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ORIGINAL ARTICLE

Impact of admission liver stiffness on long-term clinical outcomes in patients with acute decompensated heart failure

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Abstract

Liver stiffness (LS) has been reported to be a marker of liver congestion caused by elevated central venous pressure in heart failure (HF) patients. Recent studies demonstrated that LS could be non-invasively measured by virtual touch quantification (VTQ). However, its prognostic implication in patients with acute decompensated heart failure (ADHF) is unclear. This study sought to determine whether LS measured by VTQ could be a determinant of subsequent adverse events in ADHF patients. We prospectively recruited 70 ADHF patients who underwent LS measurement by VTQ on admission in our university hospital between June 2016 and April 2018. The primary outcome of interest was the composite of all-cause mortality and worsening HF. During a median follow-up period of 272 (interquartile range 122–578) days, there were 26 (37%) events, including 5 (7%) deaths and 21 (30%) cases of worsening HF. The c-index of LS for predicting the composite of adverse events was 0.77 (95% CI 0.66–0.88), and the optimal cut-off value of LS was 1.50 m/s. Adverse events were more frequently observed in patients with high LS (≥ 1.50 m/s) compared to those with low LS (< 1.50 m/s). Multivariable Cox regression analyzes revealed that higher LS was independently associated with increased subsequent risk of adverse events after adjustment for confounders. In conclusion, high admission LS was an independent determinant of worse clinical outcomes in patients with ADHF. This finding suggests that LS on admission is useful for risk stratification of patients with ADHF.

Keywords Acute decompensated heart failure · Liver stiffness · Prognosis · Venous congestion

Introduction

The prevalence and incidence of heart failure (HF) has markedly increased due to aging of the population, along with multiple therapeutic innovations in the management of cardiovascular diseases [1]. Prognostication of patients with HF could help to improve outcomes by identifying high risk patients who might potentially benefit from intensive inpatient and outpatient monitoring and early referral for advanced HF therapy.

Amongst factors related to adverse HF outcomes, central venous pressure (CVP) is one of the strongest prognostic indicators [2, 3]. To measure CVP, invasive right heart catheterization is the gold standard technique. However, its routine use is not recommended because of procedure-related complications such as bleeding and infection, and high healthcare costs [4, 5]. Therefore, accurate and non-invasive estimation of CVP is warranted.

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Liver stiffness (LS) could be a representative marker of liver congestion due to elevated CVP. Several studies have reported that LS non-invasively measured by ultrasound elastography was significantly correlated with CVP in patients with HF [6–8]. We have also reported that LS non-invasively measured by the virtual touch quantification (VTQ) technique was positively correlated with CVP in patients with HF [9]. Recently, LS measured at the time of discharge was useful for risk stratification of hospitalized patients with HF [10]. Nevertheless, the prognostic implication of LS on admission, in the acute decompensated phase, on long-term outcomes in hospitalized patients with acute decompensated HF (ADHF) is unclear. It would be useful for identifying ADHF patients at high-risk who need early intervention and careful monitoring.

Accordingly, the aim of this study was to investigate whether non-invasively measured LS by VTQ on admission could be associated with subsequent adverse events in ADHF patients.

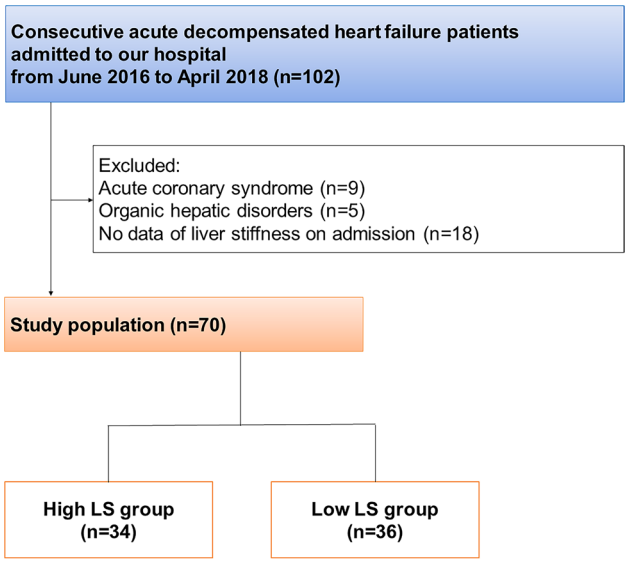

Fig. 1 Flow diagram of present study

Materials and methods

Study design

This was a single-center, observational, prospective study that included all consecutive patients aged more than 20 years requiring hospitalization at our university hospital for the first time with a diagnosis of ADHF between June 2016 and April 2018. ADHF was defined as meeting the Framingham criteria [11]. The study protocol was approved by the Ethics Committee of Hokkaido UniversityHospital (IRB No. 016-0067) and is registered under the Japanese UMIN Clinical Trials Registration (UMIN000023114). The investigation conformed with the principles outlined in the Declaration of Helsinki. All patients gave written informed consent to participate in the study.

Study population

A total of 102 consecutive patients with ADHF were registered in the present study. Patients without measurement of LS on admission ($n=18$) and those with acute coronary syndrome ($n=9$) or organic hepatic disorders ($n=5$) including cirrhosis, hepatocellular carcinoma, hepatitis B or C virus infection, and chronic alcohol abuse were excluded. Ultimately, 70 patients were included in this study (Fig. 1).

Measurement of liver stiffness

LS was measured on admission by VTQ using an ACUSON® S2000 US system (Siemens, Erlangen, Germany) with a convex probe, and was expressed as shear wave velocity [V_s (m/s)]. Imaging of the liver was performed through the right intercostal space with the patient supine and the right arm maximally abducted while holding a normal breath. The probe was held lightly against the body while observing the B-mode image. A 0.6×1.0 cm region of interest devoid of large blood vessels was located 1–2 cm below the organ surface (Fig. 2). The anatomy of the left liver lobe, which is surrounded by the diaphragm, stomach and aorta, affects the use of VTQ, and the right lobe is commonly used for LS measurement using this method. We have demonstrated that there was no difference in LS among segment 5 (S5), S6, S7 and S8 of the hepatic lobe described previously [9]. Therefore, all measurement data of LS were obtained from S5 in the present study. Measurements were repeated 10 times to obtain median V_s values (Fig. 2). Each measurement of LS was expressed as median and interquartile range (IQR). We excluded cases with an IQR to median ratio > 0.30. Inter- and intra-observer reproducibility has been confirmed in our previous study [9].

Echocardiography

Echocardiography was performed on admission using either an Aplio Artida® SSH-88-CV or Aplio® SSA-770A (Toshiba Medical Systems, Tochigi, Japan). Left ventricular ejection fraction (LVEF) was calculated from apical four- and two-chamber views using the biplane method of disks [12]. Images were evaluated by two experienced observers.

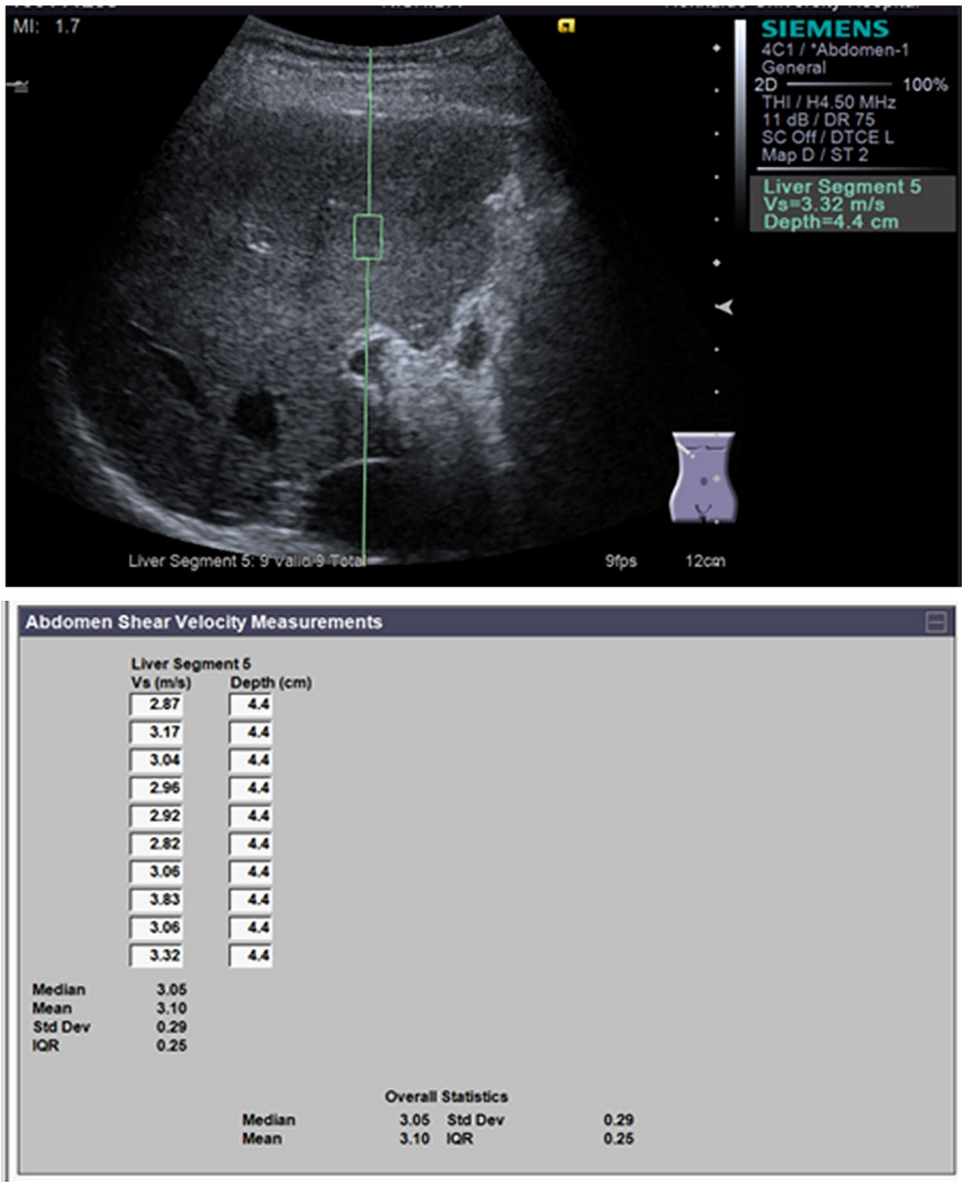

Fig. 2 Virtual touch quantification. A total of 10 valid measurements were performed in every patient and the median value in m/s was calculated

Clinical outcomes

The primary outcome of interest was the composite of all-cause death and worsening HF, which was defined as worsening of symptoms and signs of HF requiring intensification of intravenous therapy or initiation of mechanical support during hospitalization, as used in major acute heart failure clinical trials [13, 14], or readmission because of HF after discharge.

Statistical analysis

Continuous variables are presented as mean ± SD when normally distributed, and as median and IQR when non-normally distributed. Parameters were compared between two groups according to the optimal cut-off value of LS (1.50 m/s) based on receiver operating characteristic (ROC) analysis using unpaired *t* test or Mann–Whitney *U* test for continuous variables and by Chi-squared test or Fisher's exact test for dichotomous variables, when appropriate.

We performed ROC curve analysis to evaluate the discriminatory value of LS for all-cause death and worsening HF. The optimal cut-off value was chosen as the value maximizing sensitivity plus specificity. The cumulative incidence of the composite of all-cause death and worsening HF was estimated by Kaplan–Meier analysis, and log-rank test was performed to assess significance according to the LS cut-off value. To evaluate the influence of LS on all-cause death and worsening HF, we constructed a univariable and two multivariable Cox proportional hazard models as follows. Stepwise selection with a P value of < 0.05 for forward selection was used to select the best

predictive model (Model 1). Adjustment for systolic blood pressure, estimated glomerular filtration rate (eGFR) and serum sodium, which are known to be strong determinants of worse clinical outcomes in HF patients, was performed (Model 2). Discriminative ability of the multivariable model was evaluated with Harrell's c-statistics.

All tests were two tailed, and a value of $P < 0.05$ was considered statistically significant. All analyzes were performed with JMP Pro® 13.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The clinical characteristics of the total 70 studied patients are shown in Table 1. We divided them into two groups according to the optimal cut-off value of LS (1.50 m/s) based on ROC analysis. Patients with high LS (≥ 1.50 m/s) had lower age, eGFR, serum sodium levels, and higher rates of atrial fibrillation, New York Heart Association (NYHA) functional class III or IV and use of diuretics, and higher plasma brain-type natriuretic peptide (BNP) level compared to those without. There were no significant differences between the

Table 1 Baseline characteristics

Variable	Overall ($n=70$)	High LS ($n=34$)	Low LS ($n=36$)	P value
Age, years	62.7 ± 15.5	58.6 ± 15.9	66.6 ± 14.3	0.030
Male, *n* (%)	49 (70)	26 (76)	23 (64)	0.25
BMI, kg/m^2	24.9 ± 6.7	25.0 ± 6.4	24.7 ± 7.0	0.83
Past history, *n* (%)				
Hypertension	19 (27)	7 (21)	12 (33)	0.23
Diabetes	12 (17)	7 (21)	5 (14)	0.46
Atrial fibrillation	27 (39)	20 (59)	7 (19)	0.001
NYHA III or IV, *n* (%)	31 (44)	21 (62)	10 (28)	0.004
Heart rate, bpm	78.9 ± 18.5	79.3 ± 17.7	78.5 ± 19.4	0.85
Systolic BP, mmHg	112.6 ± 25.3	107.4 ± 22.7	117.5 ± 27.0	0.096
LVEF, %	37.4 ± 17.0	33.6 ± 18.1	41.0 ± 15.3	0.068
Etiology, *n* (%)				
DCM	19 (27)	12 (35)	7 (19)	0.136
ICM	11 (16)	3 (9)	8 (22)	0.124
Valvular heart disease	13 (19)	7 (21)	6 (17)	0.67
Others	27 (39)	12 (35)	15 (42)	0.58
Oral medication on admission, *n* (%)				
ACE-I or ARB	43 (61)	21 (62)	22 (61)	0.96
Beta blocker	42 (60)	23 (68)	19 (53)	0.20
Diuretic	48 (69)	31 (91)	17 (47)	< 0.001
Spironolactone	17 (24)	11 (32)	6 (17)	0.126
Laboratory tests				
Hemoglobin, g/dL	12.6 ± 2.2	12.6 ± 2.1	12.6 ± 2.3	0.86
Platelets, 10^4/μL	19.9 ± 6.8	18.6 ± 7.5	21.2 ± 5.9	0.103
eGFR, mL/min	49.9 (37.8–66.0)	41.3 (36.3–60.6)	55.5 (43.6–75.0)	0.039
Sodium, mEq/L	138.2 ± 3.8	137.1 ± 4.0	139.3 ± 3.4	0.014
AST, IU/L	29.0 (22.0–40.3)	31.0 (24.0–42.8)	28.0 (20.0–38.0)	0.160
ALT, IU/L	22.5 (18.0–38.0)	24.0 (19.8–38.0)	21.5 (17.0–40.3)	0.51
Albumin, g/dL	3.9 ± 0.5	3.9 ± 0.5	3.9 ± 0.5	1.0
BNP, pg/dL	568 (170–1110)	642 (444–1191)	409 (115–848)	0.042
CRP, mg/dL	0.32 (0.07–0.83)	0.40 (0.18–1.41)	0.26 (0.05–0.67)	0.075

ACE-I angiotensin-converting enzyme inhibitor, *ALT* alanine aminotransferase, *ARB* angiotensin II receptor blocker, *AST* aspartate aminotransferase, *BMI* body mass index, *BNP* plasma brain-type natriuretic peptide,*BP* blood pressure, *CRP* C-reactive protein, *DCM* dilated cardiomyopathy, *eGFR* estimated glomerular filtration rate, *ICM* ischemic cardiomyopathy, *LS* liver stiffness, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association

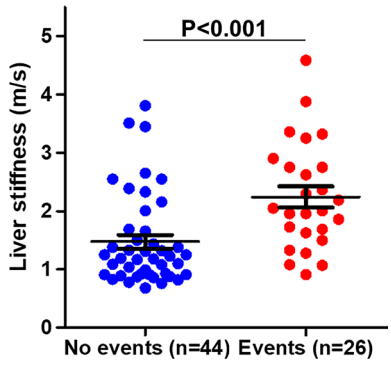

Fig. 3 Liver stiffness on admission in no event group (blue circles, $n=44$) and event group (red circles, $n=26$)

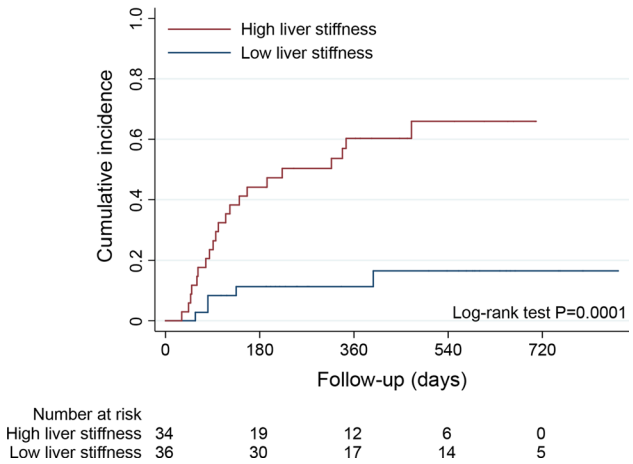

Fig. 4 Kaplan–Meier analysis of composite of all-cause death and worsening heart failure categorized by liver stiffness

two groups in terms of sex, body mass index (BMI), heart rate, systolic blood pressure, LVEF, etiology of HF, levels of hemoglobin, platelets, aspartate aminotransferase, alanine aminotransferase, albumin and C-reactive protein. The events group had significantly higher LS compared to the no events group (2.24 ± 0.91 vs. 1.48 ± 0.78, $P<0.001$) (Fig. 3).

Liver stiffness and clinical outcome

During a median follow-up period of 272 (IQR 122–578) days, adverse events occurred in 26 patients (37%), including all-cause death in 5 (7%) and worsening HF in 21 (30%). Based on ROC analysis, the optimal cut-off value of LS for the development of adverse events was 1.50 m/s, and c-index was 0.77 [95% confidence interval (CI) 0.66–0.88]. At this value, the sensitivity and specificity for predicting cardiac events were 81% and 70%, respectively. Kaplan–Meier analysis revealed that composite adverse events more frequently occurred in patients with high LS ($\geq$ 1.50 m/s) compared to those with low LS ($<$ 1.50 m/s) (log-rank; $P=0.0001$, Fig. 4). Multivariable Cox regression analyzes showed that higher LS was independently associated with increased subsequent risk of adverse events (Table 2). Harrell's c-indices of the models 1 and 2 were 0.72 and 0.75, respectively.

Discussion

The major finding of the present study was that increased admission LS non-invasively assessed by VTQ was an independent determinant of all-cause death and worsening HF in patients with ADHF.

In decompensated HF patients, enhanced concerted neurohumoral responses and renin–angiotensin–aldosterone system cause excessive sodium reabsorption through the distal convoluted tubule, and vasopressin decreases free water excretion in the collecting tubule, which result in elevation of CVP [15, 16]. Elevated CVP has been shown to be associated with impaired renal function and higher incidence of rehospitalization for HF and death in patients with acute or chronic HF [2, 3, 17, 18]. Notably, Adamson, et al. demonstrated that pressure elevation in at least one parameter among right ventricular systolic and diastolic pressure and estimated pulmonary artery diastolic pressure was observed in 75% of events before HF exacerbation in chronic HF patients, using continuously measured right ventricular hemodynamic parameters with an implantable hemodynamic monitor [19]. Elevated CVP also causes an increase in renal venous and interstitial pressure, which leads to a hypoxic state of the renal parenchyma, finally resulting in worsening renal function (WRF) [3]. WRF is well known to be an important prognostic determinant of adverse events in chronic and acute HF patients [20–23]. It is noteworthy that CVP rather than cardiac index could be a powerful predictor of subsequent risk of WRF in ADHF patients [3]. These findings indicate that evaluation of CVP, ideally based on non-invasive modalities, should be useful for identifying patients at high risk of WRF and eventual worsening HF and death.

We and other groups demonstrated that LS measured by ultrasound elastography was significantly correlated with CVP in HF patients [6–9, 24–27]. The mechanism of this correlation has been hypothesized to be that elevated CVP is followed by dilation of the inferior vena cava and hepatic veins, which causes an enlarged and firm liver because the liver is enveloped by a distensible, but non-elastic capsule [24, 28]. Accordingly, liver congestion due to CVP elevation would directly increase LS. In fact, Millonig et al. showed that CVP could directly control LS in a reversible manner during clamping or de-clamping of the inferior vena cava in Landrace pigs [26]. Interestingly, LS of these Landrace pigs measured by ultrasound elastography demonstrated perfect correlation with CVP ($r=1.0$, $P<0.01$). Furthermore,

Table 2 Cox proportional hazard models for all-cause death or worsening heart failure

Variable	Univariable		Multivariable			
			Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, 5 years	0.95 (0.84–1.07)	0.37				
Male, sex	1.07 (0.50–2.54)	0.88				
BMI, 1 kg/m^2	0.87 (0.78–0.97)	0.003				
Systolic BP, 20 mmHg	0.56 (0.40–0.79)	< 0.001			0.58 (0.40–0.83)	0.003
Atrial fibrillation	1.39 (0.64–3.00)	0.41	0.93 (0.40–2.18)	0.87		
NYHA class III or IV	3.85 (1.64–8.98)	0.001	3.20 (1.34–7.64)	0.009		
Hemoglobin, 1 g/dL	0.81 (0.67–0.98)	0.024				
eGFR, 10 mL/min	0.94 (0.86–1.03)	0.160			0.97 (0.90–1.06)	0.54
Sodium, 1 mEq/L	0.89 (0.82–0.97)	0.011			0.92 (0.83–1.01)	0.086
Albumin, 1 g/dL	0.29 (0.13–0.66)	0.003				
BNP, 100 pg/mL	1.05 (1.00–1.10)	0.045				
CRP, 1 mg/dL	1.21 (1.10–1.35)	0.002				
Liver stiffness, 1m/s	1.97 (1.34–2.90)	0.001	1.88 (1.19–2.96)	0.006	1.82 (1.22–2.71)	0.003

Model 1; stepwise selection, Model 2; adjusted for clinically important prognostic factors including systolic blood pressure, estimated glomerular filtration rate and sodium. Harrell's c-indices of the models 1 and 2 are 0.72 and 0.75

HR hazard ratio, *CI* confidence interval, other abbreviations as in Table 1

we have recently reported that LS measured by VTQ was positively correlated with CVP measured simultaneously by right heart catheterization in 38 patients with HF ($r = 0.578$, $P < 0.001$) [9].

Several studies have indicated that LS non-invasively evaluated by transient elastography (TE) using a FibroScan® (Echosens, Paris, France) may be useful to predict right HF or the requirement for a right ventricular assist device in advanced HF patients with left ventricular assist device (LVAD) implantation [25, 27]. LS measured by TE at discharge was also associated with all-cause death and HF rehospitalization in patients with HF [10]. In the present study, LS on admission was an independent determinant of subsequent adverse events in ADHF patients, even after adjustment for powerful prognostic variables for ADHF including systolic blood pressure, serum sodium level and renal function. Our present findings were consistent with previous results and provide additional information regarding the prognostic significance of admission LS in relation to subsequent worsening HF and death following ADHF, suggesting that measurement of admission LS could help to improve outcomes by identifying high-risk patients on admission and early referral for advanced HF therapy. Importantly, we measured LS based on VTQ as an alternative to TE in the present study, because the TE is known to have some disadvantages. For instance, LS acquired by TE may be unreliable in patients with obesity and/or ascites because of the increased distance between the TE probe and the liver, and the consequent attenuation of both elastic waves and ultrasound [29, 30]. A previous study showed that BMI greater than 30 kg/m^2 was an independent factor for inability to accurately assess LS with TE [29]. Indeed, our current study included 9 (13%) patients with BMI greater than 30 kg/m^2. According to these reports, there is a possible advantage on accuracy and reproducibility for estimating LS with VTQ when compared to TE regardless of the presence of obesity or ascites. Moreover, Rizzo et al. showed that VTQ was more accurate than TE for non-invasive staging of both significant and severe classes of liver fibrosis in 139 patients with chronic hepatitis C [31]. Unlike TE, VTQ allowed sampling from many different areas of the liver parenchyma. Thus, VTQ might be easier to perform than TE, and could be more useful for evaluating liver fibrosis. Further investigations regarding the superiority of VTQ over TE and the ideal timing of LS measurement for risk stratification in ADHF patients are warranted.

Study limitations

There are several potential limitations of the present study which should be acknowledged. First, this was a single-center study with a relatively small sample size, thereby limiting the ability to generalize the findings and the statistical power for detecting differences in negative data. In addition, the number of adverse events might be too small to perform perfect multivariable analyzes, although c-indices of the Cox multivariable models were fairly good. Therefore, a larger-scale multicentre study is warranted to confirm the relationship between increased LS and worse clinical outcomes in hospitalized patients with ADHF. Second, despite the

fact that we tried to exclude liver disease among registered patients as much as possible, LS might have been affected by pre-existing liver fibrosis due to non-HF etiologies in some cases. Third, there was unavoidable selection bias in our study, although variables other than LS related to CVP and the rate of adverse events were comparable between the excluded patients and the study population (Supplementary Tables S1 and S2). Finally, we could not demonstrate the data of tracking changes in LS during hospitalization and the prognostic value of discharge LS on long-term outcomes, because there were large missing data of LS at the time of discharge [27 (24%)]. Accordingly, a further study which can confirm the relationship between tracking changes in LS/LS at discharge and long-term clinical outcomes in patients with ADHF is warranted.

Conclusions

Our analyzes revealed that higher LS assessed by VTQ at the time of admission was an independent determinant of worse clinical outcomes in ADHF patients. This non-invasive emerging technique for evaluating LS is useful for risk stratification of patients with ADHF.

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Compliance with ethical standards

Conflict of interest No conflict of interest to declare.

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