARBs	124 (72)	41 (72)	44 (75)	36 (65)	0.549	−0.214	0.005
Diuretics	125 (73)	33 (58)	45 (76)	47 (85)*	0.004	0.208	0.006
Mineralocorticoid receptor antagonists	96 (56)	23 (40)	35 (59)	38 (69)*	0.008	0.233	0.002
Calcium-channel blockers	27 (16)	9 (16)	10 (18)	8 (15)	0.910	−0.049	0.525
Statins	51 (30)	15 (26)	22 (37)	14 (25)	0.300	−0.073	0.346
Digoxin	29 (17)	8 (14)	9 (15)	12 (22)	0.509	0.142	0.063
Aspirin	61 (36)	16 (28)	25 (42)	20 (36)	0.272	0.009	0.904

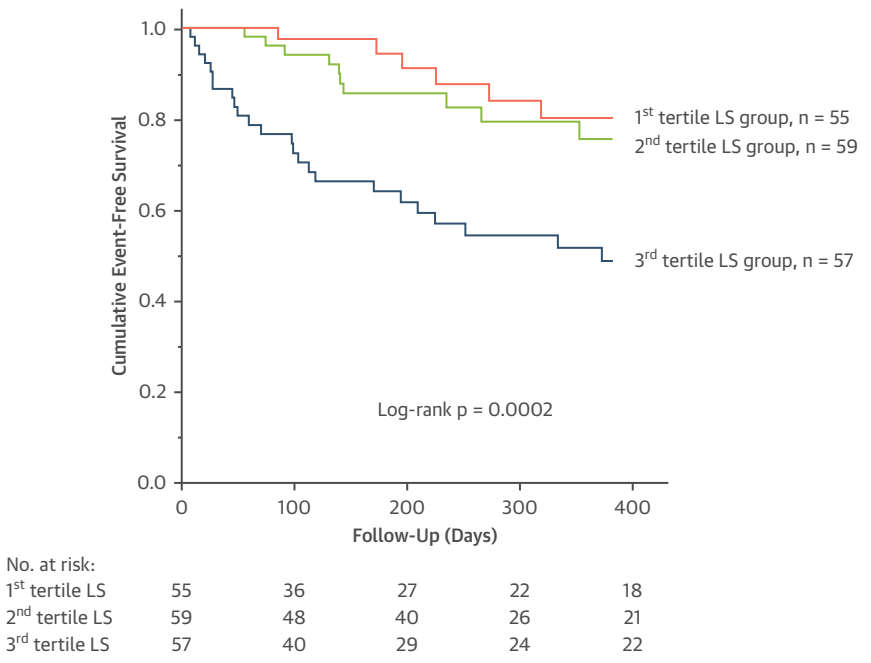
Values are median (interquartile range), n (%), or mean ± SD. Multiple comparison was performed based on the ANOVA test for symmetrical continuous variables; the Kruskal-Wallis test for nonsymmetrical continuous variables; and the chi-square test for categorical variables. For all-pair comparisons, the Tukey-Kramer test was used for symmetrical continuous variables; the Steel-Dwass test was used for nonsymmetrical continuous variables; and the chi-square test with Bonferroni correction was used for categorical variables. *$p < 0.05$ vs. first tertile. †$p < 0.05$ vs. second tertile.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ALT = alanine aminotransferase; ANOVA = analysis of variance; ARB = angiotensin receptor blocker; AST = aspartate aminotransferase; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; E = peak early diastolic transmitral flow velocity; e′ = peak early diastolic septal mitral annular velocity; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transpeptidase; HF = heart failure; IVC = inferior vena cava; LS = liver stiffness; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; MR = mitral regurgitation; Na = sodium; NYHA = New York Heart Association; TAPSE = tricuspid annual plane systolic excursion; TR = tricuspid regurgitation.

In addition, we performed category-free net reclassification index analysis and found a significant improvement in risk stratification for adverse clinical outcomes for LS in addition to clinical variables (0.691; 95% CI: 0.352 to 1.029; $p < 0.001$).

PREDICTIVE ABILITY OF LS FOR SHORT-TERM CARDIAC EVENTS. To evaluate the predictive value of LS for the risk of short-term cardiac events, we performed ROC curve analysis using data collected after 90 days of follow-up. The LS value of 10.1 kPa

FIGURE 3 Kaplan-Meier Analysis Among LS Tertile Groups



Kaplan-Meier curves show the crude cumulative survival free from cardiac events for tertiles of LS values. pink line, first tertile group; green line, second tertile group; blue line, third tertile group. LS = liver stiffness.

(estimated right-sided filling pressure: 9.7 mm Hg) yielded a sensitivity of 0.73 and a specificity of 0.90 for worse outcomes. Notably, LS showed a better discriminatory power for detecting worse outcomes (C-statistic: 0.823; 95% CI: 0.682 to 0.964; $p < 0.001$) than that of IVC diameter (C-statistic: 0.698; 95% CI: 0.576 to 0.821; $p = 0.002$) ($p = 0.029$). We also calculated the C-statistic of the model consisting of clinical variables (age, sex, estimated glomerular filtration rate, and *ln* [BNP]) for predicting cardiac events at 90-day follow-up. The addition of LS to the clinical variables resulted in augmentation of the C-statistic value from 0.704 to 0.844 ($p = 0.006$).

TABLE 2 Association Between LS and Risk of Death or Rehospitalization for HR

	LS (per 1-kPa Increase)		LS (Third Tertile vs. First and Second Tertiles)	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Unadjusted	1.13 (1.09–1.17)	<0.001	3.57 (1.93–6.83)	<0.001
Model 1	1.18 (1.06–1.30)	0.002	3.41 (1.58–7.52)	0.002
Model 2	1.11 (1.06–1.16)	<0.001	2.91 (1.50–5.83)	0.002
Model 3	1.07 (1.02–1.12)	0.009	2.21 (1.12–4.45)	0.023
Model 4	1.10 (1.05–1.14)	<0.001	2.45 (1.26–4.87)	0.008
Model 5	1.12 (1.08–1.16)	<0.001	3.97 (2.09–7.78)	<0.001

Event numbers for models 1, 2, 3, 4, and 5 are 30, 40, 41, 41, and 41, respectively.

CI = confidence interval; HF = heart failure; HR = hazard ratio; LV = left ventricular; model 1 = adjusted for age, sex, and LV function variables (LV ejection fraction, left atrial diameter, and E/e′); model 2 = adjusted for age, sex, and RV function variables (RV diameter, tricuspid annular plane systolic excursion, and tricuspid regurgitation [moderate or severe]); model 3 = adjusted for age, sex, and volume status variables (hematocrit and serum sodium level); model 4 = adjusted for age, sex, and severity of HF (New York Heart Association functional class [III or IV] and systolic blood pressure); model 5 = adjusted for age, sex, and systemic organ functions (estimated glomerular filtration ratio, total bilirubin); RV = right ventricular. Other abbreviations as in Table 1.

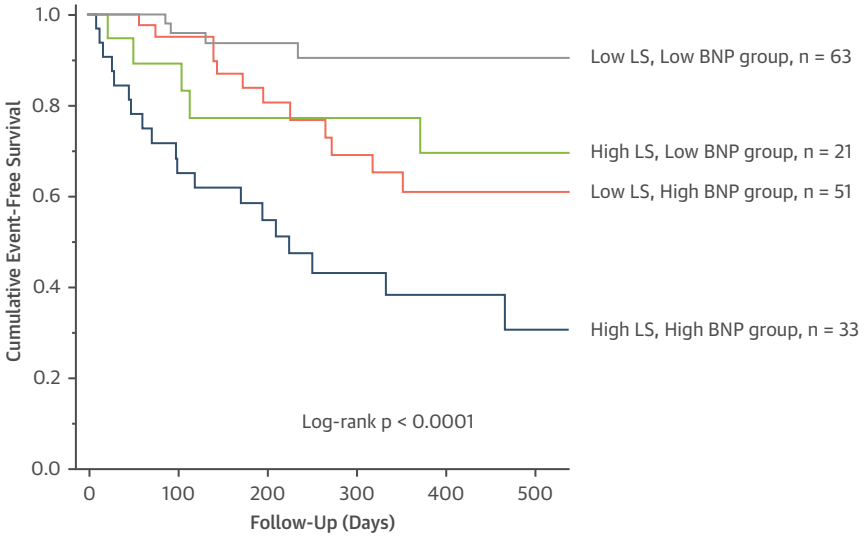
DISCUSSION

This study is an initial report evaluating the association between LS, as assessed using simple transient elastography, and adverse cardiovascular outcomes in patients with HF. Our study has 5 major findings. First, LS was associated with several parameters related to the severity of HF, including NYHA function class, BNP, volume status, and LFTs. Second, LS at discharge was a strong predictor of clinical outcomes, including cardiac death and rehospitalization because of HF. Third, LS showed an incremental prognostic value when combined with previously established variables for predicting worse outcomes, including BNP. Fourth, the additive predictive value of LS for the identification of patients at a high risk was greater than that of conventional LFTs. Finally, short-term risk stratification with LS was also superior to that based on IVC diameter, which is a commonly used noninvasive marker for systemic venous congestion. These findings suggest that the degree of LS at discharge for HF can be used as a reliable indicator of subclinical residual liver congestion, which reflects the severity of HF and adverse cardiac events, even in patients with optimized HF treatment and without visible edema or elevated LFT.

LS IN HF PATIENTS. LS was originally used for assessment of liver diseases; however, little is known about the association between LS and HF. Millonig et al. (8) first reported the effect of CVP on LS using an animal model and in patients with various HF profiles, although the data regarding the effects of diuretic therapy and hemodialysis on LS are conflicting (14,15). The LS values in approximately one-half of our study patients were higher than normal, which is reported to be <5.9 kPa (16). Because patients with chronic hepatic disease were excluded, it is conceivable that elevated right-sided filling pressure dominantly affects LS, which is a direct indicator of passive liver congestion. This is also supported by the detected positive correlation between LS and LFT. In the present study, higher LS was also associated with higher E/e′ and larger left atrial diameter, which indicate elevated left-sided filling pressure; in addition to lower hemoglobin, hematocrit, and sodium levels, which indicate increased volume status; and advanced NYHA functional class and elevated BNP, which are markers of HF severity. This finding is reasonable because right-sided filling pressure can be affected by left-sided filling pressure and volume status, and therefore is likely to be related to HF severity. Whereas the patients were given case-specific optimized therapy, there may still exist a possibility of insufficiency for precluding rehospitalization. These findings indicate that assessment of liver congestion based on LS provides information on right-sided filling pressure, which may reflect the comprehensive status of HF.

LS AND OUTCOMES. Right-sided filling pressure has been reported as one of the most important prognosticators in HF (3); however, limited studies have invasively measured CVP in patients with HF. Pellicori et al. (17) revealed that increasing IVC diameter could be used to identify patients at risk for adverse outcomes in outpatients with HF regardless of NYHA functional class. Consistent with these studies, we found that LS was associated with future cardiac events. Interestingly, in Kaplan-Meier analysis, there was no significant difference in the rate of cardiac events between the first and second LS tertiles. The same relation was confirmed in a piecewise linear Cox regression model. Only *ln*(LS)_2.0 was included as the significant variable (coefficient: 2.33; standard error: 0.34; $p < 0.001$). The relation between estimated

FIGURE 4 Kaplan-Meier Analysis by the Joint Assessment of LS and BNP



No. at risk:						
Low LS, Low BNP	63	47	43	29	29	29
Low LS, High BNP	51	38	26	19	15	15
High LS, Low BNP	21	17	14	14	10	10
High LS, High BNP	33	21	16	11	9	5

Patients were divided into 4 groups based on the second hinge of the LS tertile (6.9 kPa) as the cutoff for high and low LS and median BNP level (199 pg/ml) for high and low BNP. BNP = B-type natriuretic peptide; LS = liver stiffness.

right-sided filling pressure and log-relative risk is illustrated in Online Figure 3, showing the risk increasing soon after *ln*(LS) exceeds 2.0 (i.e., LS exceeds 7.4 kPa or estimated right-sided filling pressure exceeds 7.6 mm Hg). Our results infer that the target level of optimal right atrial pressure (RAP) in HF management may be less than 8 mm Hg at discharge. Notably, LS had better prognostic value compared with IVC diameter, which may be due to higher accuracy of LS for evaluating right-sided filling pressure. LS remained a predictor for worse outcomes even after adjustment for variables related with left and right ventricular function. LS was also associated with HF severity. Next, we assessed the predictive ability of LS for adverse outcomes in combination with BNP, which is a well-known marker of HF severity and as prognostic predictor (18), and found that addition of LS had incremental prognostic value to the model including BNP. This finding may be attributable to that, although right-sided filling

TABLE 3 Cox Proportional Hazard Analysis for Different Parameters of Liver Function Tests in 171 HF Patients

	Univariate		Multivariable (Model 1)		Multivariable (Model 2)	
	HR	p Value	HR	p Value	HR	p Value
GGT (per 10 IU/l increase)	1.07 (1.02-1.11)	0.006	1.05 (1.00-1.10)	0.034	1.04 (1.00-1.09)	0.055
ALP (per 10 IU/l increase)	1.03 (1.00-1.06)	0.023	1.03 (1.00-1.06)	0.025	1.02 (1.00-1.05)	0.068
Total bil (per 0.1 mg/dl increase)	1.02 (0.98-1.06)	0.282	1.03 (0.98-1.07)	0.194	1.01 (0.95-1.05)	0.647
Direct bil (per 0.1 mg/dl increase)	1.21 (1.06-1.36)	0.009	1.22 (1.05-1.39)	0.011	1.09 (0.90-1.28)	0.378
Indirect bil (per 0.1 mg/dl increase)	1.04 (0.96-1.10)	0.261	1.05 (0.97-1.11)	0.195	1.04 (0.95-1.11)	0.319
AST (per 10 IU/l increase)	1.06 (0.87-1.25)	0.516	1.11 (0.91-1.31)	0.288	0.99 (0.79-1.19)	0.922
ALT (per 10 IU/l increase)	0.94 (0.78-1.08)	0.401	1.00 (0.84-1.14)	0.993	0.97 (0.81-1.12)	0.739
LS (per 1 kPa increase)	1.13 (1.09-1.17)	<0.001	1.12 (1.07-1.16)	<0.001	–	–

ALP = alkaline phosphatase; bil = bilirubin; *ln* = natural log-transformation; model 1 = adjusted by age, sex, eGFR, and *ln* (BNP); model 2 = adjusted by age, sex, and LS; other abbreviations as in Table 1.

pressure is influenced by left-sided filling pressure, the latter may have a greater impact on BNP release compared with the former, whereas LS is mainly affected by right-sided filling pressure. Interestingly, two-thirds of the patients in the highest LS tertile presented NYHA functional class I/II regardless of worse outcome. We investigated the clinical characteristics of the patients with NYHA functional class I/II between third and both first and second LS tertiles (Online Appendix). In this subgroup analysis, the patients in the third tertile also had more congestive status and right ventricular dysfunction. The frequency of AF was also likely to be higher in the third LS tertile, although the difference did not reach the significant level. These results suggest that right ventricular dysfunction and AF may be associated with worse outcome in the less symptomatic situation.

COMPARISON BETWEEN LS AND LIVER ENZYMES IN PREDICTING ADVERSE CARDIAC OUTCOMES. The prognostic importance of abnormalities in liver biochemical profiles was detected in a clinical study of patients with HF (19), although this relationship was not significant after adjustment for hemodynamic factors, such as cardiac index and CVP. In the present study, GGT and direct bilirubin were associated with cardiac events in univariate analysis, but did not remain significant predictors for worse outcomes in multivariate regression models that included LS. Moreover, LS showed greater predictive power for adverse outcomes compared with liver enzymes. There are 2 possible explanations for this result. First, abnormal LFT results may reflect impaired hemodynamics, rather than hepatic damage resulting from systemic congestion in this study. The second potential reason is that LS also reflects the degree of liver damage and therefore LS overwhelms the prognostic value of LFT results.

CLINICAL IMPLICATIONS. The assessment of LS is rapid, simple, objective, and repeatable. LS provides additional information on conventional markers for future worse outcomes extending mechanistic insight into cardio-hepatic interactions (4). LS may reflect residual subclinical congestion not identifiable by physical findings such as leg edema. Also, LS may be useful among patients whose HF status is unclear or whose filling pressures cannot be assessed easily because of insufficient echocardiogram images or previous cardiovascular surgery. Elevated LS values at predischarge indicate subclinical residual liver congestion and may further be a sign of persistent hemodynamic congestion from severe HF or insufficient decongestion therapy; therefore, the assessment of LS, in addition to standard clinical practice, may be useful for the management of HF. Similar to BNP, LS may guide the selection of appropriate decongestion therapy for patients with acute decompensated HF (20). LS measurements, particularly when performed serially, may facilitate volume management and achievement of euvolemia. Furthermore, our findings may extend the use of LS measurement from hepatology to cardiology.

STUDY LIMITATIONS. A few limitations warrant mention. For ethical considerations, liver biopsy was not performed in these high-risk patients. High LS values can be reflective of elevated RAP or elevated RAP complicated with subclinical liver fibrosis from long standing HF. LS positively correlated with type IV collagen in our cohort; however, the correlation between type IV collagen and estimated RAP or maximum IVC diameter was not different between patients with ≥10 and <10 years of HF history (Online Figures 4A and 4B). We also investigated the changes in type IV collagen and weight from admission to discharge in patients with decompensated HF (not included in this study). Type IV collagen changed with weight (Online Figure 4C), and a similar pattern was observed in the change between type IV collagen and LS (Online Figure 4D). These results are consistent with a previous study reporting the impact of RAP on type IV collagen (21). Type IV collagen may not always reflect liver fibrosis because it also fluctuates with diuresis. There is only a small possibility that liver fibrosis may have existed in our cohort. Next, LS is also affected by several factors, including hepatitis, steatosis, mechanic cholestasis, and amyloid deposition (5). Lack of data on histological findings may have led to extraction of patients with organic liver disease as well as steatosis or nonalcoholic steatohepatitis, although we excluded patients with chronic hepatic disease based on ultrasound findings. Finally, because of limited sample size, we produced several models evaluating the incremental utility in particular subsets, rather than including all of the variables in a single analysis. Although this was probably the best option under the limitations of the dataset, there still remains the risk of residual confounding and inability to adjust for all relevant variables.

CONCLUSIONS

This is the first study to demonstrate the prognostic value of LS in patients with HF. LS at discharge is associated with the severity of HF and systemic volume status and, compared with IVC diameter and conventional LFTs, provides more useful information for predicting poor outcomes in patients with HF.

Taken together, these results suggest that the assessment of liver congestion at discharge may aid in the management of patients with HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: LS measurement is a rapid, simple, and noninvasive approach to predict future HF-related events in patients with HF, which may help guide the treatment of patients with HF.

TRANSLATIONAL OUTLOOK: Further randomized study is needed to reveal that LS-guided therapy improves the outcome of management in patients with HF.

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KEY WORDS elastography, heart failure, liver congestion, outcomes, right atrial pressure

APPENDIX For supplemental tables, figures, and a video, please see the online version of this paper.