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ORIGINAL RESEARCH

Prognostic Impact of Elevated Pulmonary Vascular Resistance in Group 2 Pulmonary Hypertension: Insights From a Japanese Multicenter Registry

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BACKGROUND: Group 2 pulmonary hypertension (PH), defined as PH caused due to left heart disease, remains a challenging condition. However, its prognostic impact and implications for emerging therapies are unclear. We aimed to evaluate the real-world relationship between pulmonary vascular resistance (PVR) and prognosis in Group 2 PH and assess the efficacy of emerging therapies.

METHODS: Two prospective registries supported by Japanese PH societies were analyzed: a current (2018–2024; n=563) and a previous (2012–2016; n=425) registry. The composite end points were hospitalization for heart failure, all-cause death, ventricular assist device implantation, or cardiac transplantation.

RESULTS: Stratified analyses using propensity score–matched data demonstrated a significant association between PVR >3 Wood units and prognosis in patients with Group 2 PH (6-year event-free rates, PVR >3 Wood units versus PVR ≦3 Wood units, previous registry: 72.9% versus 61.4%; current registry: 75.2% versus 55.4%). Consistent patterns were observed in both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction subgroups. The use of SGLT2 (sodium-glucose cotransporter-2) inhibitors in the current registry was associated with improved outcomes in patients with elevated PVR, showing event-free rates of 73.8% versus 35.5% in those without treatment. Among multivariate analyses including major treatment options, SGLT2 inhibitor treatment exhibited significant associations with improvement of composite end points.

CONCLUSIONS: Elevated PVR (>3 Wood units) identified a high-risk subset of patients with Group 2 PH. The association between the use of SGLT2 inhibitors and better outcomes suggests a potential therapeutic role that warrants further investigation through controlled studies.

Key Words: ejection fraction ■ pulmonary hypertension ■ pulmonary vascular remodeling ■ pulmonary vascular resistance ■ SGLT2 inhibitors

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CLINICAL PERSPECTIVE

What Is New?

- Management of Group 2 pulmonary hypertension remains challenging, and the prognostic impact of current emerging therapies for patients with Group 2 pulmonary hypertension are unclear.

What Are the Clinical Implications?

- Elevated pulmonary vascular resistance (>3 Wood units) identified a high-risk subset of patients with pulmonary hypertension in Group 2, possibly reflecting pulmonary vascular remodeling.
- The association between the use of SGLT2 (sodium-glucose cotransporter-2) inhibitors and better outcomes in this group suggests a potential therapeutic role that warrants further investigation through controlled studies.

Nonstandard Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
mPAP	mean pulmonary artery pressure
NYHA	New York Heart Association
PAWP	pulmonary artery wedge pressure
PH	pulmonary hypertension
RHC	right heart catheterization
SGLT	sodium-glucose cotransporter
WU	Wood units

Pulmonary hypertension (PH) due to left-sided heart disease, classified as Group 2 PH by the World Health Organization and European Society of Cardiology/European Respiratory Society guidelines, accounts for over half of all PH cases and is associated with poor outcomes.[1] Elevated pulmonary vascular resistance (PVR) in this population likely reflects pulmonary vascular remodeling in addition to passive congestion and identifies a subset at particularly high risk.[2,3] Although hemodynamic definitions have improved characterization of combined pre- and postcapillary PH,[4,5] effective treatments for patients with elevated PVR are still lacking.

From the aspect of left ventricular ejection fraction (LVEF), previous reports demonstrated relatively higher prevalence (58.7%) of heart failure (HF) with preserved ejection fraction (HFpEF) in Group 2 PH, than in HF with reduced ejection fraction (HFrEF) (41.2%).[3] Furthermore, survival rates of both HFpEF and HFrEF associated with PH were similarly poor.[3]

Recent advances in HF management, especially in HFrEF, have highlighted disease-modifying agents, including beta blockers, renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists (MRAs), and SGLT2 (sodium-glucose cotransporter 2) inhibitors. Among these, SGLT2 inhibitors have also demonstrated prognostic benefits in HFpEF and are now recommended for a broad spectrum of patients with HF.[6] Beyond glucose-lowering and diuretic effects, SGLT2 inhibitors have been reported to reduce left-sided filling pressures, improve endothelial function, and attenuate pulmonary vascular congestion—mechanisms that may influence right ventricular afterload and pulmonary circulation.[7]

However, whether these benefits extend to patients with Group 2 PH, especially those with an elevated PVR, remains unclear. This study aimed to evaluate the real-world relationship between PVR and prognosis in Group 2 PH and assess the potential therapeutic role of emerging therapies in this high-risk subgroup.

METHODS

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

Study Design and Participants

This study compared 2 prospective registries of patients with group 2 PH in Japan. The current registry, conducted by the JAPHR (Japanese Pulmonary Hypertension Registry) in collaboration with the Japanese Pulmonary Circulation and Pulmonary Hypertension Society, enrolled 563 patients from 15 hospitals and universities between January 2018 and December 2024. As the historical control, data from a previous registry conducted by the Japanese Pulmonary Circulation Society (the predecessor of the Japanese Pulmonary Circulation and Pulmonary Hypertension Society), in which 425 patients were enrolled between 2012 and 2016 at 6 institutions, were reanalyzed. In this study, the outcomes were analyzed as time-to-event end points over the entire follow-up period, rather than at a fixed time point. The median follow-up duration was 3.78 years (interquartile range [IQR], 2.21–5.52 years) in the 2012 to 2016 registry and 1.73 years (IQR, 0.76–3.55 years) in the 2018 to 2024 registry.

In both registries, patients with PH secondary to left heart disease were prospectively enrolled based on right heart catheterization (RHC). The diagnosis followed the 2015 European Society of Cardiology/European Respiratory Society guidelines,[4] defined as

mean pulmonary artery pressure (mPAP) ≥25 mm Hg and pulmonary artery wedge pressure (PAWP) >15 mm Hg at rest. The cause of HF was confirmed using echocardiography, chest computed tomography, spirometry, ventilation/perfusion scans, and RHC to exclude other causes. HFrEF was defined as LVEF <50%, and HFpEF as LVEF ≥50%, according to the same guidelines.[4]

Patients received guideline-directed medical therapy for HF.[4,5,8] Follow-up began at the time of RHC and continued through regular outpatient visits. The primary composite end point was defined as the first occurrence of all-cause mortality or hospitalization due to worsening HF during the follow-up period. Events were adjudicated at each participating institution based on the Framingham Criteria and medical records. Secondary end points included each component of the composite outcome. Time-to-event analyses began on the date of the RHC.

Both registries adhered to the Declaration of Helsinki and were approved by their respective institutional review boards. Written informed consent, including consent for secondary data use, was obtained from all participants (current registry: Approval No. R1919; previous registry: 2019-1-24). Secondary analysis was conducted using an opt-out process approved by the ethics committee (Approval No. 2025–1-159).

Statistical Analysis

Continuous variables are presented as mean±SD or median with (IQR, as appropriate. Categorical variables are expressed as counts and percentages. Group comparisons were performed using Student's *t* test for normally distributed variables with equal variance and the Mann–Whitney *U* test was used for skewed data or unequal variances. Categorical variables were compared using the chi-square or Fisher's exact tests.

Survival analyses were conducted using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards models were used to identify factors independently associated with the composite end point, including clinical characteristics, hemodynamic parameters, and pharmacological treatments (eg, SGLT2 inhibitors, MRAs, beta blockers).[9] Cox proportional hazard models were used to evaluate the association between composite end points and PVR, with adjustments for basic characteristics described subsequently.[10] Multivariable models included covariates with *P* values of <0.10 in univariate analyses, or those deemed clinically relevant. Hazard ratios (HRs) and 95% CIs were calculated.

Missing data were addressed using complete-case analysis for propensity score matching (PSM). There were no missing values in the primary outcome variables used for survival analyses. To account for baseline differences between patients with PVR ≤3 Wood units (WU) and those with PVR >3 WU, we applied a PS approach in combination with Cox proportional modeling. The PS was estimated using a logistic regression model in which PVR >3 WU was regressed on 8 baseline variables: age, sex, body mass index, New York Heart Association (NYHA) classification, chronic kidney disease, plasma BNP (brain natriuretic peptide), mPAP, PAWP, and enrollment periods (previous or current registry). Patients were matched 1:1 using an optimal matching algorithm with a caliper of <0.001 and without replacement. Standardized mean differences before and after matching are presented in Table S1 and Figure S2.

In the PS–matched cohort, we conducted restricted cubic spline analyses within adjusted logistic regression models to examine the association between PVR and the composite end point.

Additionally, to evaluate potential effect modification, an interaction term between EF and PVR was evaluated by multivariate linear regression model.

Statistical significance was defined as a 2-sided *P* value of <0.05. Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA) and R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics and Hemodynamic Profile

Baseline characteristics of the study population are summarized in Table 1. The previous and current registries demonstrated similar distributions of sex (female, 36.0% versus 36.5%), age (63.1±14.3 versus 63.4±15.8 years), and body mass index (23.5±4.8 versus 24.1±4.8 kg/m^2). Despite a higher median BNP level in the previous registry (444 [IQR, 195–954] versus 312 [IQR, 131–628] pg/mL), the prevalence of NYHA class III or higher was comparable (77.0% versus 78.0%), indicating similar clinical severity of HF.

In terms of echocardiographic findings, the previous registry included a higher proportion of patients with HFrEF (previous versus current registry, EF <50%: 44.6% versus 56.4%), whereas the current registry showed a higher prevalence of HFpEF (EF ≥50%: 55.3% versus 43.5%). Hemodynamic parameters, including mPAP, PVR, PAWP, and right atrial pressure, were comparable between the 2 cohorts. However, cardiac index was modestly higher in the current registry (3.2±1.4 versus 2.6±0.8 L/min/m^2, *P*=0.457) (Table 1).

Comparison of Medical Treatment for Group 2 PH Between Previous and Current Registries

Figure 1 and Table S2 present the medication use stratified by HFpEF and HFrEF at the initial treatment

Table 1. Baseline Characteristics of Patients With Group 2 Pulmonary Hypertension

	2012–2016 registry		2018–2024 registry		
	425		563		
Number	PVR ≤3 WU	PVR >3 WU	PVR ≤3 WU	PVR >3 WU	*P* value (previous vs current registry)
Age, y	61.7±15.1	66.0±12.2	62.7±16.0	65.0±14.9	0.226
Female sex, n, %	191 (68.2)	78 (53.7)	128 (31.9)	78 (47.8)	0.997
Body mass index, kg/m^2	23.8±5.1	23.0±4.2	24.3±4.8	23.6±4.5	0.239
New York Heart Association functional classification, ≥III(n, %	92 (39.1)	62 (49.2)	231 (63.1)	116 (79.4)	0.463
eGFR, mL/min/1.73 m^2	46.6 (29–60)	43.5 (29–61)	55.1 (39–69)	49.9 (37–63)	0.034
BNP, pg/mL	381.0 (157–786)	574 (223–1181)	245 (106–548)	499.4 (245–949)	0.226
	2012–2016 registry		2018–2024 registry		
Echocardiography	PVR ≤3 WU	PVR >3 WU	PVR ≤3 WU	PVR >3 WU	*P* value (previous vs current registry)
LVEF, %	50.6±19.1	50.7±21.7	44.1±20.0	44.3±20.2	<0.001
EF <50%	125 (45.2)	61 (43.5)	226 (56.5)	93 (57.0)	<0.001
EF ≥50%	151 (54.7)	79 (56.4)	175 (43.7)	70 (42.9)	<0.001
LV end-diastolic diameter, mm	No data	55.3±12.2	54.3±13.3		
Left atrial diameter	No data	45.9±10.4	46.2±9.1		
E/e'	No data	16.7±9.3	18.5±10.4		
Tricuspid annular plane systolic excursion	No data	13.5±8.7	11.5±8.1		
Transtricuspid pressure gradient, mmHg	31.8±11.5	45.3±18.0	29.7±13.4	39.6±16.3	0.068
Hemodynamic					
Mean pulmonary arterial pressure, mmHg	30.7±5.32	37.2±8.5	27.6±5.4	37.7±9.3	0.099
PVR, dyne-sec-cm^{-5}	144.1±50.8	369.9±146.2	135.6±51.8	378.7±160.0	0.149
Pulmonary arterial wedge pressure, mmHg	22.7±5.4	21.9±6.1	20.4±5.0	22.4±6.1	0.443
Right atrial pressure, mmHg	10.4±5.3	9.8±5.2	8.6±4.5	10.0±5.6	0.119
Cardiac index, L/min/min^2	2.7±0.7	2.3±0.6	3.4±3.4	2.4±2.8	0.457
Mean aortic pressure, mmHg	No data	86.4±25.2	79.2±35.5		
Heart rate, bpm	76.1±18.1	77.6±17.9	74.5±17.7	76.6±19.2	0.166
Peripheral oxygen saturation, %	No data	92.3±17.3	91.7±17.1		

Patient demographics, echocardiographic findings, and hemodynamic parameters were collected at the time of the initial hospitalization in each registry. Continuous variables are presented as mean±SD, except for eGFR and BNP, which are shown as medians with interquartile ranges. Comparisons between groups were conducted using the Mann–Whitney *U* test. BNP indicates brain natriuretic peptide; EF, ejection fraction; eGFR, estimated glomerular filtration rate; LV, left ventricular; PVR, pulmonary vascular resistance; and WU, Wood unit.

during RHC, as well as the medications during follow-up after HF management.

Consistent with guidelines at each period, patients with HFrEF had higher use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (follow-up treatment; previous versus current registry: 92.9% versus 42.6%), beta blockers (75.7% versus 86.5%), and MRAs (62.3% versus 77.4%) in both registries. Major differences between registries included the introduction of SGLT2 inhibitors (59.2% at follow-up), angiotensin receptor neprilysin inhibitors (37.6%), hyperpolarization-activated cyclic nucleotide-gated channel blockers (3.1%), and soluble guanylate cyclase stimulators (vericiguat; 13.1%) in the current registry. Medication titration during follow-up, including switching from angiotensin-converting enzyme inhibitors/angiotensin receptor blockers to angiotensin receptor neprilysin inhibitors, was also notable in the current registry (Figure 1).

For patients with HFpEF, treatment largely reflected recent guideline recommendations or the American College of Cardiology consensus, with a focus on SGLT2 inhibitors (40.4% at follow-up) and angiotensin receptor neprilysin inhibitors (21.6%). However, beta blockers were still frequently prescribed (62.0%)

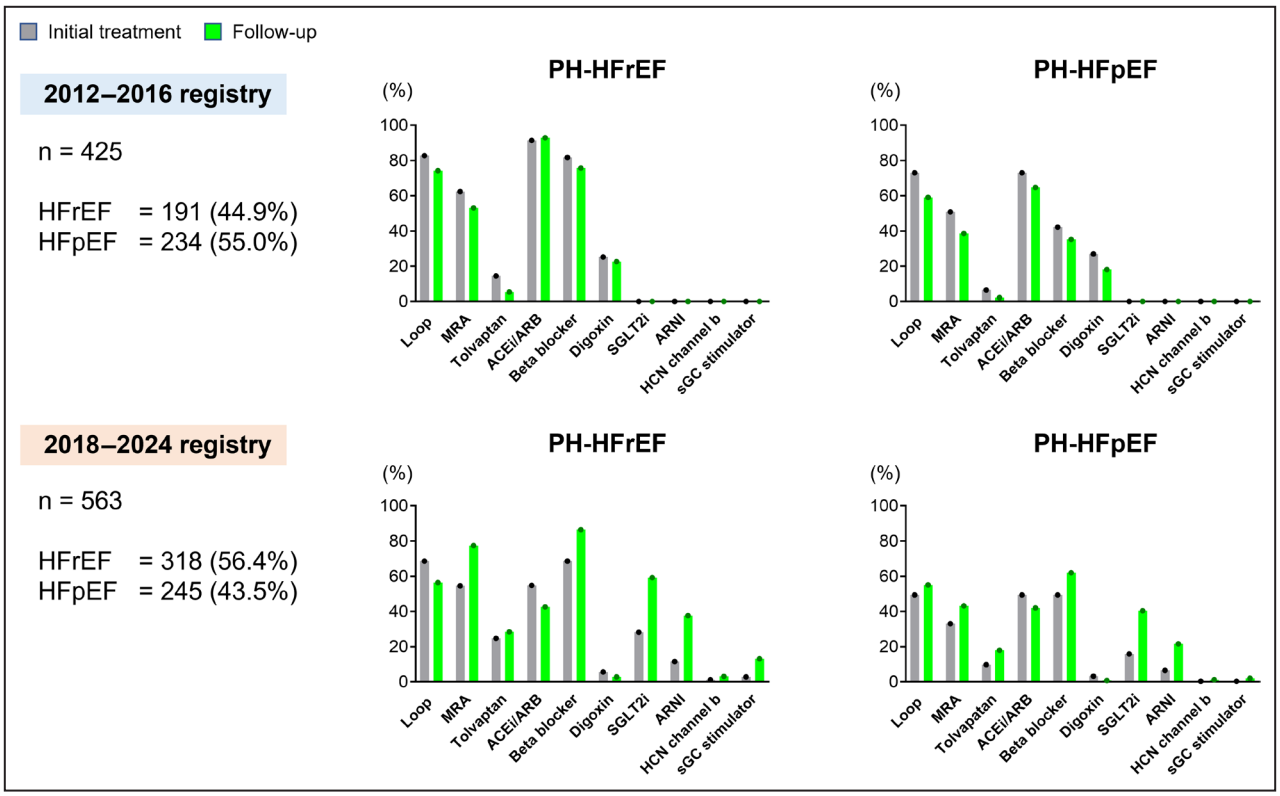

Figure 1. Medical therapies for patients with HFrEF and HFpEF in the previous and current registries.
"Initial treatment" refers to medications administered at the time of cardiac catheterization at the enrolling facility. "Follow-up" indicates treatments prescribed after initial heart failure management. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HCNi, hyperpolarization-activated cyclic nucleotide-gated channel inhibitor; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Loop, loop diuretics; MRA, mineralocorticoid receptor antagonist; PH, pulmonary hypertension; sGC, soluble guanylate cyclase stimulator; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

despite limited guideline support, reflecting real-world clinical practice.

Comparison of Prognosis for Patients With PH-HFrEF or PH-HFpEF Between Previous and Current Registries

In both the individual registries and the combined cohort, patients with Group 2 PH demonstrated comparable prognostic patterns (event-free rate at 6 years: combined cohort 61.8%, previous registry 64.4%, current registry 62.9%) (Figure 2). Multivariate analyses confirmed high PVR as an independent risk factor for adverse prognosis in patients with Group 2 PH (Table 2). In the combined PS–matched cohorts, restricted cubic spline analysis demonstrated an inflection point at ~200 dyne-second-cm^{-5} (2.5 WU). As clear numerical values are preferable from a clinical perspective, we explored the prognostic impacts of PVR >2 WU and 3 WU. After PSM as well as in the unmatched analyses, patients with Group 2 PH and PVR >3 WU had a significantly worse prognosis (HR, 1.78 [95% CI, 1.39–2.28], P<0.0001), whereas those with PVR >2 WU did not show a consistent association (HR, 1.09 [95% CI, 0.071–1.182], P=0.081) (Figure 2 and Figure S1).

These results were consistent with the criteria for combined pre- and postcapillary PH at the World Symposium on Pulmonary Hypertension in 2018 (mPAP >20 mm Hg, PAWP >15 mm Hg, PVR >3 WU).[11]

In the previous registry, patients with PVR >3 WU (n=137) had worse outcomes compared with those with PVR ≤3 WU (n=279) (HR, 1.74 [95% CI, 1.21–2.49], P=0.0035), although the association was not statistically significant after PSM, likely due to the smaller matched sample size (each group n=118; HR, 1.24 [95% CI, 0.77–1.98], P=0.184) (Figure 2). In contrast, in the current registry, PVR >3 WU was associated with significantly poorer prognosis both before (HR, 1.96 [95% CI, 1.30–2.95], P=0.0012) and after PSM (HR, 1.92 [95% CI, 1.18–3.13], P=0.010) (Figure 2 and Table 2). Consistent with these findings, multivariable

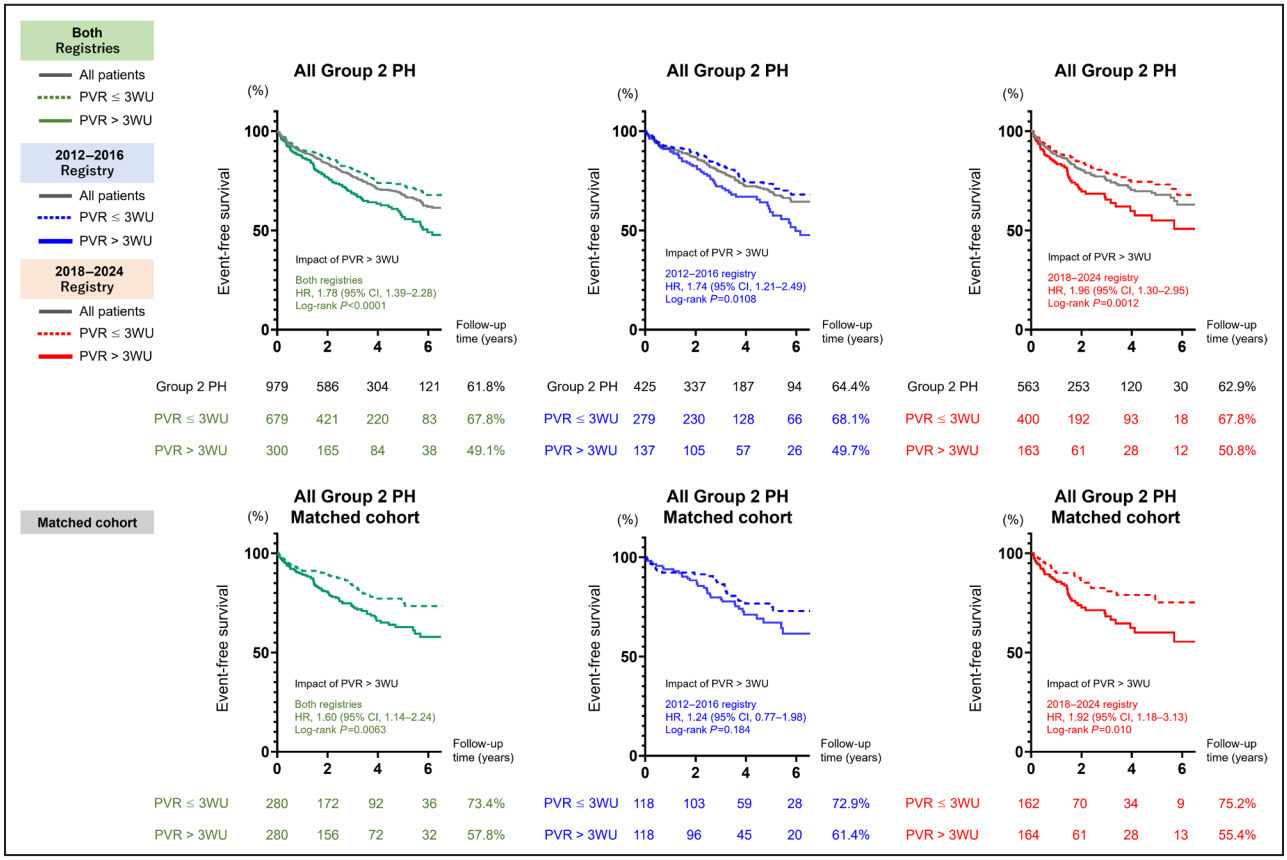

Figure 2. Prognosis of patients with Group 2 PH in previous and current registries.
Kaplan–Meier curves depicting the incidence of composite end points, including cardiac death, heart failure hospitalization, left ventricular assist device implantation, and heart transplantation, during follow-up in patients with Group 2 PH (combined cohorts, n=979, previous registry, n=425; current registry, n=563). Nine patients in the previous registries lacked PVR values, and the total number of patients classified according to PVR was 416. To account for baseline differences between patients with PVR ≤3 WU and those with PVR >3 WU, PS method was used in previous and current registries. For the calculation of PS, we used a logistic regression model in which the PVR >3 WU was regressed for the following 8 baseline characteristics: age, sex, body mass index, New York Heart Association classification, chronic kidney disease, plasma BNP and mean pulmonary artery pressure, pulmonary artery wedge pressure, and enrollment periods (current or previous). BNP indicates brain natriuretic peptide; HR, hazard ratio; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; and WU, Wood unit.

Cox proportional hazards analyses in the matched cohorts—including factors with SMD >0.1 (age, sex, mPAP, PAWP, and BNP) (Figure S2)—confirmed that PVR >3 WU was an independent risk factor in the current registry, whereas this association was not observed in the previous registry (Table 3 and Table S3).

In the current registry, the event free rate of HF hospitalization was significantly poor in patients with associated PVR >3 WU (HR 2.11, 95% CI 1.36–3.28, *P*=0.0008) while the all-cause death (HR 1.11, 95% CI 0.41–2.97, *P*=0.836) and ventricular assist device/heart implantation (HR 1.19, 95% CI 0.43–3.30, *P*=0.739) were comparable (Figure S3).

The cause of HF differed between cohorts, with a higher prevalence of valvular disease in the previous registry (41.1% versus 22.9%). As shown in Table S4, exploratory analysis suggested a higher prevalence of PVR >3 WU in patients with atrial fibrillation (42.1%) and hypertrophic cardiomyopathy (40.0%) in the current cohort; however, statistical comparisons were limited because of the small number of cases in each subgroup.

In patients with PH-HFrEF, those with PVR >3 WU in the current registry demonstrated significantly worse outcomes than those with a lower PVR (HR 1.86, 95% CI 1.15–3.00; log-rank *P*=0.004), suggesting that elevated PVR remains an important prognostic marker in PH-HFrEF despite current treatments (Figure 3).

Among patients with PH-HFpEF, those associated with PVR >3 WU exhibited a numerically higher risk of adverse outcomes than those with a lower PVR, although the difference did not reach statistical significance (HR 1.70, 95% CI 0.78–3.71; log-rank *P*=0.179) (Figure 3). This finding suggests a modest improvement in clinical outcomes in more recent practices.

Table 2. Univariate and Multivariate Cox Proportional Analyses in Patients With Group 2 PH of Associations Between Composite End Points and Each Factor

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	0.991	0.980–1.003	0.164			
Sex	1.006	0.709–1.603	0.758			
Body mass index	0.973	0.933–1.016	0.213			
Diabetes	1.229	0.795–1.899	0.352			
Chronic kidney disease	1.118	0.750–1.667	0.583			
New York Heart Association functional classification ≧III	1.595	1.047–2.431	0.029	1.284	0.825–1.998	0.268
Brain natriuretic peptide	1.000	1.000–1.001	0.010	1.000	0.999–1.000	0.345
Ejection fraction	0.985	0.976–0.995	0.003	0.990	0.978–1.001	0.078
Mean pulmonary arterial pressure at diagnosis	1.021	0.999–1.044	0.061	0.967	0.927–1.008	0.121
Pulmonary arterial wedge pressure at diagnosis	1.036	1.000–1.073	0.049	1.033	0.981–1.089	0.213
Pulmonary vascular resistance at diagnosis	1.002	1.000–1.003	0.003	1.002	1.000–1.004	0.001
Mineralocorticoid receptor antagonist	1.305	0.867–1.962	0.202			
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor	0.799	0.542–1.177	0.257			
Beta blocker	1.761	1.002–3.095	0.049	1.586	0.872–2.885	0.130
Sodium-glucose cotransporter 2 inhibitor inhibitor	0.676	0.455–1.005	0.053	0.528	0.347–0.801	0.002

Univariate analyses included baseline characteristics, left ventricular ejection fraction, hemodynamic parameters, and major treatments administered during follow-up. Variables with statistical significance or a strong trend in univariate analyses were entered into the multivariate model. HR indicates hazard ratio; and PH, pulmonary hypertension.

Impact of SGLT2 Inhibitor Treatment for Patients With Group 2 PH

SGLT2 inhibitor use was associated with improved prognosis among patients with elevated pulmonary vascular resistance (PVR >3 WU) (HR 0.30, 95% CI 0.17–0.54; log-rank *P*<0.0001), whereas no significant association was observed in those with PVR <3 WU (Figure 4).

In patients with PH-HFrEF and PVR >3 WU, SGLT2 inhibitor treatment was significantly associated with lower risk of adverse outcomes (HR 0.22, 95% CI 0.11–0.45; log-rank *P*<0.0001). A similar trend was observed in patients with PH-HFpEF, although the association did not reach statistical significance, possibly owing to the limited sample size (HR 0.34, 95% CI 0.10–1.07; log-rank *P*=0.065). In the univariate analyses, NYHA class, BNP level, EF, mPAP, PAWP, PVR, and treatment with either beta-blockers or SGLT2 inhibitors were significantly associated with the primary outcome (Table 2). In the multivariate analyses incorporating these factors, both PVR and SGLT2 inhibitor treatment remained independently associated with prognosis (Table 2). Among patients with PVR >3 WU, multivariate analysis further indicated that SGLT2 inhibitor use was independently associated with improved clinical outcomes compared with other HF therapies, such as MRA, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, and beta-blockers (Table 4). These findings suggest a potential benefit of SGLT2 inhibitors in the management of group 2 PH, particularly in the presence of elevated pulmonary vascular resistance.

DISCUSSION

This study identified the following key findings regarding Group 2 PH:

1. elevated PVR was consistently associated with worse prognosis in both the previous and current regions;
2. the adverse prognostic impact of elevated PVR was observed regardless of the LVEF or underlying cause; and
3. treatment with SGLT2 inhibitors was associated with improved prognosis in patients with Group 2 PH, particularly in those with PVR >3 WU.

Changes in Management Strategies and Remaining Challenges in Group 2 PH

Over the past decade, the European Society of Cardiology/European Respiratory Society guidelines, AHA/American College of Cardiology consensus statements, and multiple clinical trials have transformed the treatment landscape for HF, especially for HFpEF and HFrEF.[5,6] However, the prognosis of patients with

Table 3. Cox Proportional Model Analyses of Association Between Composite End Points and PVR >3 WU of Patients With Group 2 PH in Previous (2012–2016) and Current (2018–2024) Registries

Cox proportional model for composite end points				
Registry	No. of event/ total (%)	HR	95% CI	*P* value
Previous registry: Adjusted with propensity score				
PVR >3 WU of patients with Group 2 PH	71/236 (30.0)	1.380	0.863–2.208	0.178
Current registry: Adjusted with propensity score				
PVR>3 WU of patients with Group 2 PH	65/324 (20.0)	1.956	1.045–3.659	0.035
Both registries: Adjusted with propensity score				
PVR >3 WU of patients with Group 2 PH	136/560 (24.2)	1.515	1.046–2.194	0.027

To account for baseline differences between patients with PVR ≤3 WU and those with PVR >3 WU, PS method was used in previous and current registries. For the calculation of PS, we used a logistic regression model in which the PVR >3 WU was regressed for the following 8 baseline characteristics: age, sex, body mass index, New York Heart Association classification, chronic kidney disease, plasma BNP and mPAP, PAWP, and enrolled terms in both registries. In the matched samples, age, mPAP, PAWP, and BNP still showed larger standardized mean difference (>0.1) in the cohorts (Figure S2). To adjust them in the Cox proportional hazard model, multivariate analyses within each propensity score matched data. The PS was included in the Cox proportional hazards model in the cohort after PS matching. BNP indicates brain natriuretic peptide; HR, hazard ratio; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PS, propensity score; PVR, pulmonary vascular resistance; and WU, Wood unit.

Group 2 PH has not markedly improved between previous and current registries, underscoring persistent therapeutic limitations in this population.

For patients with PH-HFpEF, the current registry showed better outcomes (event-free rate at 6-year follow-up, previous versus current registry, 63.7% versus 73.4%) (Figure 3 and Figure S4) although comparison with historical controls is complicated. Several advances have contributed to the improvements observed. First, enhanced diagnostic accuracy through scoring systems such as the H_2FPEF score, which incorporates clinical and echocardiographic parameters (e.g., body mass index, atrial fibrillation, and filling pressures), has enabled earlier and more targeted management.[6] Second, the increasing use of catheter-based interventions—such as transcatheter aortic valve implantation \ and transcatheter mitral valve repair—has expanded treatment options for high-risk patients previously deemed unsuitable for surgery. Third, there has been a paradigm shift in medical therapy, which has evolved from symptom-focused diuresis to multidrug strategies validated in trials such as the DELIVER, EMPEROR-PRESERVED, and PARAGON-HF.[12–14] Although these studies did not specifically target PH, their broad inclusion criteria likely benefited a substantial proportion of patients with HFpEF and concomitant PH.

In contrast, the prognosis for patients with PH-HFrEF showed a worse prognosis (event-free rate at 6-year follow-up; previous versus current registry, 65.2% versus 54.5%) (Figure S4). Despite the implementation of guideline-directed medical therapy (the so-called "fantastic four") and the expanded use of left ventricular assist devices (LVADs) following the 2021 revision of Japanese guidelines,[15] several challenges remain. Notably, the current cohort includes a higher proportion of patients with advanced symptoms (NYHA class ≥III: 49.2% versus 70.2%), suggesting more severe HF at enrolment. Additionally, differences in the participating institutions and referral patterns between the two registries may have influenced patient characteristics and outcomes.

In both HFpEF and HFrEF, the composite end points were primarily driven by differences in HF hospitalization rather than LVAD/transplant or all-cause mortality (Figure S3). This may reflect the fact that the analysis was largely based on first events recorded at the enrolling institution. Some patients may have been transferred to other centers for LVAD implantation or heart transplantation, or lost to follow-up for other reasons, leading to censoring at the time of HF hospitalization and incomplete capture of subsequent outcomes. To address this limitation, future studies should consider revised enrollment strategies or collaborative designs involving a broader network of institutions and larger patient populations.

Potential Mechanisms Underlying Elevated PVR in Group 2 PH

The pathophysiology of elevated PVR in Group 2 PH has not been fully defined. Traditionally, the increase in PVR has been attributed to a "reactive" response to chronically elevated pulmonary venous pressure, resulting in pulmonary arterial remodeling. However, recent perspectives suggest that elevated PVR may also reflect impaired forward flow due to reduced cardiac output, complicating the interpretation of this parameter.[16] In the present study, PVR levels appeared largely independent of left atrial pressure surrogates such as PAWP, suggesting that other factors may contribute to pulmonary vascular changes in this population.

Although no specific cardiac cause was statistically linked to elevated PVR, patients with hypertrophic cardiomyopathy (40.0%) and atrial fibrillation (41.1%) more frequently exhibited PVR >3 WU (Table S4). These findings may reflect the structural or electrical influences that promote pulmonary vascular stress or impaired compliance. The current study did not include non-cardiac factors, such as connective tissue diseases or endocrine and hematologic disorders, which might also influence pulmonary vascular resistance in some patients.

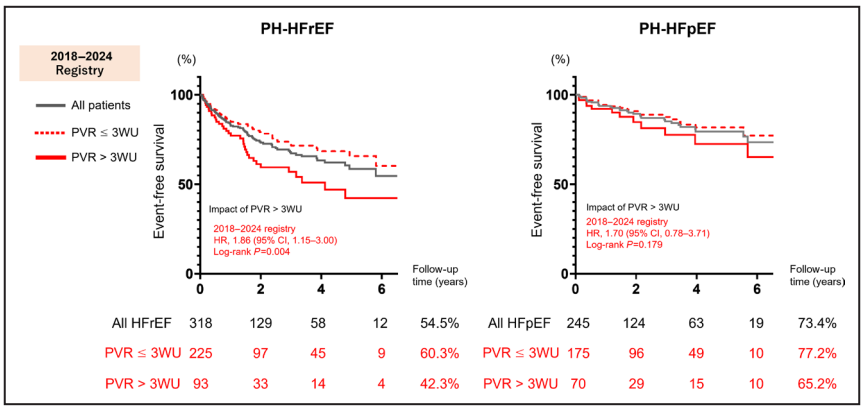

Figure 3. Prognosis of patients with PH-HFrEF in previous and current registries. Kaplan–Meier curves showing the incidence of composite end points, including cardiac death, heart failure hospitalization, left ventricular assist device implantation, and heart transplantation, during follow-up in patients with PH-HFrEF (n=318), and PH-HFpEF (n=245). HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; and WU, Wood unit.

Recent studies have described overlapping pathobiology between Group 1 and Group 2 PH, including alterations in vascular remodeling, mitochondrial function, and endothelial signaling.[17] Although such changes have not been directly assessed in this cohort, they may contribute to disproportionate PVR elevation in certain patients. Further research using tissue-level or molecular techniques may clarify the mechanisms of pulmonary vascular involvement in group 2 PH and help identify potential therapeutic targets.

Therapeutic Potential of SGLT2 Inhibitors in Group 2 PH

There was no significant difference in the parameters of cardiac function or hemodynamics in Group 2 PH patients with or without SGLT2 inhibitor treatment (Table S5). In addition to the observed parameters, RV-PA coupling, calculated by TAPSE/RVSP and assessment of the balance between RV systolic function and pulmonary flow resistance, was also evaluated but did not show significant differences in patients treated with SGLT2 inhibitors (Table S6). Our data demonstrated the clinical benefit of SGLT2 inhibitor treatment; however, the underlying mechanism remains unclear.

SGLT2 inhibitors regulate glucose homeostasis via renal glucose excretion and exert pleiotropic effects on the metabolic and vascular pathways. These include modulation of adiposity, intrarenal renin–angiotensin system activity, plasma leptin levels, and androgen metabolism, as well as improvement of mitochondrial function and oxidative stress.[7] Given that pulmonary vascular remodeling in Group 2 PH may arise from subclinical metabolic dysfunction or mechanisms not captured by conventional diagnostics, such systemic effects of SGLT2 inhibitors could contribute to improved pulmonary vascular tone and structure. Previous reports, including ours, have suggested that these agents may attenuate pulmonary vascular dysfunction by reducing oxidative stress, modulating mitochondrial activity, and altering metabolite signaling.[18–20] Further investigation is warranted to clarify these mechanisms and their relevance in group 2 PH with elevated PVR.

In the present study, 59% of patients with HFrEF and 40.4% of those with HFpEF were treated with SGLT2 inhibitors (Figure 1), a rate that appears suboptimal considering current guideline recommendations. In practice, their use may be avoided for older patients, patients with reduced appetite, or those with impaired renal function. However, baseline characteristics, including age, body mass index, and estimated glomerular filtration rate (eGFR), did not differ substantially between patients treated with or without SGLT2 inhibitors in this cohort (Table S4). These findings suggest that the broader implementation of guideline-directed medical therapy could facilitate more consistent use of SGLT2 inhibitors, potentially enhancing clinical outcomes. From a mechanistic perspective, soluble guanylate cyclase (sGC) stimulation may be relevant in patients with elevated PVR. Although vericiguat has been reported to improve RV–PA coupling,[21,22] the limited number of treated patients in this study precluded a detailed analysis. Further studies are warranted to evaluate its potential in Group 2 patients.

LIMITATIONS

This study has some limitations. First, the both registries did not collect information regarding the dose or titration

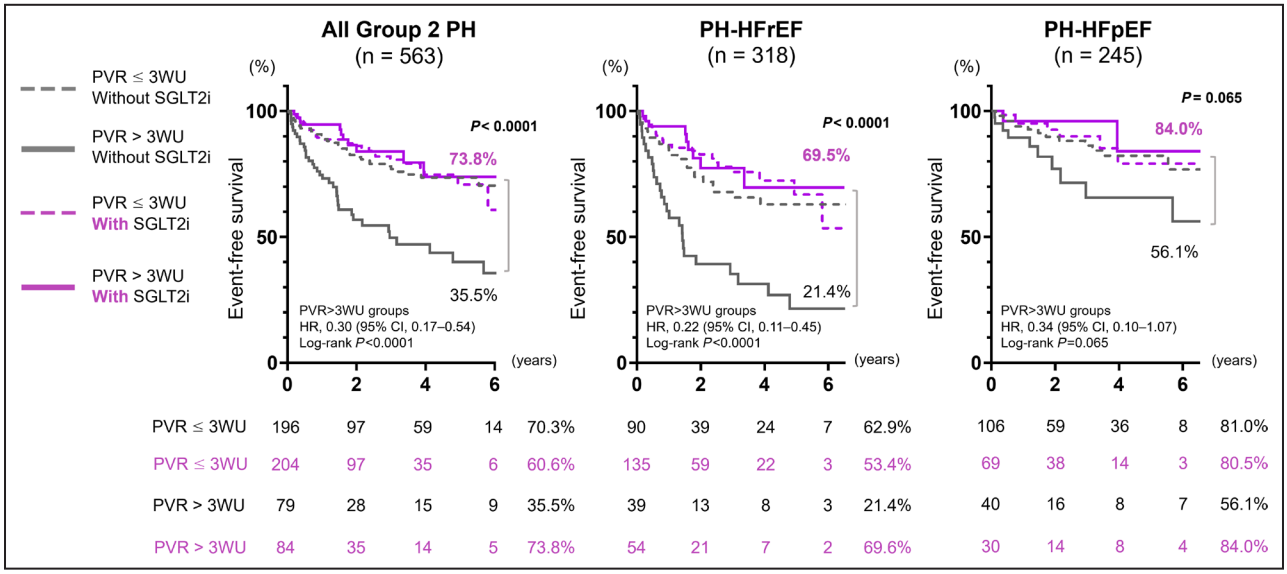

Figure 4. Treatment with SGLT2 inhibitors ameliorated the prognosis of patients with Group 2 PH associated with PVR >3 WU.

Kaplan–Meier curves for the composite end point (cardiac death, heart failure hospitalization, left ventricular assist device implantation, and heart transplantation) during follow-up in patients with Group 2 PH, HFrEF, and HFpEF treated with or without SGLT2 inhibitors. HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SGLT2i, sodium-glucose cotransporter-2 inhibitor; and WU, Wood unit.

status of each pharmacological therapy, which may have influenced the outcomes. Second, comparison between the previous and current registries has inherent limitations. Because they were conducted in different time periods, secular changes in clinical practice, diagnostic modalities, and treatment strategies may have affected patient backgrounds and outcomes. Although PSM balanced measured baseline characteristics, it cannot adequately account for bias related to temporal differences. Although this study explored the differences of clinical

Table 4. Univariate and Multivariate Cox Proportional Analyses in Patients With Group 2 PH Associated With PVR >3 WU of Associations Between Composite End Points and Each Factor

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	0.986	0.968–1.005	0.146			
Sex	1.677	0.890–3.156	0.109			
Body mass index	1.020	0.958–1.086	0.528			
New York Heart Association functional classification ≧III	1.461	0.672–3.174	0.338			
Brain natriuretic peptide	1.000	0.999–1.001	0.572			
Ejection fraction	0.989	0.975–1.004	0.164			
Mean pulmonary arterial pressure at diagnosis	1.001	0.968–1.035	0.944			
Pulmonary arterial wedge pressure at diagnosis	1.031	0.983–1.081	0.209			
PVR at diagnosis	1.001	0.998–1.002	0.548			
Mineralocorticoid receptor antagonist	0.945	0.506–1.764	0.860	1.085	0.578–2.037	0.799
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor	0.869	0.471–1.604	0.655	1.067	0.567–2.007	0.840
Beta blocker	1.207	0.557–2.614	0.633	1.717	0.778–3.792	0.180
Sodium-glucose cotransporter 2 inhibitor inhibitor	0.315	0.158–0.628	0.001	0.275	0.134–0.564	<0.001

For this analysis, the population was limited to patients with Group 2 PH and PVR >3 WU. Univariate analyses included baseline characteristics, cardiac function (ejection fraction), hemodynamic parameters, and representative treatments during follow-up. Multivariate analyses included parameters that exhibiting statistical significance or a strong trends in the univariate analyses among these factors. HR indicates hazard ratio; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; and WU, Wood unit.

impact of high PVR in HFpEF or HFrEF due to clinical perspective, in this cohort, the interaction between EF and PVR was not significant (Table S7). Another limitation of the present study is the lack of information on the clinical indication for SGLT2 inhibitor therapy—whether it was initiated for HF, diabetes, or chronic kidney disease—although SGLT2 inhibitor treatment was independently associated with prognosis (Table S8).

CONCLUSIONS

Elevated PVR (>3 WU) is a crucial factor in determining the prognosis in patients with Group 2 PH. Treatment with SGLT2 inhibitors may provide clinical benefits in this population, particularly among those with higher PVR, and warrants further investigation.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S8
Figures S1–S4

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