Clinical Investigation

Relationship of Liver Stiffness With Congestion in Patients Presenting With Acute Decompensated Heart Failure

ANZHELA SOLOVEVA, MD, PhD,[1] ZHANNA KOBALAVA, MD, PhD,[1] MARAT FUDIM, MD,[2] ANDREW P. AMBROSY, MD,[2] SVETLANA VILLEVALDE, MD, PhD,[1] MUNKHTSETSEG BAYARSAIKHAN, MD,[1] IRINA GARMASH, MD, PhD,[1] AND MAKSIM NAUMENKO, MD[3]

Moscow, Russian Federation; and Durham, North Carolina

ABSTRACT

Objective: The significance of liver stiffness (LS) in the setting of cardiovascular congestion during the course of acute decompensated heart failure (ADHF) is under investigation. The aim of this study was to assess LS with the use of transient elastography (TE) and its associations with volume overload as determined by means of bioimpedance vector analysis (BIVA) in ADHF.

Methods and Results: TE (Fibroscan 502; Echosens) and BIVA (ABC-01, Medass) were performed in the first 48 hours of admission and on the day of discharge in 149 ADHF patients without known primary chronic liver disease or acute hepatitis. During hospitalization the median value of LS decreased from 12.2 kPa (interquartile range 6.3−23.6) to 8.7 (5.9−14.4) kPa ($P < .001$). Changes in LS correlated ($P < .001$) with changes in weight and BIVA parameters. LS was compared with histologic features of livers of ADHF patients who died (n = 7). Liver fibrosis 2B-4 was observed but was not associated with LS. LS at discharge was associated with increased risk of 12-month all-cause death, HF readmission, and the combined end point.

Conclusions: There was a moderate association between LS with clinical congestion and volume overload according to BIVA and no correlation with degree of histologic liver fibrosis. LS may be a marker of negative HF outcomes. (*J Cardiac Fail 2019;25:176−187*)

Key Words: Decompensated heart failure, congestion, liver stiffness, bioimpedance vector analysis.

Congestion is the main driver of cardiac decompensation, a poor prognostic marker, and one of the main targets in the treatment in acute decompensated heart failure (ADHF).[1] Among several pathophysiologic factors, congestion is also thought to be one of the most important drivers for end-organ injury and failure in HF.[2,3] Prolonged and chronic congestion can induce liver fibrosis or even cirrhosis, with significant impairments in liver function, which are common in HF and have prognostic implications and a potential impact on treatment decisions.[4,5]

Current guidelines recommend the measurement of liver function tests (LFTs) in the setting of acute HF,[6] given that it is abnormal in 20%−30% of patients and is associated with poor clinical outcomes.[2,7−10] Notably, LFTs abnormalities represent a heterogeneous nature of liver damage in HF and could imply either permanent liver injury or temporary dysfunction. Although liver ultrasound is an indispensable tool for structural liver disease diagnosis, the typical signs of passive hepatic congestion occur in later stages of liver disease and therefore ultrasound is often inconclusive. Transjugular liver biopsy, though an accurate diagnostic and prognostic tool, is not feasible in everyday clinical practice.[11] Consequently, the routine evaluation of congestive hepatopathy remains a challenging problem, and a search for more informative and sensitive method for diagnosis of prognostic significant liver dysfunction in HF is desirable.

Transient elastography (TE) is a widely used and well validated noninvasive method for assessment of liver

disease severity in a broad spectrum of primary liver diseases. Because of its accuracy, time- and cost-effectiveness, and simplicity of use, the method has replaced the criterion standard of liver biopsy in many cases. Although the TE technology was primarily developed to survey the liver tissue, the measured liver stiffness (LS) is altered by changes in tissue edema,[12] such as that seen in acute and chronic HF. Preliminary studies to date have found strong associations of LS with central venous pressure (CVP) in different HF populations.[13–18] Nevertheless, TE technology has not been properly validated in patients with acute HF to support its value as a noninvasive measure of congestion.

Given the evidence to support TE as a potential tool for the assessment of liver congestion as well as primary liver pathology, we aimed to assess LS by means of TE and its associations with changes of congestion status measured by means of clinical examination and bioimpedance vector analysis (BIVA) as well as histologic changes in decompensated HF.

Methods

Study Overview

Patients were enrolled as part of a prospective single-center observational study that included consecutive patients hospitalized with ADHF without acute coronary syndrome (Fig. 1). In accordance with the European Society of Cardiology guidelines, patients were classified to have decompensated HF if they had deterioration of typical signs and symptoms of HF on admission to the hospital.[6] Patients with known primary liver disease, acute hepatitis with transaminases increase more than 5 times the upper limit of normal, end-stage chronic kidney disease, neoplasms, severe ascites, edema due to noncardiac reasons, severe cognitive impairment, immobilization, and an inability to undergo BIVA were excluded from the study.

All patients underwent a detailed physical examination, including assessment of body weight on admission and discharge. Clinical signs of congestion were assessed with the use of a bedside assessment scale that included orthopnea, jugular venous pressure, hepatomegaly, and edema derived from a previously described point system to quantify the degree of congestion.[1] Clinical congestion status was classified as absent (score of <1) or present (score ≥1). Outpatient therapy was reviewed with particular attention to potentially hepatotoxic drugs. Given the high societal prevalence of alcohol abuse, it was assessed with the use of the CAGE questionnaire,[19] direct contact with family members, and assessment of clinical and laboratory signs. Ascites was investigated by means of abdominal ultrasound. Signs of pulmonary congestion and hydrothorax were assessed by means of chest radiography performed in the first hour after admission. Laboratory assessment was performed locally.

The study fulfilled the principles outlined in the Declaration of Helsinki and was independently approved by the local Ethics Committee of the Institute of Medicine, Peoples' Friendship University of Russia. All study participants gave written informed consents.

Echocardiography

Transthoracic echocardiography was performed for all patients in a blinded manner on admission (Vivid-7;
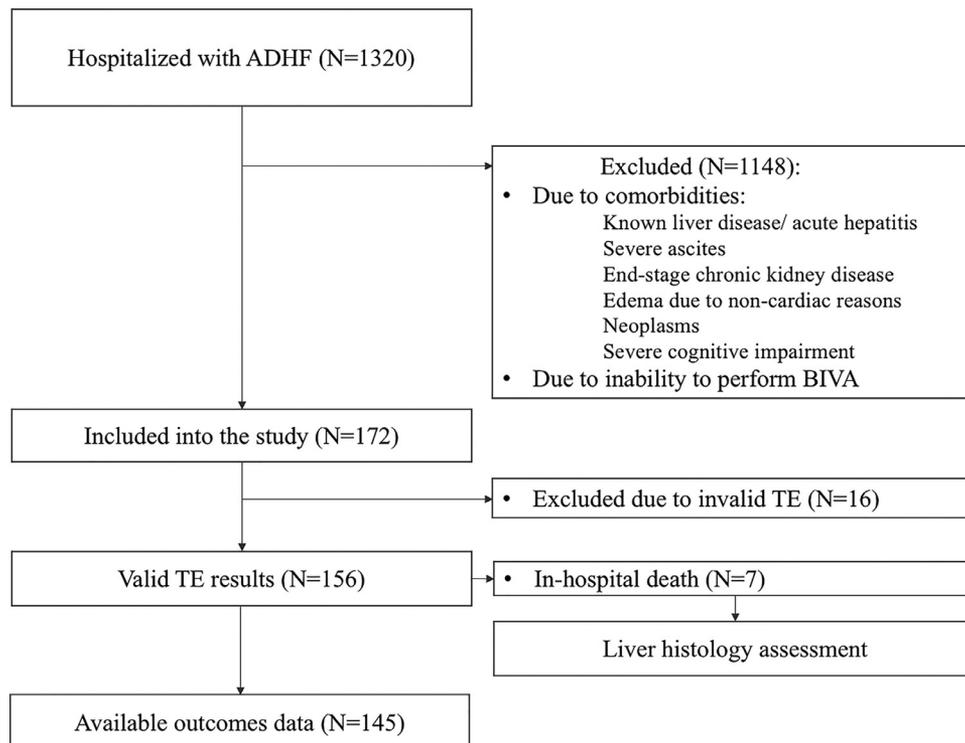

Fig. 1. Study flow chart. ADHF, acute decompensated heart failure; BIVA, bioimpedance vector analysis; TE, transient elastography.

General Electric). Left ventricular ejection fraction was measured by means of the Simpson biplane method of disks. Right ventricular dilation was defined as a midcavity end-diastolic diameter >30 mm from parasternal position. Inferior vena cava (IVC) diameter <21 mm and ≥50% collapsibility in inspiration were considered to be normal.[20]

Transient Elastography

TE was performed in the first 48 hours of admission and on the day of discharge with the use of the Fibroscan 502 (Echosens) according to standard protocol in the supine position. Measurements were performed in the 9th−11th intercostal spaces in the mid- or posterior axillary lines. At least 10 measurements were performed in each patient, and a success rate (ratio of valid shots to the total number of shots) of >60% was considered to be acceptable. The results are expressed in kilopascals (kPa) and range from 1.5 to 75 kPa. Currently, there are no HF-specific cutoff values to grade congestive hepatopathy. According to the European Association for the Study of the Liver and Asociación Latinoamericana para el Estudio del Hígado clinical practice guidelines we considered LS ≤5.0 kPa as normal, 5−13 kPa as fibrosis, and >13 kPa as cirrhosis.[12]

Bioimpedance Vector Analysis

BIVA was performed simultaneously with TE on admission and discharge by means of the bioimpedance analyzer of body composition ABC-01 (Medass). The whole-body bioimpedance measurement procedure was performed after 5 minutes in the supine position with arms and legs abducted from the midline by 30 degrees with the use of standard tetrapolar scheme on the right side of the body with the electrodes placement on ankle and wrist. Resistance (R) and reactance (Xc) values on single 50-kHz frequency were standardized by height (h). The quality of the bioimpedance analyzer calibration was checked with the use of a verifier (an equivalent electrical circuit of the bio-object). Volume status (normal, euvolemia; low, hypovolemia; or high, hypervolemia [mild, moderate, or severe]) was defined by graphical results of R/h and Xc/h depending on deviation from validated BIVA data in the normal population.

Liver Histology

Histologic features of livers of 7 in-hospital deceased patients with known baseline LS were examined by a pathologist blinded to the clinical cases. Histologic evaluation was performed with the use of hematoxylin-eosin and Mallory trichrome−stained sections. The degree of centrilobular fibrosis, which is a sign of cardiac hepatopathy, and a previously described congestive hepatic fibrosis score (CHFS)[21] were assessed.

Clinical Outcomes

Incidences of all-cause death or heart transplantation, HF readmission, and their combination were considered as a clinical study end points. The end point was assessed by structured telephone contacts with the patient or family members during 12 months of follow-up after discharge. In case of several HF rehospitalizations, the time to the first event was included in the survival analysis.

Statistical Analysis

Continuous normally distributed variables are presented as mean ± SD, asymmetrically distributed as median and interquartile range (IQR), and categoric data as percentage. Correlations of LS with clinical congestion signs and BIVA parameters were examined with the use of Spearman correlation coefficient. Variables were compared between 2 groups with the use of Mann-Whitney U test and among 3 or more groups with the use of Kruskal-Wallis H test. $P < .05$ was considered to be significant for 2-sided tests and $P < .017$ for comparisons of 3 independent groups according to Bonferroni correction. Differences by categoric data were analyzed with the use of Pearson chi-square test (χ^2). Significance of continuous variable changes during the hospital stay was assessed by means of Wilcoxon signed-rank test and significance of categoric variables changes by McNemar test. Kaplan-Meier method was used for assessment of cumulative incidence of long-term clinical outcomes. Survival curves were compared by means of log-rank test. Univariable Cox proportional hazards regression was performed for identification of variables related to outcomes in our study population. Furthermore, relevant univariate parameters with P values <.05 were added to LS in the multivariable Cox proportional hazards regression analysis with the use of the stepwise Wald forward-selection method, additionally adjusted for age and sex. The most significant variable among several variables for the same parameter was chosen. Furthermore, several clinically relevant factors and factors previously proved to have relationships with outcomes in HF (age, sex, ejection fraction, right ventricular end-diastolic diameter, IVC diameter, log N-terminal pro−B-type natriuretic peptide, body mass index, and alcohol abuse) were forced in the multivariable Cox regression analyses to confirm LS independent significance. In addition, Cox regression models based only on clinical congestion at discharge and its combination with residual congestion according to BIVA or LS at discharge >5 kPa were constructed. Model quality changes were assessed by means of omnibus tests of model coefficients and additionally with the use of area under the receiver operating characteristic curve (AUC). A 2-sided P value of <.05 was selected as the threshold for statistical significance. All statistical analysis was performed with the use of Statistica (version 8.0; Statsoft) and SPSS (version 22.0).

Results

Study Population

Among the 1320 patients hospitalized from February 2017 to September 2018, 172 met the study inclusion and

exclusion criteria. Of them, 7 patients (4.1%) died during the hospital stay and had LS measurements only on admission. In 16 cases (9.3%) baseline LS measurements did not meet the quality threshold or failed. Demographic and clinical characteristics of 149 patients with quality LS measurements on admission and discharge are presented in Table 1. We found association of higher LS with male sex, lower left ventricular ejection fraction, higher level of total and direct bilirubin, and trend toward an increase of N-terminal pro−B-type natriuretic peptide and incidence of alcohol abuse. No other statistically significant differences were found in demographics, clinical characteristics, and use of potentially hepatotoxic drugs across the different LS groups (Table 1). The majority were congested as measured by BIVA (mild, moderate, and severe in 13.4%, 26.2%, and 39.6% of cases, respectively), and in 20.8% of patients euvolemia was diagnosed.

The mean length of stay was 9.3 ± 2.8 days, and over the duration of hospitalization all patients reported improvement of symptoms congestion with concomitant decrease

Table 1. Baseline Clinical Characteristics (n = 149)

Parameter	All groups (n = 149)	LS ≤5 kPa (n = 21)	LS 5−13 kPa (n = 58)	LS >13 kPa (n = 70)	P Value*
Male	104 (70)	9 (42.9)	42 (72.4)	53 (75.7)	.014
Age, y	69 ± 12	72 ± 9	69 ± 11	68 ± 13	.494
NYHA functional class					
II	8 (5.4)	2 (9.5)	4 (6.9)	2 (2.9)	.383
III	80 (53.7)	10 (47.6)	35 (60.3)	35 (50)	
IV	61 (40.9)	9 (42.9)	19 (32.8)	33 (47.1)	
Left ventricular EF, %	40 ± 14	47 ± 12	41 ± 14	37 ± 14	.011
Left ventricular EF					
<40%	75 (50.3)	6 (28.6)	26 (44.8)	43 (61.4)	.070
40%−49%	31 (20.8)	7 (33.3)	12 (20.7)	12 (17.1)	
≥50%	43 (28.9)	8 (38.1)	20 (34.5)	15 (21.4)	
Systolic BP, mm Hg	141 ± 28	149 ± 30	142 ± 32	138 ± 24	.304
Diastolic BP, mm Hg	82 ± 14	84 ± 15	82 ± 15	82 ± 12	.613
Heart rate, beats per min	94 ± 24	89 ± 23	92 ± 21	98 ± 26	.226
NT-proBNP, pg/mL	4046 (1956−5456)	2571 (565-3900)	3605.5 (2190−5468)	4331 (2054−5320)	.116
Serum creatinine, μmol/L	104 (91−133)	103 (88−121)	105 (89−135)	106 (92−135)	.483
GFR, mL/min/1.73 m²	53.8 (43.5−69.4)	49.8 (41.7−63)	55.8 (43.6−69.4)	53.6 (43.5−69.5)	.720
GFR <60 mL/min/1.73 m²	85 (57)	14 (66.7)	32 (55.2)	39 (55.7)	.629
AST, U/L	25.3 (19.6−34)	22.7 (17.5−26.6)	25.8 (19−35.2)	25.8 (21−35.1)	.135
ALT, U/L	21 (15−30)	18.9 (15−24)	23.3 (14.9−35.4)	20.8 (15−28.5)	.222
Total bilirubin, μmol/L	19.6 (13.2−27)	15.4 (11.5−21.8)	16.9 (12.2−22.3)	23.9 (18−36.7)	<.001
Direct bilirubin, μmol/L	6 (3.2−9.6)	3.2 (3−5)	4.6 (2.8−7)	8.2 (4.4−13)	<.001
Hypertension	139 (93.3)	19 (90.5)	56 (96.6)	64 (91.4)	.441
Coronary heart disease	92 (61.7)	15 (71.4)	36 (62.1)	41 (58.6)	.567
History of myocardial infarction	71 (47.7)	12 (57.1)	28 (48.3)	31 (44.3)	.581
Atrial fibrillation	96 (64.4)	11 (52.4)	36 (62.1)	49 (70)	.298
Diabetes mellitus	61 (40.9)	8 (38.1)	22 (37.9)	31 (44.3)	.737
Chronic kidney disease	34 (22.8)	7 (33.3)	13 (22.4)	14 (20)	.441
Chronic anemia	36 (24.2)	4 (19)	11 (19)	21 (30)	.293
Alcohol abuse	43 (28.9)	5 (23.8)	12 (20.7)	26 (37.1)	.106
Acrocyanosis	70 (47)	6 (28.6)	28 (48.3)	36 (51.4)	.178
Orthopnea	110 (73.8)	13 (61.9)	43 (74.1)	54 (77.1)	.378
Pulmonary rales	125 (83.9)	14 (66.7)	50 (86.2)	61 (87.1)	.068
Jugular venous distension	41 (27.5)	1 (4.8)	13 (22.4)	27 (38.6)	.005
Hepatomegaly	90 (60.4)	1 (4.8)	32 (55.2)	57 (81.4)	<.001
Ascites	28 (18.8)	0 (0)	6 (10.3)	22 (31.4)	<.001
Peripheral edema	136 (91.3)	15 (71.4)	52 (89.7)	69 (98.6)	<.001
RV EDD, cm	3.2 (3−4)	3 (2.8−3)	3.1 (3−4)	3.4 (3.0−4.1)	<.001
RV EDD >3 cm	83 (55.7)	3 (14.3)	29 (50)	51 (72.9)	<.001
PAP, mm Hg	48 (35−64)	38 (34−46)	43 (34−54)	56.5 (45−68)	<.001
Tricuspid regurgitation					
Absence	24 (16.1)	3 (14.3)	14 (24.1)	7 (10)	.001
Mild	53 (35.6)	13 (61.9)	24 (41.4)	16 (22.9)	
Moderate	63 (42.3)	5 (23.8)	17 (29.3)	41 (58.6)	
Severe	9 (6)	0 (0)	3 (5.2)	6 (8.6)	
IVC diameter, cm	2.2 (2.0−2.5)	2.0 (1.8−2.0)	2.0 (2.0−2.5)	2.5 (2.0−2.6)	<.001
IVC dilation	79 (53)	3 (14.3)	24 (41.4)	52 (74.3)	<.001
IVC collapsibility	53 (35.6)	13 (61.9)	26 (44.8)	14 (20)	<.001

Values are expressed as n (%) of patients, mean ± SD, or median (interquartile range), depending on variable distribution.

LS, liver stiffness; NYHA, New York Heart Association; EF, ejection fraction; BP, blood pressure; NT-proBNP, N-terminal pro−B-type natriuretic peptide; GFR, glomerular filtration rate; AST, aspartate transaminase; ALT, alanine transaminase; RV EDD, right ventricular end-diastolic diameter; PAP, pulmonary artery pressure; IVC, inferior vena cava.

*Differences between groups defined by liver stiffness values.

of congestion score from 4 (1−6) to −1 (-2 to 1) points, (*P* < .001), weight from 89 ± 20 kg to 84 ± 19 kg (absolute decrease -3 kg [-7 to -2], relative decrease -4.3% [-7.6 to -2.1]; *P* < .001). 109 patients (73.2%) were free from clinical congestion at discharge.

Mean R/h and Xc/h increased, respectively, from 248 ± 62 Om/m and 21 ± 9 Om/m to 288 ± 56 Om/m and 26 ± 7 Om/m (*P* < .001), meaning decrease of volume overload. At discharge, 71 patients (47.7%) achieved euvolemia as measured by BIVA, 75 (50.3%) still had congestion (mild, moderate, and severe in 17.4%, 26.2%, and 6.7% of cases, respectively), and in 3 cases (2%) hypovolemia was diagnosed without clinical implications.

Liver Stiffness Changes During Hospitalization

On admission the median value of LS was 12.2 kPa (6.3−23.6) (range 3.3−75), and normal LS was observed in 21 cases (14.1%). LS consistent with liver fibrosis and cirrhosis values were measured in 58 (38.9%) and 70 (47%) patients, respectively. During hospitalization, LS median decreased to 8.7 (5.9−14.4) kPa (absolute decrease -2.8 kPa [-9.0 to 0.2], relative decrease -20.7% [-49.7 to 4.3]; *P* < .001; Fig. 2). At discharge normal LS was observed in 24 patients (16.1%), LS 5−13 kPa in 80 (53.7%), and LS >13 kPa in 45 (30.2%); *P* < .001.

Patients with baseline LS >13 kPa versus LS ≤13 kPa had more often a history of alcohol abuse (37.1% vs 21.5%; *P* = .036), and baseline LS values were very weakly correlated with history of alcohol abuse (*r* = 0.17; *P* = .042). Higher levels of LS on admission (17.1 kPa [7.5−36.3] vs 11.1 kPa [6.1−21]; *P* = .043) and the same tendency at discharge (10.2 kPa [6.6−17] vs 7.9 kPa [5.6−13.1]; *P* = .086) were revealed in patients with known alcohol abuse compared with patients without alcohol abuse. However, there was no difference in LS changes from admission to discharge. Further, 43 patients (28.9%) with alcohol abuse had more prominent baseline congestion according to clinical score (5 [3−7]
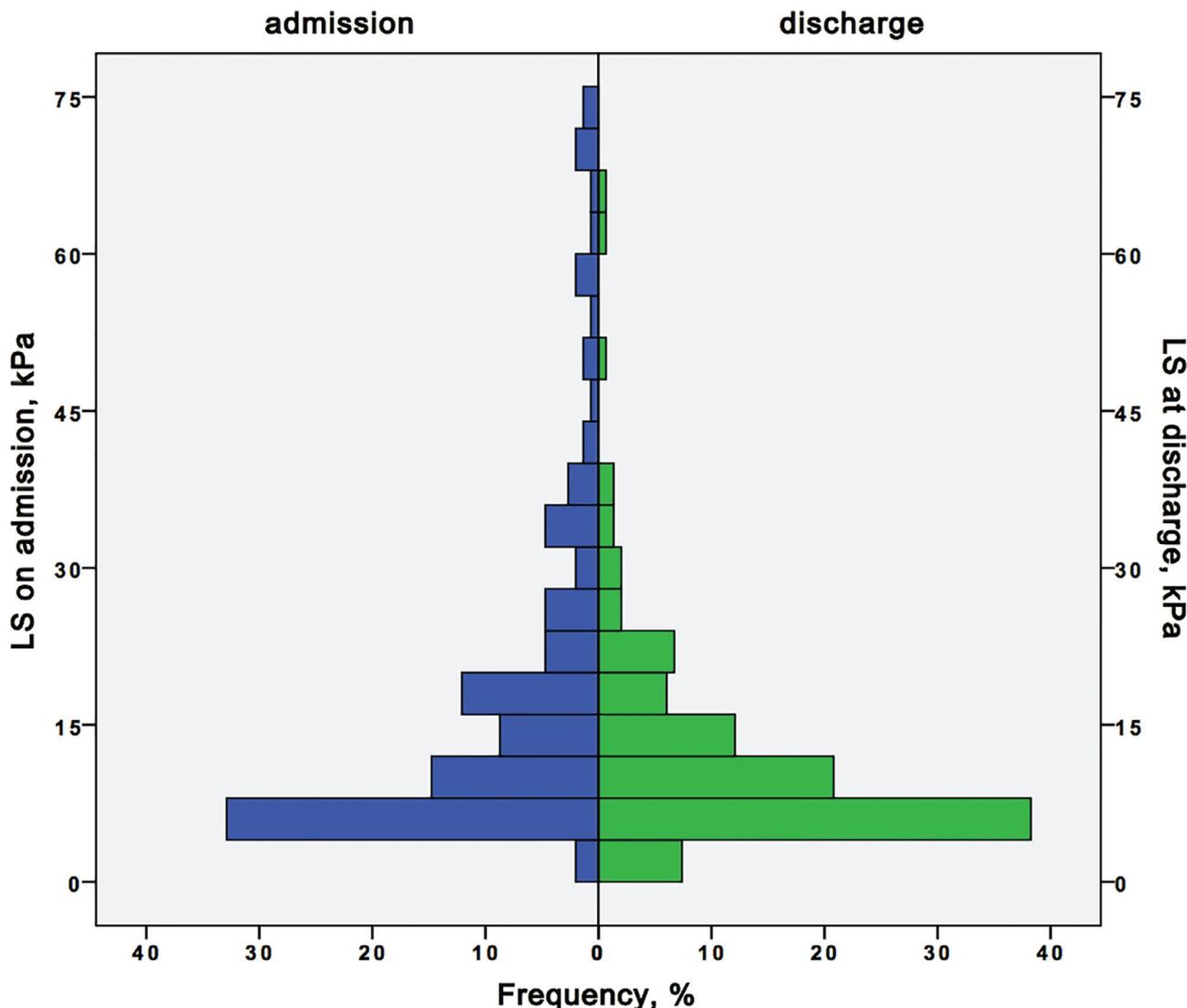

Fig. 2. Liver stiffness (LS) histograms on admission and discharge.

vs 4 [1−5] points; $P = .029$) and BIVA (R/h 226 ± 57 Om/m vs 257 ± 61 Om/m [$P = .003$], Xc/h 19 ± 7 Om/m vs 22 ± 9 Om/m [$P = .038$]). Weak and moderate correlation was found between baseline LS and AST ($r = 0.23$; $P = .007$), total bilirubin ($r = 0.38$; $P < .001$), direct bilirubin ($r = 0.48$; $P < .001$).

(20% and 7.5%, respectively, vs 0%; $P = .017$) and edema (53.3% and 28.8% vs 8.3%; $P < .001$). In patients with clinical congestion versus without, higher LS was revealed (12.6 kPa [9.7−17.8] vs 7.1 kPa [5.4−12.4]; $P < .001$).

Associations of Liver Stiffness With Clinical Congestion and Echocardiographic Data

Baseline liver stiffness moderately correlated with clinical congestion score on admission ($r = 0.53$; $P < .001$) and at discharge ($r = 0.40$; $P < .001$). Clinical signs of right-side congestion and right ventricular dysfunction with the use of echocardiography were more common in patients with elevated baseline LS values (Table 1). LS correlated with hepatomegaly ($r = 0.47$; $P < .001$), ascites ($r = 0.39$; $P < .001$), jugular venous distension ($r = 0.32$; $P < .001$), edema ($r = 0.28$; $P < .001$), IVC diameter ($r = 0.49$; $P < .001$), moderate-to severe tricuspid regurgitation ($r = 0.41$; $P < .001$), pulmonary artery systolic pressure ($r = 0.38$; $P < .001$), and right ventricular diameter ($r = 0.36$; $P < .001$). Notably, groups did not differ in acrocyanosis, orthopnea, or pulmonary rales (Table 1).

LS absolute decrease was associated with changes in clinical congestion score ($r = 0.33$; $P < .001$). At discharge, patients with midrange and high LS compared with normal LS were more likely to have jugular venous distension

### Associations of Liver Stiffness With BIVA Parameters

On both admission and discharge, an increase of congestion as measured by BIVA was associated with an increase of LS, and similarly, decrease of LS was associated with a decrease in congestion as determined with the use of BIVA ($P < .001$ for all comparisons) (Fig. 3). Patients with the same congestion status according to BIVA on admission and discharge had almost similar LS values (Fig. 3).

Baseline R/h and Xc/h values correlated with LS on admission ($r = -0.50$ and -0.59; $P < .001$), and achieved R/h and Xc/h correlated with LS at discharge ($r = -0.34$ and -0.39; $P < .001$). More prominent improvement of LS was observed in patients with baseline severe congestion, and similarly there was a more prominent improvement of BIVA parameters in patients with high LS values. Significant correlations of LS decrease were found with weight decrease and R/h and Xc/h increase (Fig. 3). Patients with prominent LS at discharge had higher incidence of residual congestion according to both clinical scale and BIVA at discharge and vice versa ($P < .001$; Fig. 4).
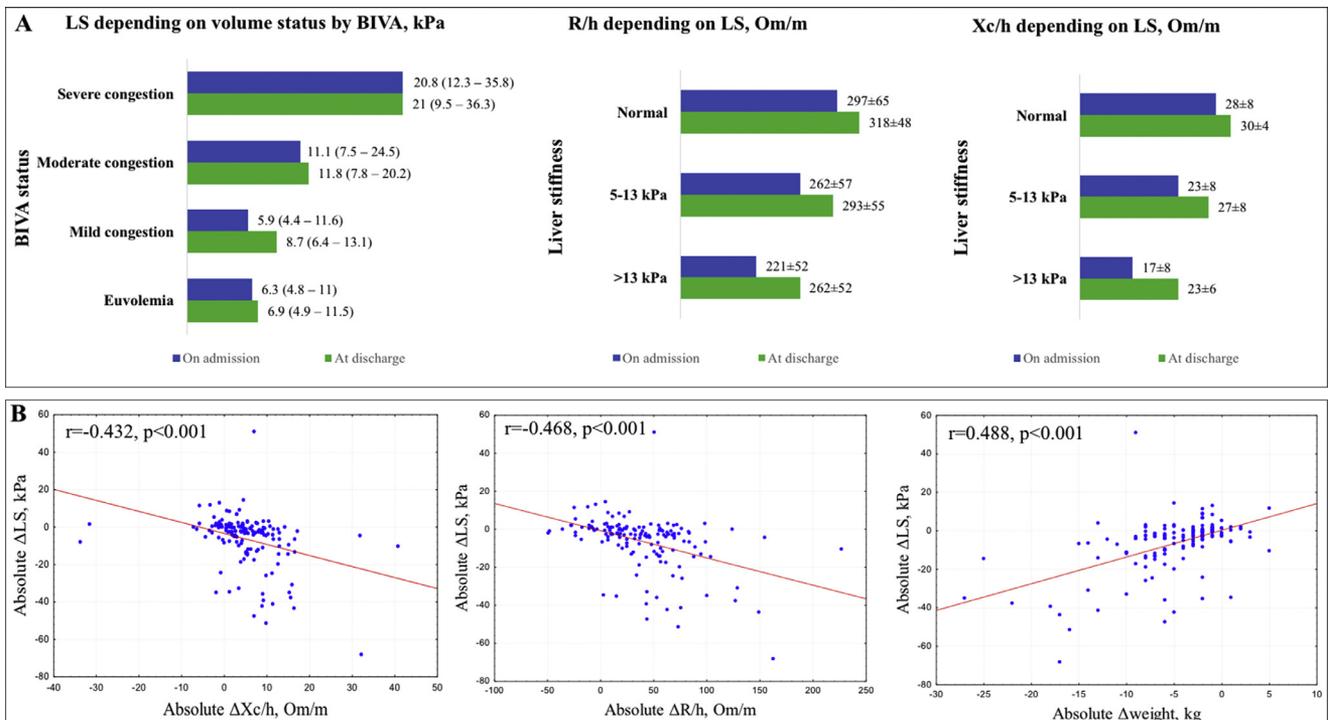
Fig. 3. (A) Liver stiffness values (kPa) on admission and discharge according to congestion by BIVA on admission and discharge respectively and BIVA parameters depending on liver stiffness on admission and discharge. Values of R/h and Xc/h are expressed as mean ± SD, LS values a median (interquartile range). LS, liver stiffness; R/h and Xc/h, resistance and reactance values standardized by height; BIVA, bioimpedance vector analysis. (B) Correlations of absolute LS changes with changes of BIVA parameters and weight. Δ, absolute changes; r, Spearman rank correlation coefficient.
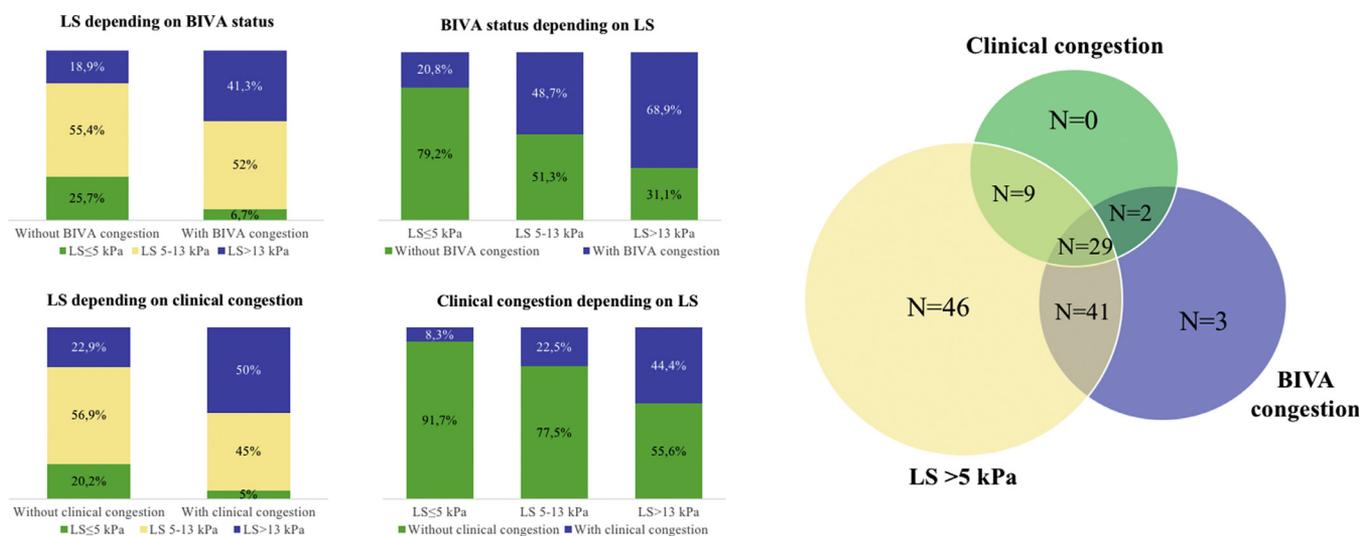
Fig. 4. Associations between liver stiffness and congestion status according to clinical congestion scale and BIVA at discharge. Forty patients (47.6%) out of 84 with at least 1 clinical sign of congestion at discharge had criteria for the congestion according to the bedside assessment scale (score ≥1). LS, liver stiffness; BIVA, bioimpedance vector analysis.

Comparisons of Liver Stiffness With Histology Features

Postmortem histologic assessment of liver specimens of 7 deceased patients revealed advanced fibrosis patterns (Fig. 5): CHFS 2B score (moderate portal and central zone fibrosis with accentuation of fibrosis in the portal zone) was revealed in 4 cases with corresponding levels of LS from 8 to 25.7 kPa. In 2 cases with LS 20.4 and 8 kPa, CHFS 3 (bridging fibrosis) was noted. In 1 case of the worse pattern of CHFS 4 (liver cirrhosis), the corresponding liver stiffness was 17.3 kPa (Supplemental Table 1). In all slides, sinusoidal and central vein dilation, mononuclear infiltration, and bile ductular proliferation were observed. Centrilobular hepatocyte necrosis and hemorrhages were noted in 4 cases.

Associations of Liver Stiffness and Clinical Outcomes

During a mean follow-up of 289 ± 108 days, 4 patients were lost to follow-up. Among 145 patients (97.3%) with known outcomes data 28 (19.3%) died and 1 (0.7%) underwent heart transplantation; 42 HF rehospitalizations (29%) were reported.

Kaplan-Meier analysis revealed that LS >13 kPa on admission and LS >5 kPa at discharge were associated with higher probability of negative outcomes with statistical significance for HF readmission and the composite end point (Fig. 6). LS at discharge as a continuous variable was associated with 1-year all-cause death (hazard ratio [HR] per 1 kPa increase 1.028, 95% confidence interval [CI] $1.000-1.057$; $P = .049$), remaining significant in the multivariable Cox regression models (Supplemental Table 2). LS at discharge (HR per 1 kPa increase 1.028, 95% CI $1.005-1.051$, $P = .016$) independently predicted HF readmission after adjustment for sex, age, hepatomegaly on admission, alcohol abuse, right ventricular dilation, IVC diameter, and severe tricuspid regurgitation (Supplemental Table 3). The composite end point was also significantly associated with LS at discharge (HR per 1 kPa increase

1.042, 95% CI $1.019-1.066$; $P < .001$; Supplemental Table 4). The relationship of LS with long-term outcomes was independent from alcohol abuse and other clinically relevant variables (Supplemental Tables $2-4$).

According to Kaplan-Meier survival analysis, both clinical and BIVA congestion at discharge were associated with higher 12-month all-cause mortality and the composite end point (Supplemental Fig. 1). Quality changes between congestion models based only on clinical status or including LS >5 kPa or residual congestion according to BIVA at discharge for the study end points were assessed by means of omnibus tests of model coefficients as well as AUC analysis, as presented in Supplemental Table 5. Residual congestion at discharge according to BIVA significantly added to the clinically based model for prediction of all-cause death risk, and LS >5 kPa at discharge significantly added to the clinically based model for prediction of HF readmission and the composite end point.

Discussion

To the best of our knowledge this is the first comprehensive and one of the largest studies exploring the significance of TE-based measurements in patients with ADHF. We found a moderate correlation between LS measured by means of TE and clinical congestion scale and BIVA-measured whole body volume status. We found discordance between TE-based LS and actual histologic appearance of livers, suggesting a potential role of TE as a tool to measure and trend congestion in ADHF. We demonstrated differences in negative outcomes probability in groups of patients depending on LS value on both admission and discharge, but only LS at discharge predicted 12-month all-cause death or heart transplantation, HF readmission, and the composite end point in multivariable Cox regression analysis. Furthermore, we showed lack of agreement between the analyzed
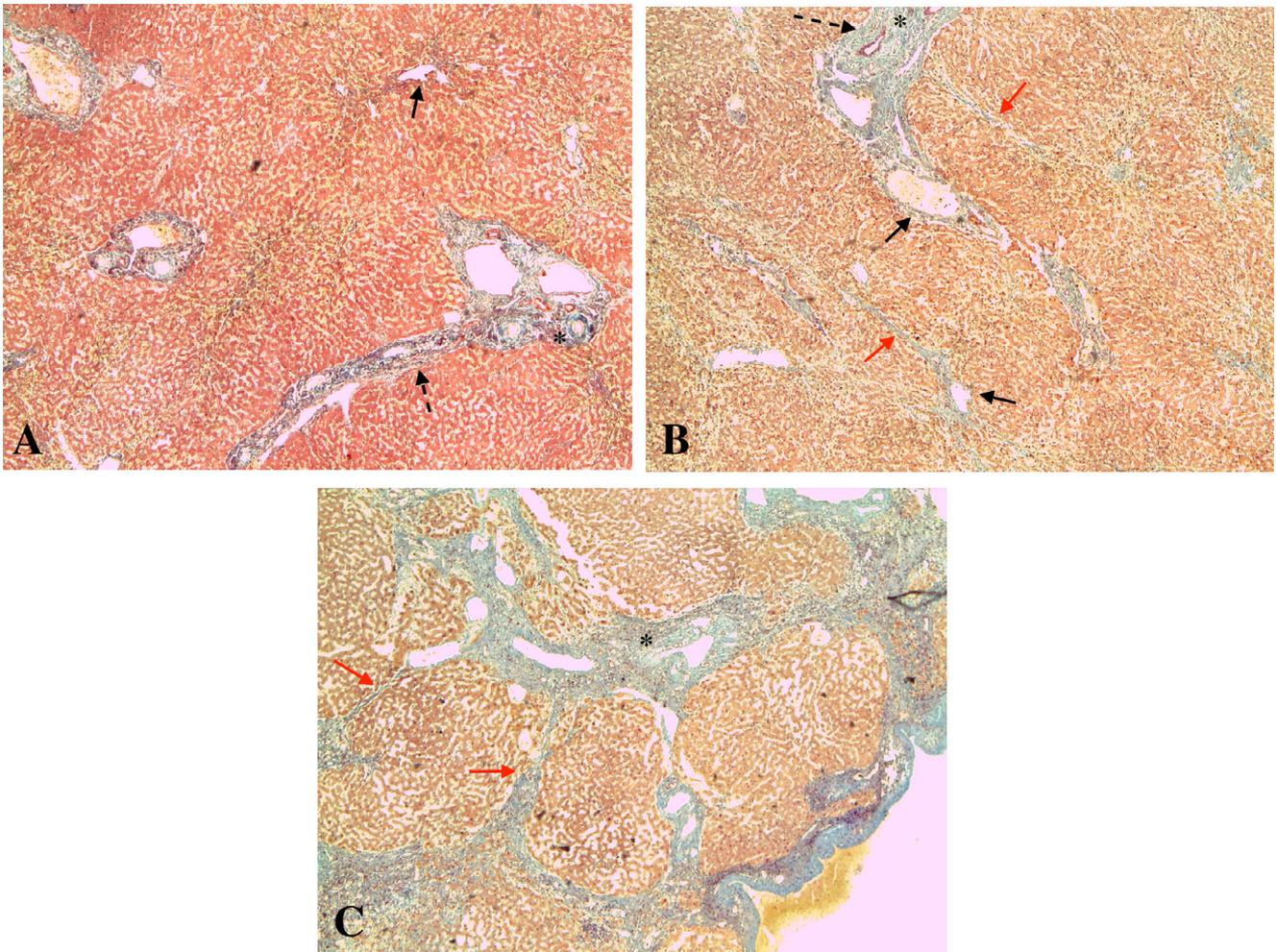
Fig. 5. Liver biopsies in patients with decompensated heart failure. Mallory trichrome stain, original magnification *x*4. Sinusoidal and central vein dilation, central zone (*black arrows*), periportal fibrosis (*dashed arrows*), and bile ductular proliferation (*asterisks*). (A) CHFS 2B (moderate portal fibrosis and central zone fibrosis, with accentuation of fibrosis at portal zone); (B) CHFS 3 (bridging fibrosis, septus between portal tracts and central veins (*red arrows*)); (C) CHFS 4 (cirrhosis), changes in liver lobules architectonic, wide fibrous connective tissue bridges between portal tracts, regenerative nodules of hepatocytes are presented. CHFS, congestive hepatic fibrosis score.

congestion status metrics for proof of decongestion and long-term outcomes.

Previously published animal data indicated that LS has diagnostic utility in the assessment of elevated CVP and liver congestion. In an experimental study in pigs, Millonig et al. showed LS dependency on hemodynamic changes in the hepatic circulation after IVC clamping and then after stepwise increase of intravenous pressure in totally vascular-isolated liver, which resulted in a subsequent increase of LS.[13] Findings in animals were confirmed by human studies suggesting that TE could serve as a novel noninvasive modality to assess congestion in patients with HF.[13-18] LS was reported to correlate with IVC dilation ($r = 0.7$; $P = .03$) in decompensated HF,[13] right atrial pressure ($r = 0.95$; $P < .0001$) in patients who underwent right-sided cardiac catheterization,[16] preoperative CVP ($r = 0.515$; $P < .01$), B-type natriuretic peptide ($r = 0.399$; $P < .05$), and C-reactive protein ($r = 0.524$; $P < .01$) in candidates for left ventricular assist device therapy.[14]

In our real-world sample of patients hospitalized for HF, we found a high incidence (86%) of baseline abnormal LS, which was similar to previous studies.[13-15,22] The obvious explanation is passive liver congestion in the setting of congestive HF impairing shear wave distribution and leading to eventual increase of LS. Importantly, we did not obtain a higher rate of LS measurements failure or unreliable results in these population compared with TE in adult patients with suspected chronic liver disease.[23] Even though patients had no primary significant liver disease or acute hepatitis in our study, a large proportion of patients with a history of alcohol abuse had demonstrated higher values of LS on both admission and discharge. However, the groups with and without alcohol abuse had no difference in LS change, indicating that LS measurement during hospitalization could apply to a broader spectrum of acute HF patients, including patients with ongoing toxic liver exposure.

In this study, elevated values of baseline LS were associated with clinical signs of right-sided HF, right ventricular
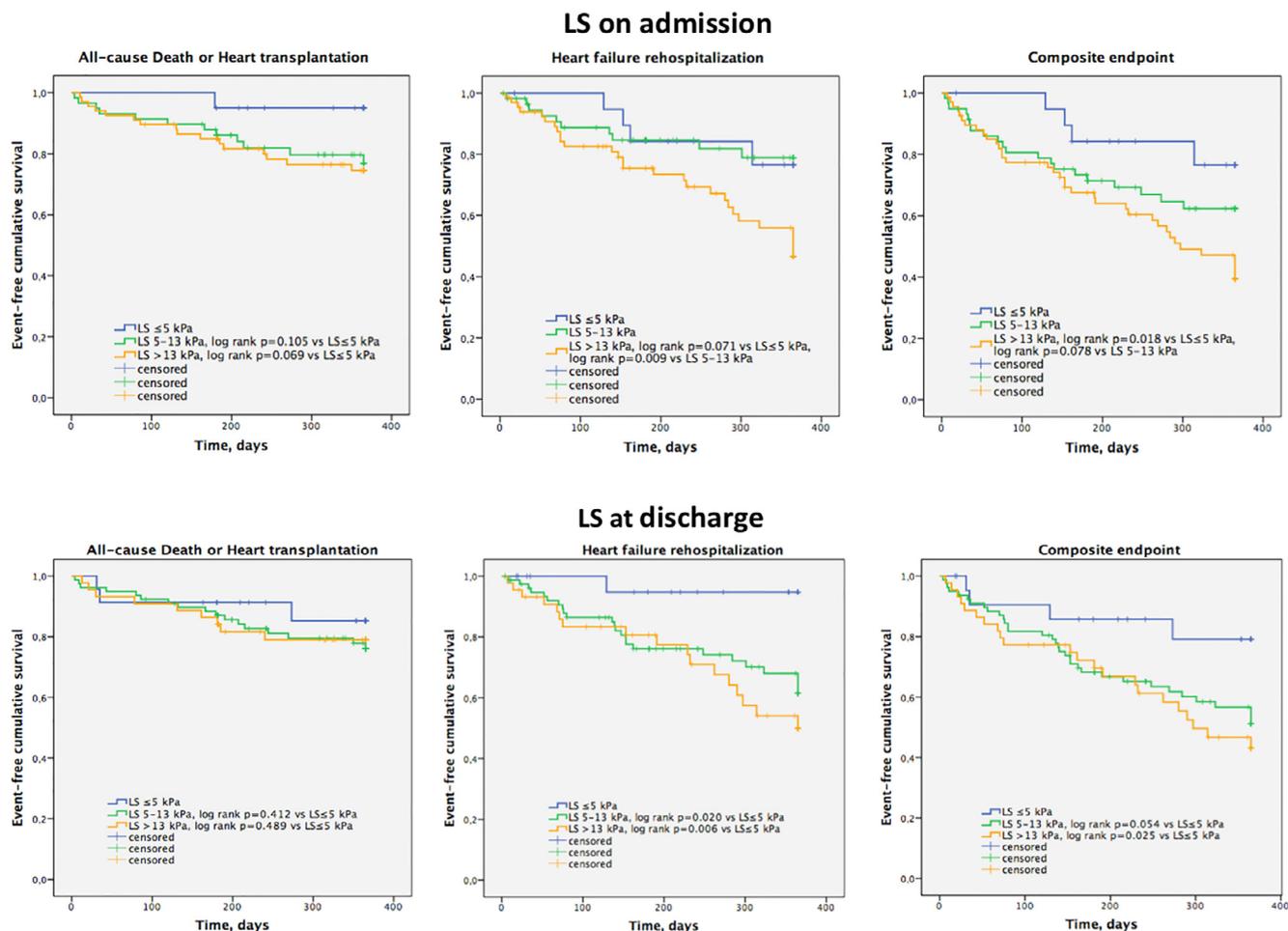
Fig. 6. Kaplan-Meier survival curves for study end points by liver stiffness values on admission and at discharge. LS, liver stiffness; HF, heart failure.

and IVC dilation, and tricuspid regurgitation as determined with the use of echocardiography, and LS moderately correlated with total and direct bilirubin—known but nonspecific markers of liver congestion.[2] The same results were found in a recently published study by Taniguchi et al.[18]

We also observed that LS tracks with clinical and BIVA-based decongestion. Our data are similar to previous smaller studies showing significant LS improvement in parallel with various other markers of clinical decongestion[13−15,22] and in contrast to the study by Hopper et al., that demonstrated the robustness of the LS in the setting of acute shifts in volume status.[24] We demonstrated that patients with baseline higher volume overload had a higher LS decrease. Intriguing data about almost similar LS in patients with the same degree of congestion according to BIVA on admission and discharge indicate the steadiness of LS values in case of unchanged volume status and potentially could propose cutoff values of LS for the grading of liver congestion. LS in euvolemia according to BIVA at discharge was similar to LS in clinically decongested patients. Taken together with associations of LS at discharge with risk of negative clinical outcomes, these data also signify that decrease of LS could be one of the

treatment targets in volume management strategy of decompensated HF patients.

Clinical Implications

Significant correlations of changes of LS with changes of clinical congestion, weight and BIVA parameters in our study emphasize that LS reflects congestion in decompensated HF and could be used as a noninvasive method for quantification and monitoring of congestive hepatopathy. This concept is supported by the absence of obvious associations of LS with corresponding severity of fibrosis according to histology. Notably, the high proportion of patients with abnormal LS at discharge despite parallel significant improvement of clinical symptoms and decongestion according to BIVA could be of particular significance. Our study identified that only 25.7% and 20.2% of patients free of BIVA and clinical congestion, respectively, had normal LS at discharge. This finding suggests that (1) elevated LS reflects persistent concealed congestion on discharge or (2) elevated LS reflects a combination of hepatic congestion from elevated hepatic venous pressure coupled with actual

liver fibrosis. Therefore, measurement of LS trajectory in the course of decompensated HF could provide information about reversibility of cardiogenic liver injury, identifying 2 phenotypes of the organ damage: "acute" with eventual normalization of LS and "acute on chronic" with persisting high LS observed at discharge. We may speculate that the latter scenario could be either a marker of presence of true liver dysfunction or much more likely a marker of residual liver congestion, similar to pre-discharge delayed reduction of natriuretic peptides and LV filling pressure owing to inadequate hemodynamic decongestion despite clinical compensation.[25] Numerous acute HF studies have demonstrated the high incidence of incomplete decongestion with the use of different indicators and its independent negative post-discharge prognosis.[26–30] Recent investigations[18] also have suggested that the presence of high values of LS at discharge is associated with worse outcomes in patients with HF. According to our results, higher LS at discharge is expected to be associated with negative outcomes, particularly a higher risk of HF readmission. Taken together, these data provide a new perspective for TE as a useful method of liver assessment and assisting with HF management. It should be emphasized, however, that LS increase is a non-specific sign and it would be difficult to use the method for the differential diagnosis of liver dysfunction. But in the clinical setting of an already established diagnosis of HF, especially when multiple confounding factors are excluded, this limitation is not so relevant and LS increase and its associations with negative prognosis in ADHF may be interpreted through the prism of 2 interrelated and inseparable mechanisms of congestive hepatopathy: parenchymal congestion and congestion-induced fibrosis, both related to unfavorable outcomes.

Finally, lack of agreement between different metrics of residual congestion and its prognostic significance was observed. Analysis of the contributing role of different methods revealed no patients with clinical congestion only, and the vast majority of such cases were identified using though quite strict criteria of LS >5 kPa or BIVA. These data support the current proposed concept that clinical signs are a tip of the iceberg of hemodynamic congestion. It is important to note that BIVA-measured whole body congestion and TE-measured LS increase were associated with diverse negative outcomes, also signifying heterogeneity of congestion in its entirety. The study results again emphasize the current lack of consensus and need for further larger randomized studies to provide powerful algorithms for precise diagnostic and prognostic congestion evaluation.

Study Limitations

A potential limitation is the single-center design of this study. LS was assessed in routine clinical practice in a diverse clinical spectrum of patients in whom different concomitant factors could potentially have had an impact on TE results, especially alcohol abuse. Because of a high proportion of such patients, we did not exclude them and

performed a separate analysis for LS associations in a non-alcohol subgroup as well as forced this factor into multivariable models. LS change data outliers, even if not influential, also confirmed that multiple circumstances should to be taken into account with LS interpretation. Currently there are no validated threshold values for LS in patients with HF. Notably, different LS cutoffs have been proposed for cirrhosis due to primary liver diseases, depending on etiology, ranging from 9.7 kPa in hepatitis B virus infection to 22.7 kPa.[12] In this study we used guideline-recommended approximate cutoff values of 5 kPa for normal LS and 13 kPa for cirrhosis.[12] Furthermore, the analysis of associations of LS on admission with histologic autopsy data is limited in its validity because of the time mismatch between LS measurement and autopsy. However, an invasive liver biopsy appeared to be unethical and it is reasonable to think that during hospital stay no significant changes of liver fibrosis degree would occur. To confirm the lack of relationship of LS with intrinsic liver fibrosis, it would be necessary to do the biopsy at the same time as TE, for example, in an advanced HF population in whom liver biopsy is frequently a part of routine assessment before left ventricular assist device therapy or transplantation. Also, we assessed survival with the use of only laboratory and echocardiography variables on hospitalization, but consideration of different metrics of congestion would be stronger in case of available echocardiography with IVC assessment data at discharge, which was not performed in this study. We were also limited by incomplete LFTs panel in all patients to compare their prognostic significance with LS in a multivariable model.

Importantly, the small study population and low event number in general limits the ability to perform an appropriate multivariable analysis and creates a potential risk for statistical bias. Therefore we can not rule out residual confounding from unknown or unmeasured variables. Next, estimation of LS >5 kPa prognostic significance compared with clinical and BIVA-based congestion at discharge seems to be imprecise, as characterized by the too-wide CI. This underscores our concerns about strictness of the LS 5 kPa cutoff value and the requirement for further research in this area.

Still, our focus was on the relationship of LS with congestion, and although the survival analysis results were promising, they still need refinement in larger populations. Based on the above-mentioned statistical limitations we can suggest only a hypothesis-generating nature for the reported data. Generalizability of our findings, given the small selected population, is restricted and should be confirmed in other HF populations and countries.

Conclusion

In this study, LS increase as measured with the use of TE was modestly associated with congestion, tracked well with decongestion, and provides information beyond the fibrotic state of the liver. LS could be a complimentary marker of congestion/decongestion, provide valuable information on

underlying liver disease in patients with HF, and indicate a subgroup of HF patients at higher risk of post-discharge negative outcomes beyond clinical signs and traditional risk predictors.

Acknowledgments

Disclosures

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.01.020.

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