

ORIGINAL RESEARCH

# Clinical Implications of Hepatic Hemodynamic Evaluation by Abdominal Ultrasonographic Imaging in Patients With Heart Failure

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**BACKGROUND:** It has been reported that liver stiffness assessed by transient elastography are correlated with right atrial pressure, which is associated with worse outcome in patients with heart failure (HF). We aimed to clarify clinical implications of hepatic hemodynamic evaluation (liver congestion and hypoperfusion) by abdominal ultrasonography in patients with HF.

**METHODS AND RESULTS:** We performed abdominal ultrasonography, right-heart catheterization, and echocardiography, then followed up for cardiac events such as cardiac death or worsening HF in patients with HF. Regarding liver congestion, liver stiffness assessed by shear wave elastography (SWE) of the liver was significantly correlated with right atrial pressure determined by right-heart catheterization ( $R=0.343$ ;  $P<0.01$ ), right atrial end-systolic area, and inferior vena cava diameter determined by echocardiography. Regarding liver hypoperfusion, peak systolic velocity (PSV) of the celiac artery was correlated with cardiac index determined by right-heart catheterization ( $R=0.291$ ;  $P<0.001$ ) and tricuspid annular plane systolic excursion determined by echocardiography. According to the Kaplan–Meier analysis, HF patients with high SWE and low PSV had the highest cardiac event rate (log-rank  $P=0.033$ ). In the Cox proportional hazard analysis, high SWE and low PSV were associated with high cardiac event rate (high SWE: hazard ratio [HR], 2.039; 95% CI, 1.131–4.290; low PSV: HR, 2.211; 95% CI, 1.199–4.449), and the combination of high SWE and low PSV was a predictor of cardiac events (HR, 4.811; 95% CI, 1.562–14.818).

**CONCLUSIONS:** Intrahepatic congestion and hypoperfusion determined by abdominal ultrasonography (liver SWE and celiac PSV) are associated with adverse prognosis in patients with HF.

**Key Words:** hemodynamics ■ liver ■ liver congestion ■ liver function test ■ liver perfusion ■ prognosis ■ right-heart catheterization

**H**eat failure (HF) is a widespread and serious problem that has been reported in many countries.<sup>1</sup> Nohria-Stevenson profiles demonstrated the clinical importance of assessments of perfusion (“cold” versus “warm”), as well as congestion (“wet” versus “dry”).<sup>2,3</sup> The abdominal compartment, which includes the liver, splanchnic vasculature, gut, and so on, has recently been investigated to determine whether it significantly contributes to a deranged cardiac function

as well as multiple organ function in patients with HF.<sup>4,5</sup> HF causes liver dysfunction with a combination of reduced arterial perfusion and passive congestion, and this association is called “cardiohepatic interaction.”<sup>6–9</sup>

With regard to liver function tests (LFTs), liver dysfunction, such as the elevation of serum bilirubin, ALP, gamma-glutamyl transferase, AST, and ALT, frequently occurs in HF related to reduced arterial perfusion and passive congestion, and is associated with disease

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## CLINICAL PERSPECTIVE

### What Is New?

- Intrahepatic congestion and hypoperfusion can be determined by abdominal ultrasonography.

### What Are the Clinical Implications?

- Intrahepatic congestion and hypoperfusion are associated with adverse prognosis.

## Nonstandard Abbreviations and Acronyms

<b>BNP</b>	B-type natriuretic peptide
<b>eGFR</b>	estimated glomerular filtration rate
<b>HF</b>	heart failure
<b>LFTs</b>	liver function tests
<b>LS</b>	liver stiffness
<b>LVEF</b>	left ventricular ejection fraction
<b>PSV</b>	peak systolic velocity
<b>RAP</b>	right atrial pressure
<b>RHC</b>	right-heart catheterization
<b>SWE</b>	shear wave elastography

severity and prognosis.<sup>5,7,10–12</sup> Liver congestion attributable to increased central venous pressure might directly contribute to a state of impaired natriuresis.<sup>5,13</sup> In addition, elevated central venous pressure and right atrial pressure (RAP) may contribute to cholestatic abnormalities (elevated bilirubin, ALP, gamma-glutamyl transferase), as well as impairment of both hepatocyte function and liver reserve in patients with HF.<sup>6–8</sup>

With regard to image testing, evaluation of chronic liver disease based on liver stiffness (LS) assessed by transient elastography has attracted growing interest in the field of clinical hepatology. LS is recently calculated on the basis of shear wave velocity measurements, and is used as a noninvasive method to assess liver fibrosis. It has been reported that LS is highly reflective of right-sided filling pressure, and might be a marker of liver congestion in patients with HF.<sup>14–17</sup> Congestive hepatopathy<sup>6,7</sup> attributable to HF causes functional abnormalities of the liver,<sup>8</sup> and increased LS indicates adverse prognosis.<sup>14–16,18–21</sup> However, associations between low liver perfusion and LFTs or prognosis have not been investigated in previous studies.<sup>14–16,18–21</sup> Clinical implications of a possible marker of liver perfusion (peak systolic velocity [PSV] of celiac artery), as well as congestion (liver shear wave elastography [SWE]) determined by abdominal ultrasonography in patients with HF have not been examined.

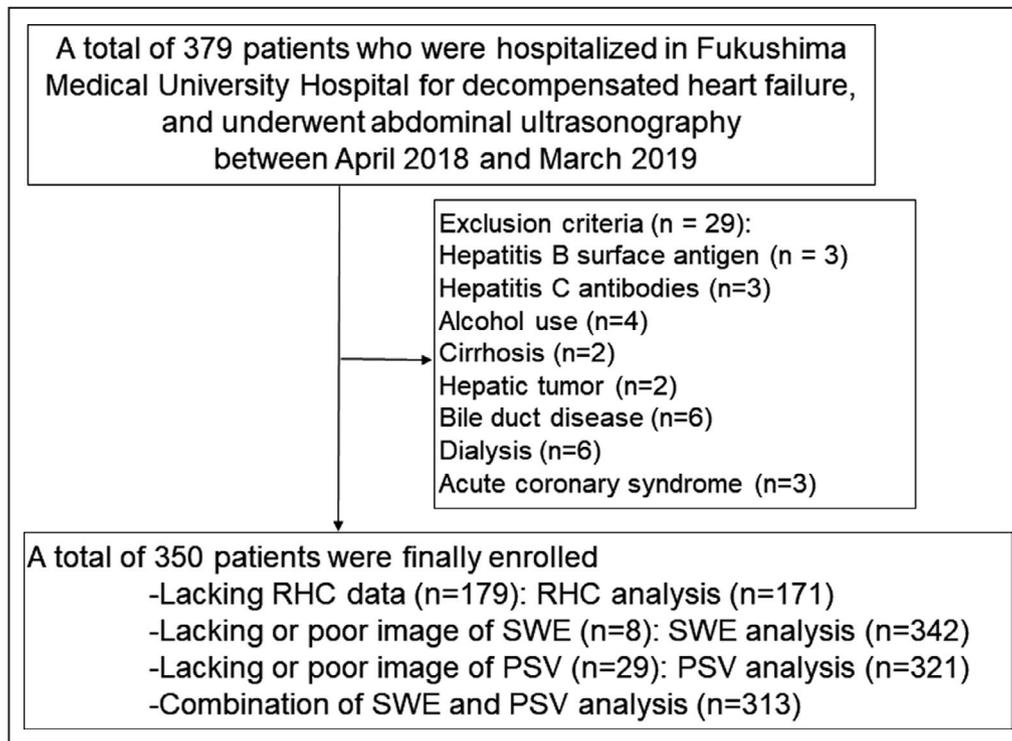
Thus, in the current study, we aimed to clarify (1) the relationships between hemodynamics (right-heart catheter) and the parameters of liver SWE and celiac PSV, as well as LFTs; (2) the associations between the parameters of liver SWE, celiac PSV, and those of echocardiography; and (3) the prognostic impacts of liver SWE and celiac PSV on patients with HF.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Subjects and Study Protocol

The patient flow is described in Figure 1. This was a prospective observational study of 379 decompensated patients with HF who had undergone abdominal ultrasonography and were discharged from Fukushima Medical University Hospital between April 2018 and March 2019. Diagnosis of decompensated HF was made by each patient's attending cardiologist on the basis of the established HF guidelines.<sup>22–24</sup> Blood samples, abdominal ultrasonography, and echocardiography were obtained at hospital discharge. All patients underwent testing for hepatitis B surface antigen and hepatitis C antibodies, and their medical histories were checked for chronic liver disease (cirrhosis, hepatic tumors, bile duct disease, etc) and alcohol abuse ( $\geq 30$  g/day for men,  $\geq 20$  g/day for women). Patients with the above-mentioned liver diseases, alcohol abuse, acute coronary syndrome, advanced cancer, or were undergoing dialysis, were excluded. Finally, 350 patients were enrolled. Of these 350 patients, right-heart catheterization (RHC) was partly performed within 3 days of abdominal ultrasonography. Because of lack or poor image of specific data (RHC, SWE, and PSV), 171 were used for the RHC analysis, 342 were used for the SWE analysis, 321 were used for the PSV analysis, and 313 were used for a combination of SWE and PSV analysis. Patients were divided on the basis of the median levels of liver SWE or celiac PSV: (1) the low-SWE group (SWE  $< 1.31$  m/s;  $n=171$ ) or high-SWE group (SWE  $\geq 1.31$  m/s;  $n=171$ ), and (2) low-PSV group (PSV  $< 65$  m/s;  $n=158$ ) or high-PSV group (celiac PSV  $\geq 65$  cm/s;  $n=163$ ). First, we compared the clinical features and results from laboratory tests and echocardiography between the 2 groups. In addition, we performed a correlation analysis of interaction between levels of both liver SWE or celiac PSV and parameters of laboratory tests and echocardiography. Second, the patients were followed up until August 2019 for cardiac events as composites of cardiac death or unplanned rehospitalization for HF treatment. For patients who experienced  $\geq 2$  events, only the first event was included



**Figure 1. Patient flow chart.**

PSV indicates peak systolic velocity; RHC, right-heart catheterization; and SWE, shear wave elastography.

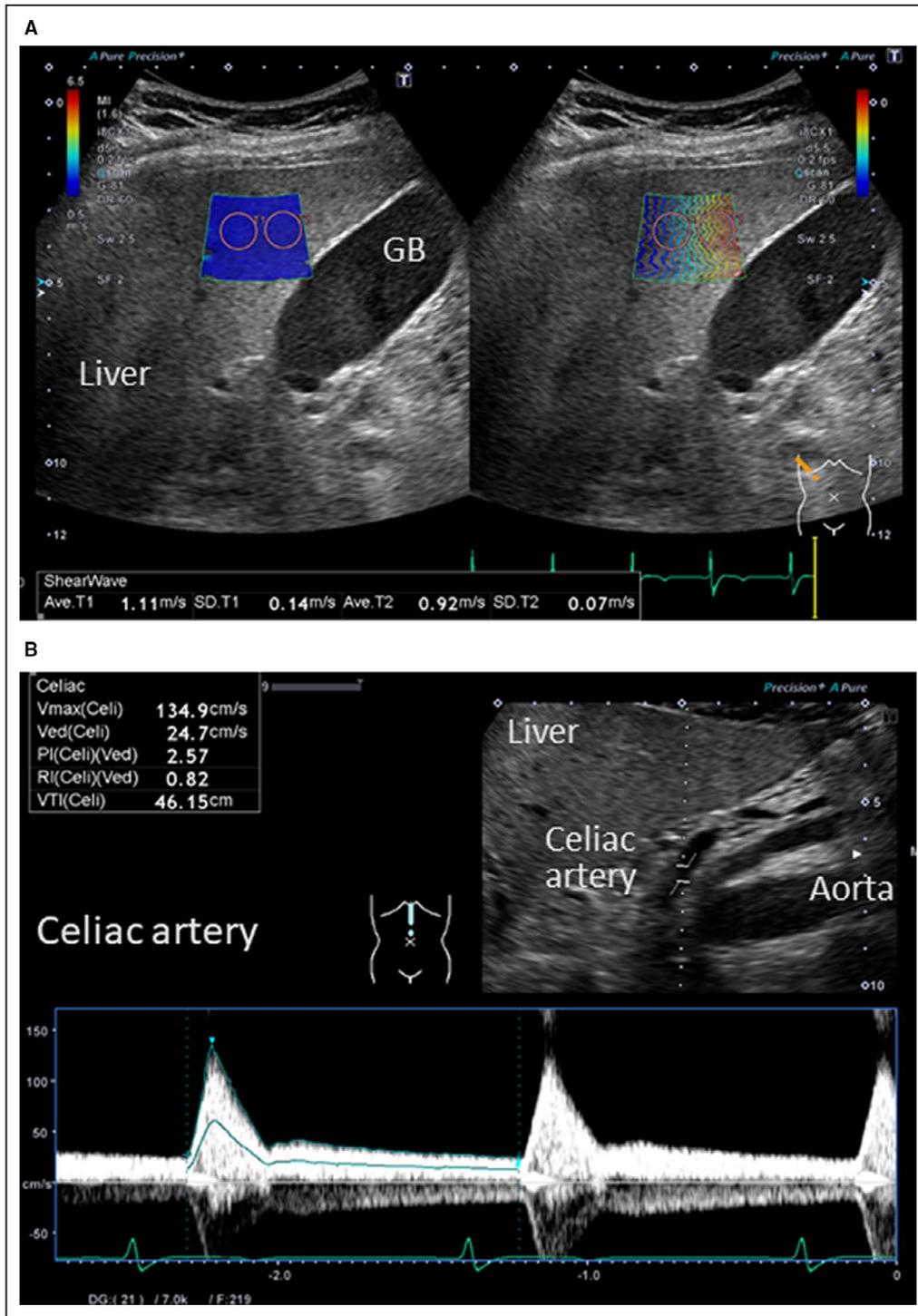
in the analysis. Since these patients visited patient's referring hospital monthly or bimonthly, we were able to follow up on all patients. Status and dates of death were obtained from the patient's medical records. Those administering the survey were blind to the analyses, and written informed consent was obtained from all study subjects. The study protocol was approved by the Ethics Committee of Fukushima Medical University, and was carried out in accordance with the principles outlined in the Declaration of Helsinki. Reporting of the study conforms to Strengthening the Reporting of Observational Studies in Epidemiology along with references to Strengthening the Reporting of Observational Studies in Epidemiology and the Enhancing the Quality and Transparency of Health Research guidelines.<sup>25</sup>

Hypertension was defined as the recent use of antihypertensive drugs, systolic blood pressure  $\geq 140$  mm Hg, or diastolic blood pressure  $\geq 90$  mm Hg. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of  $\geq 150$  mg/dL, a low-density lipoprotein cholesterol value of  $\geq 140$  mg/dL, or a high-density lipoprotein cholesterol value of  $< 40$  mg/dL. Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) of  $< 60$  mL/min per  $1.73$   $\text{cm}^2$ ,<sup>26</sup> and anemia was defined as hemoglobin levels of  $< 12.0$  g/dL in women and  $< 13.0$  g/dL in men.<sup>1</sup> Atrial fibrillation was identified by an ECG

performed during hospitalization or from medical records, including past history.

### Abdominal Ultrasonography

Abdominal ultrasonography was performed with the patients in a stable condition without changes in medications at hospital discharge, by 2 experienced sonographers (S.I., with 15 years of experience in abdominal ultrasonography, and M.M., with 23 years of experience), who were blinded to all clinical data, before discharge using an ultrasound system (Aplio i800, Canon Medical Systems, Tochigi, Japan) equipped with a wideband convex i8CX1 multifrequency probe (central frequency, 4.0 MHz; range, 1.8–6.4 MHz). Patients fasted for at least 12 hours before the abdominal ultrasonography. Images were obtained from patients in the supine or decubitus position through the subcostal, transverse, oblique, sagittal, and intercostal planes.<sup>27</sup> As shown in Figure 2, we measured liver SWE and celiac PSV. SWE examination was performed in the right liver lobe through the intercostal space to obtain a proper sonic window. 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. The detection site was fixed at 1.0 to 2.0 cm beneath the right liver capsule, away from the intrahepatic



**Figure 2. Abdominal ultrasonography.**

**A**, Liver-SWE (m/s), **(B)** Celiac-PSV (cm/s). GB indicates gallbladder; PSV, peak systolic velocity; and SWE, shear wave elastography.

vessels and the gallbladder.<sup>28</sup> The convex probe was kept still for 1 second during acquisition in one-shot mode, and participants were requested to hold their breath during acquisition.<sup>29</sup> When the measurement area was located, the operator initiated the SWE

sequence measurements that targeted the region of interest. A sample box  $\approx 2 \times 2$  cm was placed on a gray-scale image at least 1 cm beneath the Glisson capsule to avoid reverberation artifacts.<sup>29</sup> The median value from 7 measurements of SWE performed

at the depths ranging from 25 to 65 mm was defined as the liver SWE (m/s).<sup>28</sup> Since selective depiction of the common hepatic artery was technically difficult, we evaluated the celiac artery. PSV of the celiac artery was defined as celiac PSV (cm/s). The intraobserver variability (standard deviation of the differences/average value) of SWE was  $7\pm 2\%$ , whereas that of PSV was  $8\pm 2\%$ .

## Echocardiography

Echocardiography was performed by experienced echocardiographers using standard techniques as previously reported.<sup>30</sup> The echocardiographic parameters included left ventricular ejection fraction (LVEF), left atrial volume, early transmitral flow velocity to mitral annular velocity ratio (mitral valve E/e'), right atrium and ventricle areas, right ventricular fractional area change, inferior vena cava diameter, tricuspid regurgitation pressure gradient, tissue Doppler-derived tricuspid lateral annular systolic velocity (tricuspid valve S'), and tricuspid annular plane systolic excursion.<sup>31</sup> The LVEF was calculated using Simpson's method. The right ventricular fractional area change, defined as (end diastolic area–end-systolic area)/end-diastolic area $\times 100$ , was a measure of right ventricular systolic function.<sup>31</sup> All measurements were performed using ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc, Mountain View, CA, USA).

## RHCs and Hemodynamic Measurements

Of 350 patients, RHC was partly performed based on remedial judgment of the attending physician in 171 patients. RHC were performed within 3 days of abdominal ultrasonography, with the patients in a stable condition without changes in medications including doses, similar to setting of abdominal ultrasonography. All right-heart catheterizations were performed with the patients in a stable condition, in a resting supine position under fluoroscopic guidance, at room air, and at rest for more than 30 minutes after catheter placement. Mean RAP and cardiac output were measured using a 7F Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA). Cardiac output was calculated based on the direct Fick method.<sup>32</sup>

## Measurement of Laboratory Data

The BNP (B-type natriuretic peptide) levels were measured using a specific immunoradiometric assay (Shionoria BNP kit; Shionogi, Osaka, Japan). The serum 7S domain of collagen type IV, which indicates liver fibrosis, was measured by radioimmunoassay (type IV collagen 7S kit; SCETI MEDICAL LABO K.K., Tokyo, Japan).<sup>32,33</sup> These assays were blindly performed by experienced laboratory technicians.

## Statistical Analysis

Normally distributed data are presented as mean $\pm$ SD, and nonnormally distributed data are presented as median and interquartile range. The categorical variables are expressed as numbers and percentages, and the chi-square test was used for their comparisons. Parametric variables were compared using Student *t* test, and nonparametric variables were compared using the Mann–Whitney *U* test. Correlations between both SWE and celiac PSV and the parameters of laboratory data, echocardiography, or RHC were assessed using Pearson's correlation analysis for parametric variables and Spearman's correlation analysis for nonparametric variables. Kaplan–Meier analysis was used with a log-rank test to assess cardiac event rates as composites of cardiac death or unplanned rehospitalization for HF treatment. These curves helped in identifying non-proportionality patterns in hazard function such as convergence (difference in risk between the groups decreases with time), divergence, or crossing of the curves. In addition, a Schoenfeld test for the violation of proportional hazards, which can be used to assess the correlation between scaled residuals and time, was also conducted. Cox proportional hazard analyses were used to evaluate SWE and PSV levels as a predictor of cardiac events. A *P* value of  $<0.05$  was considered statistically significant for all comparisons. These analyses were performed using a statistical software package (SPSS ver. 24.0; IBM, Armonk, NY).

## RESULTS

Correlation analysis with mean RAP, cardiac index and LFTs, liver SWE, and celiac PSV are presented in Table 1. There were significant positive correlations between total bilirubin, gamma-glutamyl transferase, 7S domain of collagen type IV, SWE and mean RAP, as well as significant positive correlations between total protein, albumin, cholinesterase, PSV, and cardiac index, suggesting that SWE is a marker of central venous pressure, and PSV is a marker of liver perfusion.

Comparisons of patients with low and high SWE groups are summarized in Table 2. The high SWE group were older, had a higher body mass index, and New York Heart Association class, higher prevalence of AF, chronic kidney disease and anemia, higher levels of direct bilirubin, alkaline phosphatase, gamma-glutamyl transferase, 7S domain of collagen type IV and creatinine, lower levels of hemoglobin, albumin, cholinesterase and eGFR, higher levels of left atrial volume, mitral valve E/e', right atrial end-systolic area, and inferior vena cava diameter. In addition,

**Table 1. Correlation Analyses With RAP, Cardiac Index, and Other Variables (n=171)**

	<i>r</i>	<i>P</i> Value
Right atrium pressure, mm Hg		
Laboratory data		
Total protein, g/dL	-0.077	0.316
Albumin, g/dL	-0.047	0.539
Total bilirubin, mg/dL	0.168	0.028
Direct bilirubin, mg/dL	0.136	0.075
Aspartate aminotransferase, U/L	0.097	0.208
Alanine aminotransferase, U/L	0.121	0.113
Alkaline phosphatase, U/L	0.130	0.089
Gamma-glutamyl transferase, U/L	0.211	0.005
Cholinesterase, U/L	0.001	0.992
P4NP 7S, ng/mL	0.231	0.002
Abdominal ultrasonography		
Liver SWE, m/s	0.343	<0.001
Celiac PSV, cm/s	0.053	0.504
Cardiac index, L/min per m <sup>2</sup>		
Laboratory data		
Total protein, g/dL	0.187	0.014
Albumin, g/dL	0.294	<0.001
Total bilirubin, mg/dL	-0.173	0.024
Direct bilirubin, mg/dL	-0.168	0.028
Aspartate aminotransferase, U/L	-0.089	0.247
Alanine aminotransferase, U/L	-0.048	0.537
Alkaline phosphatase, U/L	-0.046	0.553
Gamma-glutamyl transferase, U/L	-0.054	0.486
Cholinesterase, U/L	0.271	<0.001
P4NP 7S, ng/mL	-0.154	0.074
Abdominal ultrasonography		
Liver SWE, m/s	-0.060	0.442
Celiac PSV, cm/s	0.291	<0.001

P4NP 7S indicates 7S domain of collagen type IV; PSV, peak systolic velocity; RAP, right atrial pressure; and SWE, shear wave elastography.

there were significant associations between SWE and age, body mass index, levels of albumin, direct bilirubin, ALP, gamma-glutamyl transferase, 7S domain of collagen type IV, log BNP, eGFR, left atrial volume, mitral valve E/e', right atrial end-systolic area, and inferior vena cava diameter. These results suggest that elevated SWE indicates liver congestion, and underlying increased central venous pressure or right-heart volume overload.

Comparisons of the low and high PSV groups are summarized in Table 3. The low-PSV group was older; had a lower body mass index, higher prevalence of New York Heart Association class III or IV, female sex, chronic kidney disease and anemia; had higher levels of log BNP and lower levels of total protein, cholinesterase, eGFR; and sodium; and had higher levels of mitral valve E/e' and lower levels of tricuspid annular

plane systolic excursion. In addition, there were significant associations between PSV and age, body mass index, levels of total protein, eGFR, LVEF, mitral valve E/e', tricuspid valve S' and tricuspid annular plane systolic excursion. These results suggest that decreased PSV indicates liver hypoperfusion, underlying low cardiac output, and leads to protein synthesis decrease.

During the follow-up period (mean, 231 days; range, 12–523 days), 40 cardiac events including 6 cardiac deaths and 34 worsening HF occurred. As shown in Figure 3, in the Kaplan–Meier analysis, cardiac event rates were significantly higher in the high-SWE group than in the low-SWE group (log-rank  $P=0.024$ ), as well as in the low-PSV group than in the high-PSV group (log-rank  $P=0.022$ ). In addition, we further classified patients into four subsets in consideration of Nohria-Stevenson clinical profiles<sup>2</sup>: subset 1, low SWE and high PSV (warm-dry); subset 2, high SWE and high PSV (warm-wet); subset 3, low SWE and low PSV (cold-dry); and subset 4, high SWE and low PSV (cold-wet). HF patients with high SWE and low PSV had the highest cardiac event rate (Figure 4; log-rank  $P=0.033$ ), followed by high-SWE and high-PSV group, low-SWE and low-PSV group, and low-SWE and high-PSV group. In the Cox proportional hazard analysis (Table 4), high SWE and low PSV were associated with high cardiac event rates (high SWE: hazard ratio [HR], 2.039; 95% CI, 1.131–4.290; low PSV: HR, 2.211; 95% CI, 1.199–4.449), and the combination of high SWE and low PSV was a predictor of cardiac events in patients with HF (HR, 4.811; 95% CI, 1.562–14.818). As limited number of events (40 events), we selected only 4 confounding factors (age, sex, BNP, and LVEF) in the multivariable adjusted Cox proportional hazard analyses. These results suggest that the combination of SWE and PSV might be a useful tool for evaluating hepatic hemodynamic subsets like in the Nohria-Stevenson classification (Figure 5).

## DISCUSSION

To the best of our knowledge, the present study is the first to report that the associations between parameters of not only liver congestion (right-sided HF), but also liver hypoperfusion (left-sided HF) determined by abdominal ultrasonography and LFTs, RHC, and echocardiography, as well as its prognostic impact in HF.

Cardiohepatic interaction has been reported previously.<sup>6,9</sup> Systemic venous congestion rises to neurohormonal activation (eg, renin-angiotensin system), decreases plasma natriuretic peptide,<sup>34,35</sup> leads to HF progression, may contribute to worsening multiple organ failure,<sup>20,36,37</sup> and results in adverse prognosis.<sup>38</sup> HF causes increased right-sided pressure overload, and leads to LS increase.<sup>20,39,40</sup> Liver transient

**Table 2. Comparisons of Patient Characteristics (N=342)**

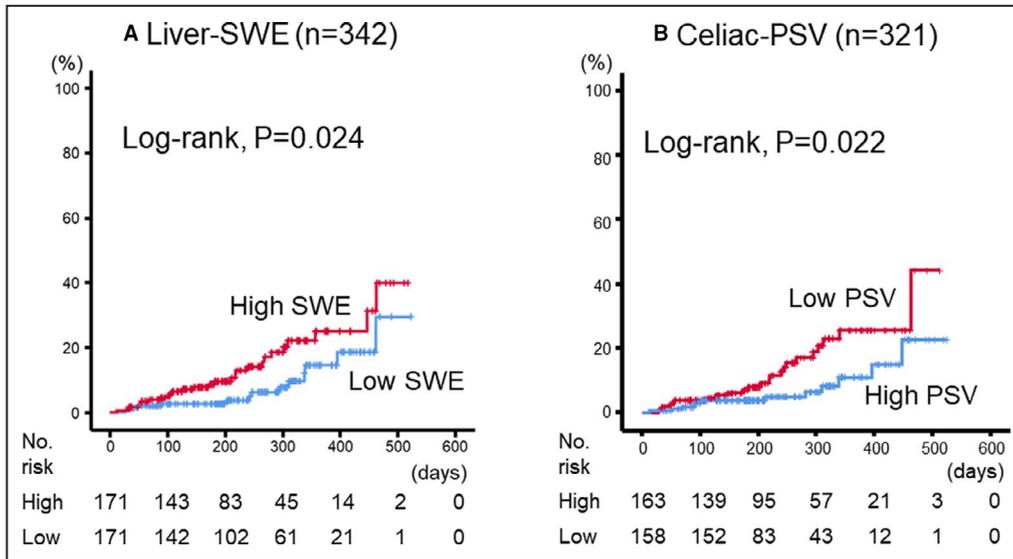
	SWE Group (Low vs High)			Correlation With SWE	
	Low SWE (SWE <1.31, n=171)	High SWE (1.31 ≤ SWE, n=171)	P Value	Correlation Coefficient	P Value
SWE, m/s	1.22±0.14	1.49±0.23	<0.001	...	...
Demographics					
Age, y	65.6±12.3	69.3±12.7	0.006	0.198	<0.001
Male sex (n, %)	104 (60.8)	108 (63.2)	0.656	-0.010	0.849
Body mass index, kg/m <sup>2</sup>	22.9±3.7	24.1±4.3	0.005	0.136	0.012
Systolic BP, mm Hg	118.2±17.8	121.0±18.2	0.153	-0.011	0.845
Diastolic BP, mm Hg	69.1±12.1	68.4±13.0	0.630	-0.096	0.076
Heart rate, bpm	71.5±14.1	69.3±13.8	0.142	-0.102	0.059
NYHA class III or IV	5 (2.9)	17 (9.9)	0.008	0.066	0.222
Etiology ischemic/myopathy/valvular/arrhythmia/pulmonary/congenital/others	52 (30.4)/45 (26.3)/33 (19.3)/18 (10.5)/18 (10.5)/3 (1.8)/2 (1.2)	45 (26.3)/39 (22.8)/46 (26.9)/22 (12.9)/13 (7.6)/4 (2.3)/2 (1.2)	0.620	...	...
Comorbidities					
CAD, n (%)	47 (27.5)	49 (28.7)	0.810	...	...
Atrial fibrillation, n (%)	46 (26.9)	74 (43.3)	0.002	...	...
Hypertension, n (%)	96 (56.1)	112 (65.5)	0.076	...	...
Dyslipidemia, n (%)	127 (74.3)	115 (67.3)	0.154	...	...
Diabetes mellitus, n (%)	48 (28.1)	62 (36.3)	0.105	...	...
CKD, n (%)	79 (46.2)	103 (60.2)	0.009	...	...
Anemia, n (%)	67 (39.2)	90 (52.6)	0.013	...	...
Laboratory data					
Total protein, g/dL	7.0±0.7	6.9±0.8	0.424	-0.001	0.984
Albumin, g/dL	4.0±0.5	3.9±0.6	0.008	-0.114	0.035
Total bilirubin, mg/dL	0.9±0.8	0.9±0.4	0.612	0.066	0.220
Direct bilirubin, mg/dL	0.1±0.0	0.1±0.1	0.026	0.343	<0.001
Aspartate aminotransferase, U/L	24.8±12.3	27.2±15.7	0.121	0.084	0.118
Alanine aminotransferase, U/L	23.3±17.9	26.7±17.3	0.293	0.045	0.411
Alkaline phosphatase, U/L	239.8±71.0	260.2±112.0	0.045	0.137	0.011
Gamma-glutamyl transferase, U/L	43.9±42.5	63.5±74.3	0.003	0.224	<0.001
Cholinesterase, U/L	303.2±82.6	270.9±108.1	0.002	-0.206	<0.001
P4NP 7S, ng/mL	5.3±1.6	6.2±2.2	<0.001	0.344	<0.001
Log BNP, pg/mL	1.9±0.7	2.0±0.6	0.169	0.140	0.009
Creatinine, mg/dL	1.0±0.5	1.2±0.9	0.049	0.106	0.050
eGFR, mL/min per 1.73 cm <sup>2</sup>	59.3±18.1	55.1±19.3	0.037	-0.201	<0.001
Sodium, mEq/L	139.7±2.9	139.7±2.6	0.871	-0.021	0.697
Echocardiography					
LVEF, %	55.1±15.8	54.4±15.7	0.858	0.017	0.756
Left atrial volume, mL	77.8±41.0	96.7±55.5	0.001	0.299	<0.001
Mitral valve E/e'	12.7±8.3	14.8±8.5	0.029	0.248	<0.001
RA end-systolic area, cm <sup>2</sup>	16.6±6.6	20.0±7.5	0.006	0.293	<0.001
RV area diastole, cm <sup>2</sup>	19.5±7.8	21.7±7.7	0.154	0.151	0.116
RV area systole, cm <sup>2</sup>	12.4±6.6	13.8±7.0	0.303	0.096	0.320
RV fractional area change, %	38.1±11.3	38.6±11.7	0.808	0.030	0.717
Inferior vena cava diameter, mm	14.7±3.6	16.1±4.8	0.004	0.203	<0.001
TRPG, mm Hg	25.3±12.2	26.8±12.8	0.350	0.098	0.108
Tricuspid valve S', cm	10.9±3.6	10.2±3.3	0.161	-0.096	0.173
TAPSE	18.7±4.3	18.4±4.9	0.607	-0.059	0.352

BNP indicates B-type natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; P4NP 7S, 7S domain of collagen type IV; RA, right atrial; RV, right ventricular; SWE, shear wave elastography; TAPSE, tricuspid annular plane systolic excursion; and TRPG, tricuspid regurgitation pressure gradient.

**Table 3. Comparisons of Patient Characteristics (N=321)**

	Celiac PSV Group (Low vs High)			Correlation With SWE	
	Low PSV (PSV <65, n=158)	High PSV (65 ≤ PSV, n=163)	P Value	Correlation Coefficient	P Value
PSV, cm/s	51.7±9.8	84.7±17.9	<0.001	...	...
Demographics					
Age, y	69.9±11.2	65.6±12.9	0.001	-0.166	0.003
Male sex (n, %)	84 (53.2)	110 (67.5)	0.009	0.118	0.035
Body mass index, kg/m <sup>2</sup>	23.0±3.6	24.1±4.3	0.008	0.156	0.005
Systolic BP, mm Hg	119.3±19.0	120.0±17.3	0.746	0.024	0.665
Diastolic BP, mm Hg	68.4±12.8	68.8±12.6	0.757	0.028	0.625
Heart rate, bpm	69.3±13.2	70.9±14.6	0.310	0.104	0.064
NYHA class III or IV	15 (9.5)	6 (3.7)	0.035	...	...
Etiology ischemic/myopathy/valvular/arrhythmia/pulmonary/congenital/others	48 (30.4)/30 (19.0)/38 (24.1)/22 (13.9)/14 (8.9)/3 (1.9)/3 (1.9)	46 (28.2)/47 (28.8)/29 (17.8)/17 (10.4)/19 (11.7)/4 (2.5)/1 (0.6)	0.280	...	...
Comorbidities					
CAD, n (%)	52 (32.9)	39 (23.9)	0.074	...	...
Atrial fibrillation, n (%)	50 (31.6)	59 (36.2)	0.389	...	...
Hypertension, n (%)	99 (62.7)	94 (57.7)	0.361	...	...
Dyslipidemia, n (%)	108 (68.4)	118 (72.4)	0.428	...	...
Diabetes mellitus, n (%)	49 (31.0)	54 (33.1)	0.685	...	...
CKD, n (%)	97 (61.4)	74 (45.4)	0.004	...	...
Anemia, n (%)	81 (51.3)	62 (38.0)	0.017	...	...
Laboratory data					
Total protein, g/dL	6.8±0.7	7.0±0.7	0.022	0.157	0.046
Albumin, g/dL	3.9±0.6	4.0±0.5	0.218	0.043	0.442
Total bilirubin, mg/dL	0.9±0.9	0.9±0.4	0.361	-0.101	0.073
Direct bilirubin, mg/dL	0.1±0.1	0.1±0.0	0.075	-0.108	0.055
Aspartate aminotransferase, U/L	25.7±12.3	25.8±15.9	0.940	-0.005	0.930
Alanine aminotransferase, U/L	25.3±18.1	24.7±18.5	0.858	0.003	0.953
Alkaline phosphatase, U/L	247.9±110.9	247.8±73.0	0.991	-0.049	0.388
Gamma-glutamyl transferase, U/L	53.6±65.2	49.9±45.8	0.564	-0.021	0.713
Cholinesterase, U/L	271.2±87.9	298.4±102.0	0.012	0.082	0.148
P4NP 7S, ng/mL	5.8±2.0	5.6±1.9	0.332	-0.059	0.305
Log BNP, pg/mL	2.0±0.6	1.9±0.6	0.028	-0.106	0.058
Creatinine, mg/dL	1.2±0.9	1.0±0.7	0.141	-0.057	0.310
eGFR, mL/min per 1.73 cm <sup>2</sup>	54.6±20.9	59.9±17.5	0.015	0.143	0.011
Sodium, mEq/L	139.4±3.0	140.0±2.6	0.034	0.090	0.107
Echocardiography					
LVEF, %	53.6±16.5	55.5±14.3	0.261	0.206	<0.001
Left atrial volume, mL	87.2±52.7	85.6±45.7	0.787	-0.060	0.298
Mitral valve E/e'	15.1±9.7	12.5±7.0	0.008	-0.215	<0.001
RA end-systolic area, cm <sup>2</sup>	19.0±8.1	18.4±6.5	0.666	0.026	0.773
RV area diastole, cm <sup>2</sup>	20.0±8.4	20.9±7.2	0.551	0.133	0.180
RV area systole, cm <sup>2</sup>	13.2±7.7	12.5±5.5	0.583	0.089	0.370
RV fractional area change, %	37.7±12.3	40.1±10.7	0.225	-0.067	0.434
Inferior vena cava diameter, mm	15.5±4.6	15.4±3.6	0.877	0.039	0.488
TRPG, mm Hg	27.5±13.9	24.9±11.7	0.105	-0.070	0.266
Tricuspid valve S', cm	10.0±3.2	10.8±3.7	0.099	0.201	0.004
TAPSE	17.8±4.8	19.1±4.5	0.034	0.162	0.013

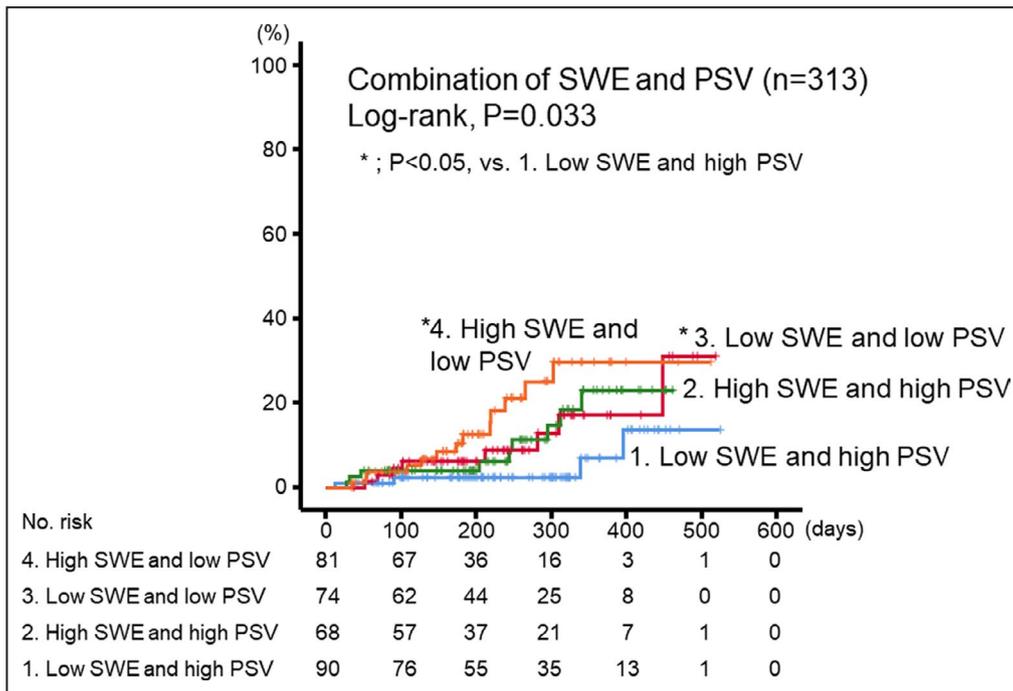
BNP indicates B-type natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; P4NP 7S, 7S domain of collagen type IV; PSV, peak systolic velocity; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and TRPG, tricuspid regurgitation pressure gradient.



**Figure 3.** Kaplan–Meier analysis for cardiac event rates stratified by (A) liver-SWE or (B) celiac-PSV levels. PSV indicates peak systolic velocity; and SWE, shear wave elastography.

elastography showed increased LS at admission attributable to HF and an improvement at discharge.<sup>18</sup> Increased central venous pressure causes hepatocyte atrophy and perisinusoidal edema in the liver.<sup>6,8</sup> Increased pressure within the hepatic sinusoid favors bile duct damage by disrupting endothelial cells and the interhepatocytic tight junctions that separate the

extravascular space from the bile canaliculus. Further, stagnant flow favors thrombosis within sinusoids, hepatic venules, and portal tracts, thereby contributing to liver fibrosis.<sup>7,41</sup> Centrilobular liver cell necrosis can extend to peripheral areas if HF persists and worsens and is followed by the deposition and spread of connective tissue bridging one central vein to another,



**Figure 4.** Kaplan–Meier analysis for cardiac event rates stratified by combination of liver SWE and celiac PSV levels. PSV indicates peak systolic velocity; and SWE, shear wave elastography.

**Table 4. Cox Proportional Hazard Model of Cardiac Events (Factors in Parameters of Liver Ultrasonography)**

Cardiac Events	HR	95% CI	P Value
Liver SWE group			
SWE (high vs low)	2.039	1.131–4.290	0.013
SWE (high vs low)*	2.113	1.069–4.060	0.033
Celiac PSV group			
PSV (low vs high)	2.211	1.199–4.449	0.010
PSV (low vs high)*	2.046	1.029–4.147	0.041
Combination of liver SWE and celiac PSV group			
Subset 1 (low SWE and high PSV)	Reference	...	...
Subset 2 (high SWE and high PSV)	2.789	0.938–9.279	0.059
Subset 3 (low SWE and low PSV)	3.088	1.118–9.850	0.030
Subset 3 (low SWE and low PSV)*	2.430	1.045–8.410	0.045
Subset 4 (high SWE and low PSV)	4.811	1.562–14.818	0.006
Subset 4 (high SWE and low PSV)*	4.153	1.476–13.043	0.018

HR indicates hazard ratio; PSV, peak systolic velocity; and SWE, shear wave elastography.  
 \*Adjusted for age, sex, B-type natriuretic peptide, and left ventricular ejection fraction.

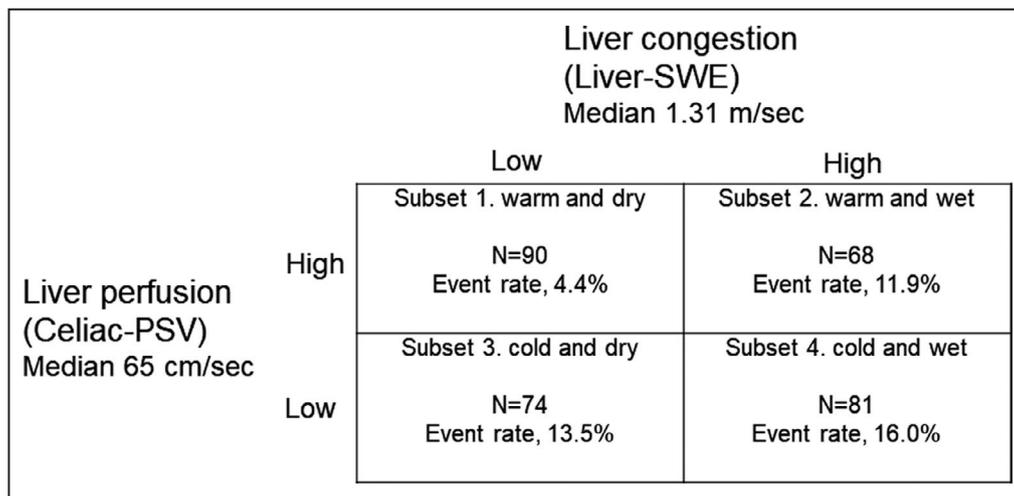
ultimately leading to liver cirrhosis.<sup>7</sup> Concordant with these findings, increased right-sided pressure (RAP) in the current study was associated with higher levels of total bilirubin, gamma-glutamyl transferase, and SWE. In addition, high SWE was associated with right and left volume overload (RAP, left atrial volume, mitral E/e', right atrial end-systolic area, and inferior vena cava diameter) and high cardiac event rates.

On the other hand, although HF consists of not only congestion (right-sided HF), but also reduced

arterial flow called hypoxic hepatopathy, liver hypoperfusion (left-sided HF) determined by image testing has not yet been reported. Hypoxia has been reported to cause centrilobular necrosis and sinusoidal damage in the liver, and leads to impaired transaminase clearance.<sup>42,43</sup> In the present study, decreased cardiac output was associated with celiac hypoperfusion, and lower levels of nutrients (total protein, albumin, cholinesterase), which are established predictors of patients with HF.<sup>44</sup> Furthermore, low PSV was associated with impaired right and left systolic function (cardiac index, LVEF, tricuspid valve S', tricuspid annular plane systolic excursion) and high cardiac event rate. The current study is the first to report the associations between impaired liver perfusion and impaired nutrients, cardiac function, LFTs, and prognosis. In addition, the combination of SWE and PSV might be a useful tool for evaluating abdominal hemodynamic subsets like in the Nohria-Stevenson clinical profiles.<sup>2</sup>

**Study Limitations**

The current study has several limitations. First, as a prospective cohort study of a single center with a relatively small number of patients and short follow-up period, the study may be somewhat underpowered. However, our sample size was larger than those of previous studies.<sup>14–16,18–21</sup> Second, although patients with HF with documented liver disease were excluded, we were unable to completely exclude the presence of liver diseases, which may affect hepatic ultrasound imaging results. Therefore, if these patients with HF already had disorders of liver stiffness or fibrosis, it would not be related to only cardiac load. The relationships between SWE and other fibrosis evaluations, such as liver biopsy, which is not



**Figure 5. Cardiac event rates stratified by combination of liver-SWE and celiac-PSV levels.** PSV indicates peak systolic velocity; and SWE, shear wave elastography.

generally performed in patients with HF, or imaging (eg, computed tomography, magnetic resonance imaging) should be assessed in further studies. In addition, novel imaging technique such as shear wave dispersion may be useful for evaluating LS.<sup>29,45</sup> Third, we conducted the present study using only variables regarding hospitalization, without taking into consideration changes in medical parameters or treatments. Fourth, since the attending physician decided to perform RHC, there might be potential selection bias. Therefore, the present results should be viewed as preliminary, and further studies with a larger population are needed.

## CONCLUSIONS

Intrahepatic congestion and hypoperfusion determined by abdominal ultrasonography (liver SWE and celiac PSV) are associated with LFT abnormality, cardiac function, and adverse prognosis in patients with HF.

## ARTICLE INFORMATION

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