

Shear Wave Dispersion Slope of the Liver Can Predict Adverse Outcomes in Patients with Pulmonary Hypertension

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Summary

Pulmonary hypertension (PH) often causes right-sided heart failure (HF), inducing organ damage. Shear wave elastography (SWE) is a novel ultrasound technique for characterizing tissue. Some studies have reported that shear wave dispersion slope (SWDS) enables the assessment of early hepatic damage in HF. This study aimed to evaluate the prognostic impact of SWDS in patients with PH.

This single-center cohort study enrolled 36 patients with PH who underwent SWE at Okayama University Hospital between March 2018 and April 2021. Patients were divided into 2 groups on the basis of the median value of SWDS: low SWDS group (SWDS < 12.4 m/second/kHz, $n = 18$) and high SWDS group (SWDS ≥ 12.4 m/second/kHz, $n = 18$). The primary endpoint was the complex of all-cause death or hospitalization for HF. During the follow-up of 391 ± 288 days, all-cause death or hospitalization for HF occurred in 8 patients. One patient died in the low SWDS group. Three patients died and 4 patients were hospitalized for HF in the high group. Kaplan-Meier analysis revealed that the event-free survival rate was significantly worse in the high SWDS group than in the low SWDS group (log-rank, $P = 0.01$). In univariate Cox proportional hazards analysis, high SWDS was associated with the events (hazard ratio 10.8; 95% confidence interval 1.89-202, $P = 0.005$).

An elevated SWDS was associated with a high rate of events in patients with PH. SWDS has the potential to predict adverse outcomes in patients with PH.

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Key words: Shear wave elastography, Right-sided heart failure

Pulmonary hypertension (PH) causes worsened clinical symptoms and prognosis. PH often leads to the development of right ventricular dysfunction, leading to right-sided heart failure (HF). PH complicated with right-sided HF results in low output, hypoxemia, and venous congestion, which affect multiple organ systems, including the liver.^{1,2)} It is important to detect organ damage in the early stage of the disease for planning therapeutic strategies in order to improve clinical outcomes.

Shear wave elastography (SWE) is a novel ultrasound technique for assessing tissue characteristics based on shear wave (SW) velocity.³⁻⁵⁾ SW is generated by a push pulse of ultrasound wave, which deforms a part of the tissue. SW within the tissue is detected by tracking pulse. SWE measures 2 parameters such as SW elasticity, which is related to tissue hardness, and SW dispersion slope (SWDS), which reflects tissue viscosity.^{6,7)}

SWE has been used for assessing liver disease in clinical practice. SW elasticity is correlated with fibrosis, and SWDS is associated with inflammation.^{6,8,9)} In the

field of heart disease, one study has reported that SWDS is elevated in the early stage of HF.¹⁰⁾ Therefore, we hypothesized that the assessment of SWDS, which reflects early hepatic damage, would be valuable for risk stratification in patients with PH stabilized by PH specific medications. The aim of this study was to evaluate the prognostic impact of SWDS in patients with PH.

Methods

Study protocol: This prospective, single-center, cohort study was approved by the institutional review board at our hospital. Among the 800 consecutive patients who underwent SWE at Okayama University Hospital between March 2018 and April 2021, patients who were diagnosed to have PH were included in this study. The diagnosis of PH was based on current clinical guidelines.¹¹⁾ Patients with PH due to left-sided heart disease were excluded. We also excluded patients with a previous diagnosis of organic liver disease. Finally, 36 patients were enrolled. Figure 1 shows the patient selection process. All patients

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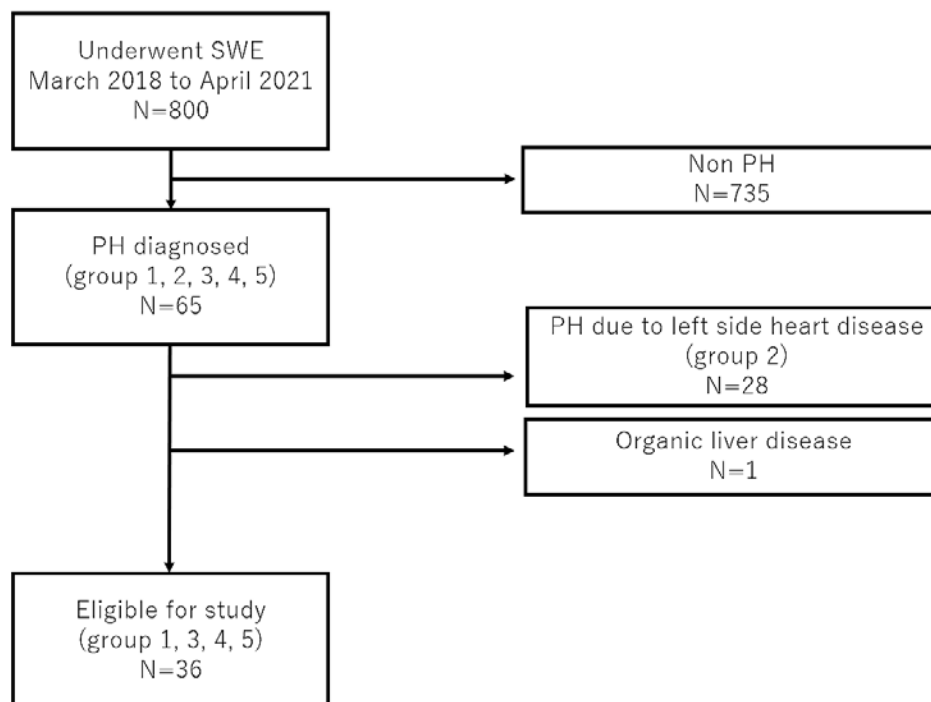


Figure 1. Flow chart of the patient selection. SWE indicates shear wave elastography; and PH, pulmonary hypertension.

gave informed consent before undergoing the examinations.

Shear wave elastography: SWE measurements were performed on the liver using an Aplio i900 with a 3.5-5.0 MHz convex probe (Canon Medical Systems, Otawara, Japan) in an outpatient clinic. SWE was obtained on the right lobe of the liver through the intercostal spaces at the end-expiratory period in the supine position. Patients were requested to hold their breath during the acquisition. The gray-scale image was optimized for the best acoustic window and best gain setting. A sample box of 2.0 × 2.0 cm was placed on the gray-scale image at a depth of 1.0-1.5 cm from the liver capsule to avoid reverberation artefacts and intrahepatic vessels. A 1.0 cm in diameter circular region of interest was placed on the propagation map and exhibited smooth and parallel lines. SWE was measured 10 times in each patient, and the average value was calculated.¹⁰⁾

Laboratory tests and echocardiography: Laboratory data, including liver function tests and plasma B-type natriuretic peptide (BNP) level, were collected under stable conditions in an outpatient setting. Transthoracic echocardiography was performed at the same time of SWE measurements. Left ventricular (LV) end-diastolic diameter, LV end-systolic diameter, LV ejection fraction, LV mass index, left atrial volume index, early diastolic mitral inflow velocity to mitral annular velocity ratio, tricuspid regurgitation pressure gradient, fractional area change, right atrial area, and inferior vena cava diameter were measured.

Right heart catheterization: Right heart catheterization was performed in 34 of the 36 patients within a month after the SWE measurement, on remedial judgment of the

attending physician. Pulmonary artery wedge pressure, pulmonary artery pressure, right ventricular pressure, right atrial pressure, and cardiac index were measured. The measurements were determined at the end-expiratory period, with an average of 5 cardiac cycles. Cardiac index was calculated using the indirect Fick method.

Follow-up and endpoint: Patients were followed up by clinical visits. Mortality and morbidity data were obtained from the available medical records. The primary endpoint was the complex of all-cause death or hospitalization for HF. For patients who experienced ≥ 2 events, the first event was included in the analysis.

Statistical analysis: Data are presented as the number (percentage) for categorical variables and the mean ± standard deviation for continuous variables if symmetrically distributed or the median (interquartile range) if asymmetrically distributed. The χ^2 test was used to compare categorical variables. Parametric continuous variables were compared using the Student's *t*-test, and nonparametric continuous variables were compared using the Wilcoxon rank-sum test. Kaplan-Meier curves were constructed to compare the time to an initial event between 2 groups, and were compared using the log-rank test. The univariate Cox proportional hazards analysis was performed to assess variables associated with the primary endpoint. Confidence intervals (CIs) were reported at the 95% level. Statistical analysis was performed using JMP statistical software version 14.0 (SAS Institute Inc., Cary, NC, USA). A *P* value of < 0.05 was considered statistically significant.

Table I. Baseline Characteristics

	Low SWDS group (<i>n</i> = 18)	High SWDS group (<i>n</i> = 18)	<i>P</i> value
Age, years	56 ± 20	59 ± 20	0.62
BMI, kg/m ²	22 ± 4	19 ± 4	0.02
Male sex, <i>n</i> (%)	2 (11)	5 (28)	0.40
Smoking history, <i>n</i> (%)	0 (0)	1 (6)	0.23
Home oxygen therapy, <i>n</i> (%)	11 (61)	12 (67)	0.73
Clinical classification of PH, <i>n</i> (%)			
Pulmonary arterial hypertension	15 (83)	14 (78)	0.83
PH due to left heart disease	0 (0)	0 (0)	
PH due to lung diseases and/or hypoxia	1 (6)	2 (11)	
CTEPH	2 (11)	2 (11)	
PH with unclear and/or multifactorial mechanisms	0 (0)	0 (0)	
WHO functional class, <i>n</i> (%)			0.39
Class I	4 (22)	2 (11)	
Class II	9 (50)	7 (39)	
Class III	5 (28)	8 (44)	
Class IV	0 (0)	1 (6)	
Complication, <i>n</i> (%)			
Hypertension	4 (22)	2 (11)	0.33
Diabetes mellitus	1 (6)	4 (22)	0.14
Dyslipidemia	2 (11)	2 (11)	1.0
Old myocardial infarction	1 (6)	0 (0)	0.23
Valvular heart disease	1 (6)	0 (0)	0.23
Atrial fibrillation	0 (0)	3 (17)	< 0.05
Medication for PH, <i>n</i> (%)			
Endothelin receptor antagonist	9 (50)	11 (61)	0.50
Phosphodiesterase type 5 inhibitors	7 (39)	9 (50)	0.50
Guanylate cyclase simulator	5 (28)	3 (17)	0.42
Prostacyclin analogue/prostacyclin receptor agonist	5 (28)	7 (39)	0.48
Other medications, <i>n</i> (%)			
ACE-I/ARB	1 (6)	2 (11)	0.54
Beta blockers	3 (17)	4 (22)	0.67
Calcium channel blockers	5 (28)	2 (11)	0.20
Diuretics	10 (56)	14 (78)	0.15
Statins	1 (6)	4 (22)	0.14

Data are presented as the number (percentage) or the mean ± standard deviation. SWDS indicates shear wave dispersion slope; BMI, body mass index; PH, pulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; WHO, World Health Organization; ACE-I, angiotensin converting enzyme inhibitor; and ARB, angiotensin receptor antagonist.

Results

Patient characteristics: Among the 800 patients, 65 were diagnosed with PH. Twenty-eight patients were excluded because of PH due to left-sided heart disease. One patient was excluded because of organic liver disease. Finally, 36 patients were enrolled in this study. In the whole cohort, the median age was 57 years, and 7 patients (19%) were male. Twenty-nine patients (81%) had pulmonary arterial hypertension, 3 (8%) had PH due to lung disease, and 4 (11%) had chronic thromboembolic pulmonary hypertension. Regarding World Health Organization (WHO) functional class, there were 6 patients (17%) in class I, 16 patients (44%) in class II, 13 patients (36%) in class III, and 1 patient (3%) in class IV.

The median value of SWDS was 12.4 m/second/kHz (interquartile range, 11.0, 13.4). Patients were divided into 2 groups on the basis of the median value of SWDS: a low SWDS group (SWDS < 12.4 m/second/kHz, *n* = 18) and a high SWDS group (SWDS ≥ 12.4 m/second/kHz, *n*

= 18). A comparison of the clinical characteristics is shown in Table I. The high SWDS group had a higher prevalence of atrial fibrillation. There were no significant differences in PH classification, WHO functional class, or medications between the 2 groups. A comparison of the laboratory data, echocardiographic parameters, and right heart catheterization between the 2 groups is shown in Table II. The high SWDS group had a higher tricuspid regurgitation pressure gradient and a lower tricuspid annular plane systolic excursion (TAPSE). The value of SWDS had negative mild correlation with TAPSE. There were no significant differences in plasma BNP level, aspartate transaminase level, pulmonary artery pressure, or right atrial pressure between the 2 groups.

Endpoint: During the follow-up period of 391 ± 288 days (range, 57-1197), all-cause death or hospitalization for HF occurred in 8 patients. In the high SWDS group, 3 patients died (all of whom were diagnosed with group 1 PH) and 4 patients were hospitalized for HF (3 of whom were diagnosed with group 1 PH, and 1 of whom was di-

Table II. Comparisons of Laboratory Data, Echocardiographic Parameters, and Right Heart Catheterization

	Low SWDS group (<i>n</i> = 18)	High SWDS group (<i>n</i> = 18)	<i>P</i> value
Laboratory data			
Hemoglobin, mg/dL	12.6 ± 1.9	12.5 ± 1.5	0.87
Creatinine, mg/dL	0.74 ± 0.18	0.82 ± 0.51	0.55
Estimated glomerular filtration rate, mL/minute/1.73 m ²	68 ± 19	72 ± 24	0.54
C-reactive protein, mg/dL	0.08 (0.05-0.28)	0.13 (0.06-0.91)	0.78
B-type natriuretic peptide, pg/mL	154 ± 288	179 ± 225	0.78
Platelet count, 10 ⁴ /mL	239 ± 57	209 ± 93.0	0.25
Albumin, g/dL	4.2 ± 0.5	4.0 ± 0.5	0.28
Cholinesterase, U/L	278 ± 53	250 ± 82	0.35
Total bilirubin, mg/dL	0.57 ± 0.25	0.73 ± 0.29	0.10
Aspartate aminotransferase, IU/L	20 ± 6	23 ± 5	0.16
Alanine aminotransferase, IU/L	14 ± 11	16 ± 8	0.56
Gamma-glutamyl transpeptidase, IU/L	22 ± 11	47 ± 55	0.06
Echocardiographic parameters			
Left ventricular ejection fraction, %	66 ± 4	65 ± 5	0.69
Left ventricular end-diastolic dimension, mm	42 ± 6	40 ± 7	0.26
Left ventricular end-systolic dimension, mm	27 ± 4	25 ± 5	0.12
Left ventricular mass index, g/m ²	72 ± 20	71 ± 21	0.82
Left atrial volume index, mL/m ²	32 ± 11	48 ± 32	0.06
E/e' ratio	10.3 ± 4.4	13.6 ± 5.8	0.06
Tricuspid regurgitation pressure gradient, mmHg	40 ± 16	52 ± 16	< 0.05
Tricuspid annular plane systolic excursion, mm	21 ± 5	16 ± 4	< 0.05
Fractional area change, %	38 ± 8	36 ± 7	0.29
Right atrial area, cm ²	19 ± 5	21 ± 10	0.37
Inferior vena cava diameter, mm	12 ± 4	13 ± 6	0.83
Estimated right atrial pressure, mmHg	7 ± 3	8 ± 4	0.50
Right-sided heart catheterization*			
Pulmonary artery wedge pressure, mmHg	8 ± 4	8 ± 3	0.94
Systolic pulmonary artery pressure, mmHg	47 ± 24	57 ± 15	0.17
Mean pulmonary artery pressure, mmHg	28 ± 14	35 ± 10	0.10
Systolic right ventricular pressure, mmHg	50 ± 25	60 ± 17	0.19
Right atrial pressure, mmHg	4 ± 3	5 ± 4	0.77
Cardiac index, L/m ²	2.7 ± 0.7	2.8 ± 1.0	0.89

Data are presented as the median (interquartile range) or the mean ± standard deviation. SWDS indicates shear wave dispersion slope; E/e', early diastolic mitral inflow velocity to mitral annular velocity ratio. *High SWDS group (*n* = 16).

agnosed with group 3 PH). Two of the 4 patients eventually died. In the low SWDS group, 1 patient who was diagnosed with group 1 PH died and no patients were hospitalized for HF. As shown in Figure 2, Kaplan-Meier analysis revealed that the event-free survival rate was significantly worse in the high SWDS group than in the low SWDS group (Log-rank, *P* = 0.01). In univariate Cox proportional hazards analysis, high SWDS was associated with the events (hazard ratio 10.8; 95% CI 1.89-202, *P* = 0.005). Body mass index (hazard ratio 0.74; 95% CI 0.54-0.95, *P* = 0.02) and LV ejection fraction (hazard ratio 0.74; 95% CI 0.54-0.96, *P* = 0.02) were also associated with the events.

When the patients were divided into 2 groups on the basis of the median value of SW elasticity of 6.5 kPa: low SW elasticity group (SW elasticity ≤ 6.5 kPa, *n* = 19) or high SW elasticity (SW elasticity > 6.5 kPa, *n* = 17), Kaplan-Meier analysis showed no significant difference in the event-free survival rate between the 2 groups (Log-rank, *P* = 0.14) (Figure 3).

Discussion

The major finding of this study was that SWDS was a predictor of clinical outcomes such as all-cause death or hospitalization for HF in patients with PH. There has been little research on SWE in patients with PH. To the best of our knowledge, this is the first report to show an association between SWDS and adverse outcomes in patients with PH.

PH involves multiple clinical conditions, including cardiovascular and respiratory diseases.¹¹⁾ PH consists of 5 groups: pulmonary arterial hypertension; PH due to left-sided heart disease; PH due to chronic lung disease and/or hypoxia; chronic thromboembolic pulmonary hypertension; and PH due to unclear multifactorial mechanisms.¹²⁾ Although these entities are distinct from a pathogenetic perspective, they cause severe PH and right ventricular dysfunction, leading to right-sided HF.¹³⁾ Right-sided HF develops liver congestion and further induces fibrosis and cirrhosis.^{1,2,14)}

Although medical treatments for PH have been progressing over recent decades, the prognosis remains poor. The mortality rate of patients with PH is almost 40% over

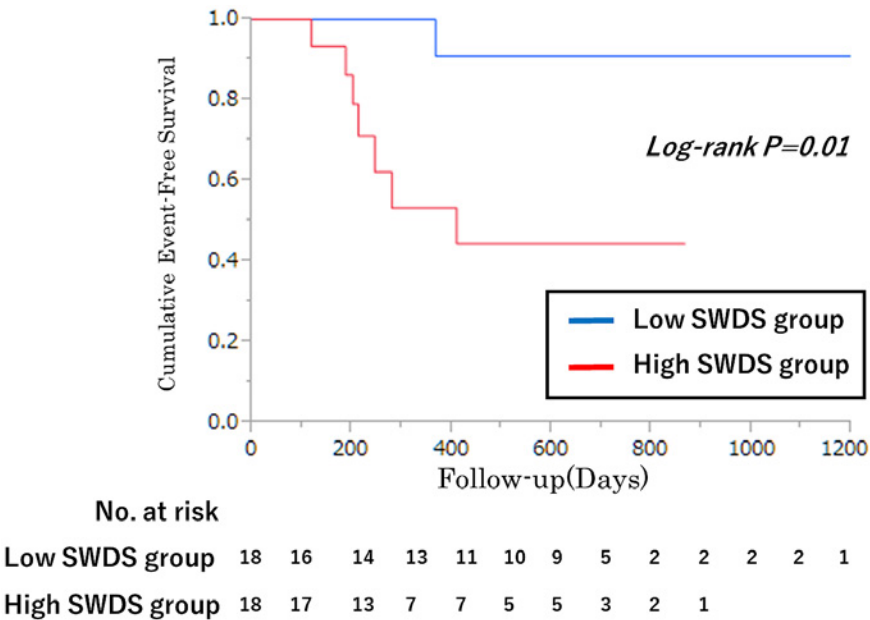


Figure 2. Kaplan-Meier curves for the event-free survival between the low SWDS group and high SWDS group. SWDS indicates shear wave dispersion slope.

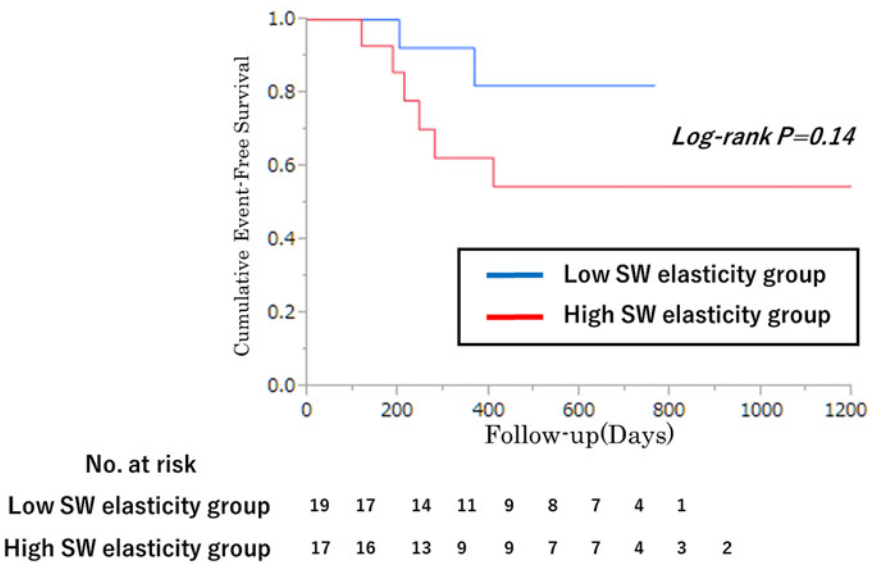


Figure 3. Kaplan-Meier curves for the event-free survival between the low SW elasticity group and high SW elasticity group. SW indicates shear wave.

5 years.¹⁵⁾ In the United States nation-wide registry, WHO functional class, 6-minute walk distance, plasma BNP level, and cardiac index are identified as prognostic factors.¹⁶⁾ In the current clinical guideline, a comprehensive assessment has been proposed for predicting the prognosis.¹¹⁾ In terms of organ damage, PH with right-sided HF causes decreased arterial perfusion, hypoxemia, and venous congestion.²⁾ Hepatic damage is one of the most important factors associated with poor prognosis in the setting of HF.¹⁷⁻¹⁹⁾ A few small studies have reported that the serum bilirubin level or serum 7S domain of collagen type

IV is a prognostic factor in patients with PH.^{20,21)} However, limited information is available regarding the evaluation of hepatic damage as a predictor of prognosis in patients with PH.

SWE enables noninvasive quantification of liver tissue by measuring the SW speed, which is generated by push pulse.³⁻⁵⁾ SWDS provides information for liver viscosity by calculating the SW speed versus frequency.^{6,7,22,23)} Ohara, *et al.* reported that SWDS was related to adverse prognosis in patients with HF.²⁴⁾ Nakayama, *et al.* reported that SWDS was elevated in the earlier HF stage compared

to SW elasticity, indicating the utility of SWDS for assessing early hepatic damage.¹⁰⁾ The present study showed that SWDS was associated with all-cause death or hospitalization for HF in patients with PH. In the population of this study, PH was well controlled by medical therapies. Right heart catheterization showed an elevation of pulmonary artery pressure but no increase in right atrial pressure or decrease in cardiac index. No elevation of liver function tests was observed. Our findings suggest that SWDS is effective for assessing the disease severity in patients with PH whose medical condition has been stabilized by PH specific medications. Whereas, in the present study, SW elasticity was not associated with all-cause death or hospitalization for HF. The persistence of hepatic congestion leads to hepatocyte atrophy around central veins, resulting in fibrosis and cirrhosis.^{14,25)} SW elasticity has been reported to increase in cirrhosis.^{8,26-28)} SW elasticity may reflect liver fibrosis caused by longstanding right-sided HF with uncontrolled PH. Thus, in the present study, SWDS, rather than SW elasticity, might be more useful to predict cardiac events.

Limitations: There are some limitations in the present study. First, the sample size was small. A larger sample size is required to confirm our finding. Second, no histological examination was performed. Validation studies of the association between histology and SWDS are required.

Conclusion

An elevated SWDS was associated with a high rate of all-cause death or hospitalization for HF in patients with PH. SWDS can be valuable to predict adverse outcomes in patients with PH.

Disclosure

Conflicts of interest: None.

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