<Original Article>

Elevated Pulmonary Vascular Resistance Assessed was Related to Poor Prognosis in Heart Failure Patients Even Without Established Pulmonary Hypertension

Sayuri NAKAYAMA, Kazushi SAKANE, Yumiko KANZAKI, Kosuke TSUDA, Takahiro OKUNO, Kanako AKAMATSU, Yuka SAKATANI, Shuichi FUJITA, Tomohiro FUJISAKA, Hideaki MORITA, and Masaaki HOSHIGA

Department of Cardiology, Osaka Medical and Pharmaceutical University, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan

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ABSTRACT

Background: Elevated pulmonary vascular resistance (PVR) exceeding 3.0 Wood units (WU) is associated with poor prognosis in patients with heart failure (HF) with pulmonary hypertension (PH). However, the prognostic value of elevated PVR in HF patients without PH remains unclear. This study evaluates the clinical and prognostic significance of elevated PVR in these patients.

Methods: This study included 511 HF patients underwent right heart catheterization in a clinically compensated state after conventional HF treatment. We investigated the prognostic importance of high PVR (> 3.0 WU) in HF patients with and without PH (mean pulmonary artery pressure ≤ 20 mmHg).

Results: Of the patients, 236 (46 %) were absent of PH (nonPH group). Elevated PVR was found in 22 (9.7 %) of the nonPH group. Age, BNP levels, and estimated glomerular filtration rates were comparable between nonPH patients with and without elevated PVR. However, those with elevated PVR showed significantly lower cardiac output (2.6 vs. 4.0 L/min, $p < 0.001$) and a higher rate of major adverse cardiac events (death or HF rehospitalization) over a median follow-up of 1028 days (59.1 % vs. 36.0 %, $p = 0.04$).

Conclusions: Elevated PVR was associated with lower cardiac output, and poorer prognosis in HF patients, even in the absence of PH.

INTRODUCTION

Despite many therapeutic advances, the prognosis of heart failure (HF) remains discouraging [1–4]. Pulmonary hypertension (PH) is a key determinant of adverse prognosis in patients with chronic HF [5]. In HF, PH manifests as World Health Organization group 2 PH [6], which is characterized by pulmonary vascular congestion due to increased pulmonary venous pressure resulting from chronically elevated pulmonary artery wedge pressure (PAWP). There is

Address correspondence to:
Yumiko Kanzaki, MD, PhD and Kazushi Sakane, MD, PhD, Department of Cardiology, Osaka Medical and Pharmaceutical University, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan.
Phone: +81-726-83-1221 Fax: +81-726-84-6598 Email: yumiko.kanzaki@ompu.ac.jp, kazushi.sakane@ompu.ac.jp

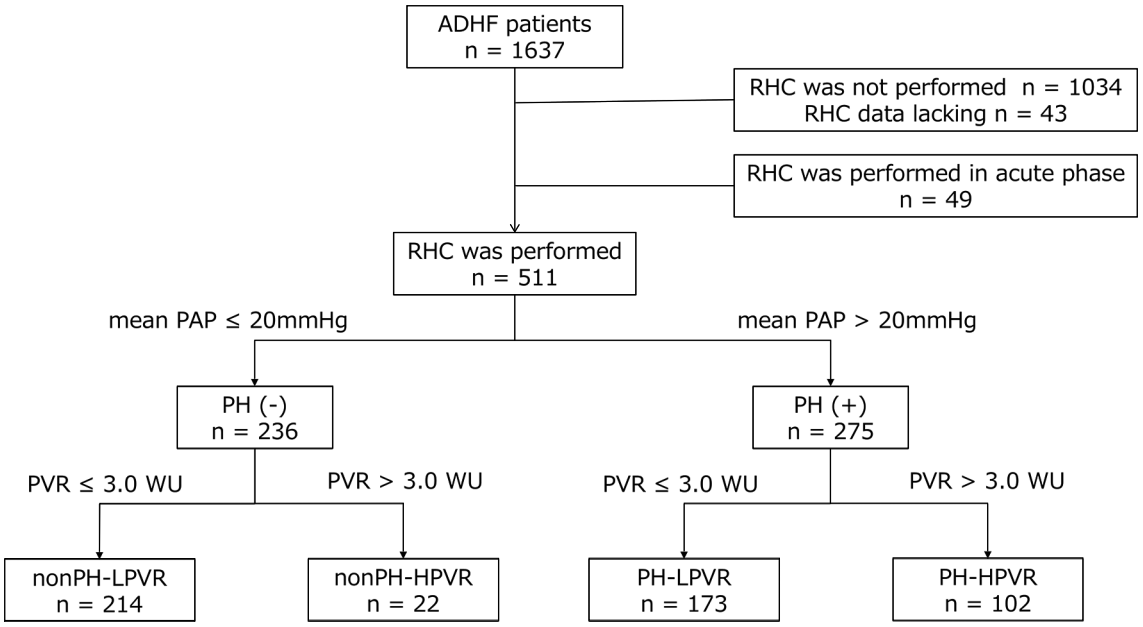

Figure 1 **Study flow chart**
ADHF, acute decompensated heart failure; RHC, right heart catheterization; PH, pulmanary hypertension; WU, wood units; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; LPVR, low PVR; HPVR, high PVR

an expectation of complete or partial reversibility of PH with normalization of PAWP by improvement of the left HF. However, persistent elevation of pulmonary venous pressure induces pulmonary arterial remodeling, culminating in increased pulmonary vascular resistance (PVR) and worsening prognosis.

Elevated PVR may occur in patients with HF, not only within group 2, but also across other classifications of PH. In such cases, the predictability of PH reversibility after normalization of left ventricular hemodynamics remains uncertain. In addition, chronic PH can induce right ventricular (RV) remodeling, potentially leading to RV failure, which is a critical prognostic marker of HF.

In addition, there are concerns regarding the potential underestimation of pulmonary artery pressure (PAP) or right heart dysfunction using echocardiography. Despite the abundance of data on PH with elevated PVR in patients with HF, there is little evidence on patients with elevated PVR in the absence of PH. This study aimed to investigate the clinical and prognostic significance of elevated PVR in patients with HF without established PH.

METHODS

This retrospective observational study was conducted at a small-single center. All study procedures were performed in accordance with the ethical standards of the Institutional and National Research Committee and the Declaration of Helsinki and its later amendments or comparable ethical standards. The Ethics Review Board of Osaka Medical and Pharmaceutical University approved this retrospective study and waived the requirement for informed consent (2022-074). Between January 2015 and December 2021, 1637 patients were admitted to our institution for acute decompensated heart failure. Well-trained cardiologists diagnosed HF based on the Framingham criteria or the universal definition of HF. Of these patients, we excluded 1,034 who had not undergone right heart catheterization (RHC) and 43 who lacked RHC data. We also excluded 49 patients who underwent RHC during the acute phase. Therefore, 511 patients were included in this study (**Figure 1**).

We collected data on age, sex, HF symptoms evaluated by the New York Heart Association (NYHA), body mass index (BMI), vital signs, coronary risk factors and prescribed medications on admission. Blood samples were also collected on admission. The estimated glomerular filtration rate (eGFR) was calculated using the serum creatinine level, age, and sex [7].

Echocardiography was performed using standard ultrasound equipment (Vivid E9, GE Vingmed, Horten, Norway; EPIQ 7G, Philips Healthcare, Andover, Massachusetts, USA; Artida, Canon Medical Systems, Tokyo, Japan). All patients underwent standard comprehensive two-dimensional and Doppler echocardiography.

All hemodynamic measurements were obtained invasively using a pulmonary artery catheter at the time of right-sided cardiac catheterization. Cardiac output (CO) was then calculated using the thermodilution method or the direct

Fick method (oxygen consumption / arteriovenous O_2 difference). PVR [(mean PAP − PAWP) / CO] was calculated using standard equations. The pulmonary artery pulsatility index (PAPI) was calculated as (systolic PAP − diastolic PAP) / right atrial pressure. The hemodynamic definition of PH in this study consisted of a PAP > 20 mmHg measured during a catheterization study. We defined elevated PVR as > 3.0 Wood units (WU) [6, 8].

All clinical events were retrospectively reviewed from medical records. The primary outcomes were all-cause mortality and HF rehospitalization. Patient survival or all-cause mortality status was confirmed on January 31, 2024, using the Osaka Medical and Pharmacological University (OMPU) HF database.

Statistical Analysis

Categorical variables are presented as numbers (%) and were compared using the chi-square test or Fisher's exact test depending on the cell size category. The Shapiro–Wilk test was used to assess the normality of continuous variables. All continuous variables were expressed as means ± standard deviation or median with interquartile ranges (IQRs). Normally distributed variables were compared between the groups using the Student's t-tests, and non-normally distributed variables were compared using the Wilcoxon rank-sum tests. To compare multiple groups, Tukey's honestly significant difference test was used for normally distributed variables, and the Steel–Dwass test was used for non-normally distributed variables. Cumulative clinical endpoints were assessed using Kaplan–Meier curves with post hoc comparisons using the log-rank tests. The factors associated with the end-point were investigated using univariate and multivariate logistic regression analyses. A p value of < 0.05 was taken to be indicative of statistical significance. Data were analyzed using JMP Pro version 17.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 551 patients with HF were included in this study, comprising 275 (53.8 %) with PH and 236 (46.2 %) without. The PH group had a higher BMI, and higher incidences of all-cause death and/or rehospitalization for HF compared to those of the nonPH group (**Table 1**). Echocardiography revealed that the left atrial dimension was significantly larger in the PH group than in the nonPH group, with no significant difference in left ventricular ejection fraction (LVEF) between the two groups (**Table 2**).

Further stratification based on PVR > 3 or PVR ≤ 3 WU categorized the subjects into four groups: nonPH with low PVR (nonPH-LPVR, n = 214, 41.9 %), nonPH with high PVR (nonPH-HPVR, n = 22, 4.3 %), PH with low PVR (PH-LPVR, n = 173, 33.9 %), and PH with high PVR (PH-HPVR, n = 102, 20.0 %, **Figure 1**). Significant intergroup differences were observed in sex distribution, BMI, B-type natriuretic peptide levels, hematocrit, left atrial diameter, and left ventricular diameter (**Tables 3** and **4**). Hemodynamic parameters indicated that CO and cardiac index (CI) were the lowest in the nonPH-HPVR group among all groups. Furthermore, in the nonPH group, CI was significantly associated with LVEF (r = 0.19, p = 0.0017) but not with PAPI (r = 0.04, p = 0.55).

During a mean follow-up period of 1,125 ± 745 days (median [IQR]: 1,028 [514–1,668] days), there were 217 cases (42.5 %) of rehospitalizations for HF or all-cause deaths. There were significant differences in the rates of all-cause mortality or heart failure rehospitalization among the four groups (log-rank p = 0.03; **Figure 2**). The nonPH-HPVR group had significantly higher rates of all-cause mortality or heart failure rehospitalization (log-rank p = 0.02) than the nonPH-LPVR group. Even in the absence of PH, an elevated PVR was associated with a poor prognosis, similar to the patients with PH (nonPH-HPVR vs. PH-HPVR, log-rank p = 0.51; nonPH-HPVR vs. PH-LPVR, log-rank p = 0.22, respectively).

The results of the univariate and multivariate logistic regression analyses for factors associated with all-cause mortality or rehospitalization for HF were presented in **Table 5**. Among patients without PH, female gender and elevated PVR (> 3.0 WU) were independently associated with poor prognosis.

DISCUSSION

Among the HF patients without PH who participated in this study, approximately 10 % exhibited elevated PVR. The nonPH-HPVR group had the lowest CO level among the groups. Even in patients without PH, an elevated PVR was independently associated with all-cause mortality or rehospitalization for HF. This study demonstrated that, even in the absence of PH, elevated PVR is associated with a poor prognosis, similar to that of patients with PH.

PH in the patients with HF

The presence of PH is common in patients with HF [9–11], and is associated with worse prognosis [5, 12–14]. Moreover, elevated PVR is also known to be associated with increased risk of disease progression and mortality [15–17]. The pathophysiology of PH in left HF is complex and highly heterogeneous. Two distinct categories of PH in left HF have been identified based on the pathological, pathophysiological, and hemodynamic characteristics. The first category, isolated post-capillary PH (Ipc-PH), is characterized by the exclusive backward transmission of elevated left atrial pressure through the pulmonary veins and capillaries to the pulmonary arteries, with normal PVR [18, 19]. In contrast, the second category, combined post- and pre-capillary PH (Cpc-PH), involves a specific distal

Table 1 Clinical characteristics between PH and nonPH groups

Variables	total	non-PH	PH	
		mPAP ≤ 20 mmHg	mPAP > 20 mmHg	*p* value
n	511	236	275	
age (yrs)	72.4 ± 11.9	73.3 ± 11.5	71.6 ± 12.2	0.09
male, *n* (%)	314 (61.4)	146 (61.9)	168 (61.1)	0.86
BMI (kg/m^2)	24.2 ± 4.5	23.5 ± 3.9	24.8 ± 4.8	0.01
NYHA				
NYHA II, *n* (%)	63 (12.3)	24 (10.2)	39 (14.2)	
NYHA III, *n* (%)	242 (47.4)	111 (47.0)	131 (47.6)	0.31
NYHA IV, *n* (%)	206 (40.3)	101 (42.8)	105 (38.2)	
Vital signs on Admission				
systolic BP (mmHg)	136 (117–159)	138 (120–161)	134 (115–157)	0.17
diastolic BP (mmHg)	82 (69–97)	82 (70–97)	82 (69–96)	0.66
HR (bpm)	91 (75–110)	93 (76–109)	90 (75–110)	0.61
Etiologies of heart disease				
Ischemic heart disease, *n* (%)	151 (29.9)	72 (30.5)	79 (29.4)	0.78
Cardiomyopathy, *n* (%)	139 (27.5)	64 (27.1)	75 (27.9)	0.85
Risk factors				
Hypertension, *n* (%)	362 (70.8)	161 (68.2)	201 (73.1)	0.23
Dyslipidemia, *n* (%)	239 (46.8)	105 (44.5)	134 (48.7)	0.34
Diabetes Mellitus, *n* (%)	166 (32.5)	66 (28.0)	100 (36.4)	0.04
Smoking				
never, *n* (%)	261 (51.3)	121 (51.7)	140 (50.9)	
past, *n* (%)	206 (40.5)	94 (40.2)	112 (40.7)	0.98
current, *n* (%)	42 (8.3)	19 (8.1)	23 (8.4)	
Laboratory data				
Albumin (g/dL)	3.6 (3.2–3.8)	3.6 (3.2–3.8)	3.6 (3.2–3.9)	0.36
estimated GFR (ml/min/1.73 m^2)	49.0 (36.0–61.0)	50.0 (37.0–64.0)	48.0 (35.0–59.8)	0.09
BNP at admission (pg/mL)	485.2 (229.2–945.4)	491.1 (222.2–923.2)	480.3 (234.8–964.7)	0.85
Hematocrit (%)	37.6 (33.2–41.9)	37.3 (33.0–41.2)	37.9 (33.5–42.7)	0.25
Medication at Admission				
ACE-inhibitor or ARB, *n* (%)	210 (41.2)	98 (41.7)	112 (40.7)	0.82
β blocker, *n* (%)	195 (38.2)	91 (38.7)	104 (37.8)	0.83
MRA, *n* (%)	104 (20.4)	45 (19.2)	59 (21.5)	0.52
loop diuretics, *n* (%)	221 (43.3)	92 (39.2)	129 (46.9)	0.08
Tolvapton, *n* (%)	29 (5.7)	9 (3.8)	20 (7.3)	0.09
Outcomes				
Heart failure rehospitalization, *n* (%)	171 (33.7)	66 (28.0)	105 (38.6)	0.01
All cause death, *n* (%)	109 (21.3)	44 (18.6)	65 (23.6)	0.17
All cause death or heart failure rehospitalization, *n* (%)	217 (42.5)	90 (38.1)	127 (46.2)	0.07

PH, pulmonary hypertension; mPAP, mean pulmonary arterial pressure; BMI, body mass index; NYHA, New York Heart Association; BP, blood pressure; HR, heart rate; GFR, glomerular filtration rate; BNP, B-type natriuretic peptide; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; MRA, mineralcorticoid receptor antagonists.

pulmonary artery pathology that leads to elevated PVR and exacerbates PAP elevation beyond the passive component [6, 20, 21]. Clinicians believed that PAP decreases in response to a decrease in left atrial pressure after conventional HF treatment. However, a previous report suggested that PH remains at approximately 80 % even after conventional HF treatment in patients admitted with acute HF [22]. Therefore, it is important to consider the causes of PH even after HF treatments.

On the other hand, left ventricular assist devices (LVAD) have been proven to be an effective therapy for end-stage HF and related PH. Previous studies have demonstrated that LVAD implantation may normalize PVR by unloading the left ventricle [23]. This suggests that elevated PVR in left HF may be reversible and that PVR may increase to protect the left ventricle [10, 24–26]. In this study, the nonPH-HPVR group exhibited lower LVEF and PAWP, supporting the hypothesis that PVR may increase to protect against left HF. According to the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH, measuring PVR in addition to PAP is important because it helps differentiate between IpcPH and CpcPH, provides the essential prognostic information, and guides the appropriate management of patients with left HF.

Elevated PVR without PH

It is generally believed that HF patients without PH

Table 2 Echocardiographic and hemodynamic data between PH and nonPH groups

Variables	total	nonPH	PH	
		mPAP ≤ 20 mmHg	mPAP > 20 mmHg	*p* value
n	511	236	275	
Echogcardiographic data				
LAD (mm)	47 (41–52)	45 (40–50)	49 (43–55)	< .0001
IVSd (mm)	10 (8–11)	10 (9–11)	10 (8–11)	0.70
PWd (mm)	10 (8–11)	10 (8–11)	10 (8–11)	0.94
LVEDD (mm)	53.0 (47.0–59.0)	53.0 (46.0–57.5)	54.0 (48.0–60.8)	0.08
LVESD (mm)	41.0 (33.0–50.0)	40.0 (31.5–48.0)	42.0 (33.0–51.0)	0.10
LVEDVI (ml/m^2)	67.5 (48.8–95.2)	64.6 (48.0–95.4)	69.1 (49.5–95.0)	0.51
LVESVI (ml/m^2)	36.9 (20.9–59.9)	36.8 (20.9–59.5)	36.9 (20.7–60.4)	0.63
LVEF (%)	45 (34–59)	45 (35–59)	44 (32–60)	0.59
HFrEF, *n* (%)	303 (60.5)	140 (61.1)	163 (59.9)	0.78
AR ≥ moderate-severe, *n* (%)	35 (6.8)	19 (8.1)	16 (5.8)	0.32
MR ≥ moderate-severe, *n* (%)	142 (27.8)	56 (23.7)	86 (31.3)	0.06
TR ≥ moderate-severe, *n* (%)	61 (11.9)	23 (9.8)	38 (13.8)	0.16
Hemodynamic data				
mean PAWP (mmHg)	13 (8–18)	8 (5–10)	18 (14–23)	< .0001
systolic PAP (mmHg)	32 (25–42)	25 (21–28)	41 (34–51)	< .0001
diastoic PAP (mmHg)	15 (10–20)	10 (8–13)	19 (16–23)	< .0001
mean PAP (mmHg)	22 (15–28)	15 (12–18)	28 (23–34)	< .0001
mean RAP (mmHg)	5 (2–8)	3 (1–5)	7 (4–10)	< .0001
CO (L/min)	4.0 (3.3–4.8)	3.9 (3.3–4.7)	4.0 (3.3–4.8)	0.56
CI (L/min/m^2)	2.4 (2.0–2.8)	2.4 (2.1–2.9)	2.4 (2.0–2.8)	0.58
PVR (WU)	2.0 (1.4–3.0)	1.8 (1.3–2.3)	2.5 (1.6–3.8)	< .0001
PAPI	3.6 (2.2–7.3)	4.5 (2.6–8.5)	3.3 (2.0–5.6)	< .0001

PH, pulmonary hypertension; mPAP, mean pulmonary arterial pressure; LAD, left atrial diameter, IVSd, interventricular septal thickness at end-diastole; PWd, posterior wall thickness at end-diastole; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; PAWP, pulmonary artery wedge pressure; PAP, pulmonary arerial pressure; RAP, right atrial pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; WU, wood units; PAPI, Pulmonary Artery Pulsatility Index.

have a better prognosis than those with PH, this study demonstrated that, even in the absence of PH, elevated PVR is associated with a poor prognosis similar to that of patients with PH. In this study, the nonPH-HPVR group exhibited a significantly higher proportion of NYHA class 4, a higher proportion of female patients, and a lower CI than the nonPH-LPVR group. Generally, the association between elevated PVR and decreased CO can be attributed to the following factors: 1. Elevated PVR causes right HF, which leads to decreased CO; 2. left HF results in decreased CO, chronically increasing left ventricular filling pressure and subsequently causing pulmonary vascular remodeling changes, which lead to elevated PVR; or 3. a combination of these factors. The results of this study indicate that, among patients with HF, decreased CO was significantly associated with low LVEF, while the PAPI, which reflects

Table 3 Clinical characteristics according to the presence of PH and comparison between LPVR and HPVR

	nonPH			PH			
	nonPH-LPVR	nonPH-HPVR	nonPH-LPVR vs HPVR	PH-LPVR	PH-HPVR	PH-LPVR vs HPVR	ALL
Variables	PVR ≤ 3.0 WU	PVR > 3.0 WU	*p* value	PVR ≤ 3.0 WU	PVR > 3.0 WU	*p* value	*p* value
n	214	22		173	102		
age (yrs)	72.9 ± 11.7	77.4 ± 7.7	0.08	71.0 ± 12.9	72.7 ± 10.9	0.42	0.08
male, *n* (%)	141 (65.9)	5 (22.7)	<.0001	115 (66.5)	53 (52.0)	0.02	< .0001
BMI (kg/m^2)	23.6 ± 3.8	23.3 ± 4.4	0.72	25.6 ± 4.5	23.4 ± 5.1	<.0001	< .0001
NYHA							
NYHA II, *n* (%)	23 (10.8)	1 (4.6)		28 (16.2)	11 (10.8)		
NYHA III, *n* (%)	105 (49.1)	6 (27.3)	0.04	74 (42.8)	57 (55.9)	0.10	0.03
NYHA IV, *n* (%)	86 (40.2)	15 (68.2)		71 (41.0)	34 (33.3)		
Vital signs on Admission							
systolic BP (mmHg)	136 (120–160)	143 (128–168)	0.23	133 (115–158)	136 (114–155)	0.90	0.34
diastolic BP (mmHg)	82 (69–97)	85 (71–103)	0.46	82 (68–95)	82 (71–98)	0.41	0.72
HR (bpm)	94 (76–108)	88 (75–111)	0.99	89 (73–110)	92 (78–110)	0.35	0.77
Etiologies of heart disease							
Ischemic heart disease, *n* (%)	64 (29.9)	8 (36.4)	0.53	47 (27.8)	32 (32.0)	0.47	0.80
Cardiomyopathy, *n* (%)	60 (28.0)	4 (18.2)	0.32	45 (26.6)	30 (30.0)	0.55	0.75
Risk factors							
Hypertension, *n* (%)	148 (69.2)	13 (59.1)	0.33	132 (76.3)	69 (67.7)	0.12	0.19
Dyslipidemia, *n* (%)	92 (43.0)	13 (59.1)	0.15	86 (49.7)	48 (47.1)	0.67	0.37
Diabetes Mellitus, *n* (%)	59 (27.6)	7 (31.8)	0.67	65 (37.6)	35 (34.3)	0.59	0.21
Smoking							
never, *n* (%)	106 (50.0)	15 (68.2)		80 (46.2)	60 (58.8)		
past, *n* (%)	87 (41.0)	7 (31.8)	0.16	74 (42.8)	38 (37.3)	0.04	0.12
current, *n* (%)	19 (9.0)	0 (0.0)		19 (11.0)	4 (3.9)		
Laboratory data							
Albumin (g/dL)	3.6 (3.2–3.8)	3.7 (3.4–3.9)	0.41	3.6 (3.3–3.9)	3.6 (3.2–3.8)	0.20	0.37
estimated GFR (ml/min/1.73 m^2)	49.5 (36.0–64.0)	50.0 (41.0–64.0)	0.58	48.0 (34.0–59.0)	48.5 (37.0–60.3)	0.53	0.31
BNP at admission (pg/mL)	497 (214–927)	478 (268–977)	0.60	447 (164–751)	705 (304–1431)	0.0001	0.001
Hematocrit (%)	36.7 (32.5–41.1)	39.1 (36.7–42.1)	0.04	37.0 (32.9–42.4)	38.8 (34.5–43.2)	0.05	0.02
Medication at Admission							
ACE-inhibitor or ARB, *n* (%)	89 (41.8)	9 (40.9)	0.94	80 (46.2)	32 (31.4)	0.02	0.12
β blocker, *n* (%)	79 (37.1)	12 (54.6)	0.11	62 (35.8)	42 (41.2)	0.38	0.34
MRA, *n* (%)	41 (19.3)	4 (18.2)	0.90	37 (21.4)	22 (21.6)	0.97	0.93
loop diuretics, *n* (%)	82 (38.5)	10 (45.5)	0.52	81 (46.8)	48 (47.1)	0.97	0.32
Tolvapton, *n* (%)	9 (4.2)	0 (0)	0.33	14 (8.1)	6 (5.9)	0.50	0.25
Outcomes							
Heart failure rehospitalization, *n* (%)	57 (26.6)	9 (40.9)	0.16	68 (39.8)	37 (36.6)	0.61	0.04
All cause death, *n* (%)	38 (17.8)	6 (27.3)	0.28	38 (22.0)	27 (26.5)	0.40	0.29
All cause death or heart failure rehospitalization, *n* (%)	77 (36.0)	13 (59.1)	0.03	82 (47.4)	45 (44.1)	0.60	0.05

PH, pulmonary hypertension; PVR, pulmonary vascular resistance; LPVR, low pulmonary vascular resistance; HPVR, high pulmonary vascular resistance; WU, wood units; BMI, body mass index; NYHA, New York Heart Association; BP, blood pressure; HR, heart rate; GFR, glomerular filtration rate; BNP, B-type natriuretic peptide; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; MRA, mineralcorticoid receptor antagonists.

Table 4 Echocardiographic and hemodynamic data to the presence of PH and comparison between LPVR and HPVR

	non-PH			PH			
	nonPH-LPVR	nonPH-HPVR	nonPH-LPVR vs HPVR	PH-LPVR	PH-HPVR	PH-LPVR vs HPVR	ALL
Variables	PVR ≤ 3.0 WUL	PVR > 3.0 WU	*p* value	PVR ≤ 3.0 WU	PVR > 3.0 WU	*p* value	*p* value
n	214	22		173	102		
Echogcardiographic data							
LAD (mm)	44 (40–50)	47 (42–54)	0.29	50 (44–55)	47 (40–53)	0.01	< .0001
IVSd (mm)	10 (9–11)	10 (9–11)	0.88	10 (9–11)	10 (8–11)	0.37	0.81
PWd (mm)	10 (8–11)	9 (8–11)	0.50	10 (9–11)	9 (8–11)	0.01	0.03
LVEDD (mm)	53 (47–58)	49 (44–56)	0.13	55 (50–62)	52 (44–59)	0.86	0.32
LVESD (mm)	40 (31–48)	38 (32–48)	0.67	43 (33–52)	42 (33–51)	0.29	0.24
LVEDVI (ml/m^2)	66.6 (48.3–96.2)	56.5 (45.0–72.8)	0.10	71.8 (53.6–90.7)	66.9 (45.1–98.6)	0.40	0.25
LVESVI (ml/m^2)	37.3 (20.9–62.0)	31.9 (22.3–46.6)	0.62	37.0 (20.6–59.8)	36.6 (20.8–61.0)	0.91	0.91
LVEF (%)	46 (35–59)	38 (34–52)	0.16	44 (33–60)	44 (30–60)	0.61	0.53
HFrEF, *n* (%)	124 (59.6)	16 (76.2)	0.14	100 (58.5)	63 (62.4)	0.53	0.45
AR ≥ moderate-severe, *n* (%)	18 (8.4)	1 (4.6)	0.53	10 (5.8)	6 (5.9)	0.97	0.69
MR ≥ moderate-severe, *n* (%)	48 (22.4)	8 (36.4)	0.14	56 (32.4)	30 (29.4)	0.61	0.12
TR ≥ moderate-severe, *n* (%)	20 (9.4)	3 (13.6)	0.52	22 (12.7)	16 (15.7)	0.49	0.41
Hemodynamic data							
mean PAWP (mmHg)	8 (6–11)	5 (2–7)	0.0001	18 (15–23)	17 (12–22)	0.02	< .0001
systolic PAP (mmHg)	25 (22–28)	24 (20–27)	0.45	38 (33–45)	49 (40–58)	<.0001	< .0001
diastoic PAP (mmHg)	10 (8–13)	10 (8–13)	0.84	18 (16–21)	22 (18–28)	<.0001	< .0001
mean PAP (mmHg)	15 (12–18)	15 (13–18)	0.87	25 (23–30)	32 (27–38)	<.0001	< .0001
mean RAP (mmHg)	3 (1–5)	2 (1–4)	0.15	7 (5–10)	5 (3–8)	<.001	< .0001
CO (L/min)	4.0 (3.4–4.8)	2.6 (2.3–3.2)	<.0001	4.4 (3.6–5.4)	3.4 (2.8–4.0)	<.0001	< .0001
CI (L/min/m^2)	2.5 (2.2–2.9)	1.8 (1.6–2.1)	<.0001	2.6 (2.2–3.2)	2.2 (1.9–2.4)	<.0001	< .0001
PVR (WU)	1.7 (1.2–2.1)	3.4 (3.2–4.1)	<.0001	1.9 (1.4–2.3)	4.2 (3.5–5.5)	<.0001	< .0001
PAPI	4.5 (2.6–8.5)	5.3 (2.8–12.3)	0.52	2.8 (1.7–4.3)	4.2 (2.5–8.6)	<.0001	< .0001

PH, pulmonary hypertension; LPVR, low pulmonary vascular resistance; HPVR, high pulmonary vascular resistance; LAD, left atrial diameter, IVSd, interventricular septal thickness at end-diastole; PWd, posterior wall thickness at end-diastole; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; PAWP, pulmonary artery wedge pressure; PAP, pulmonary arerial pressure; RAP, right atrial pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; WU, wood units; PAPI, Pulmonary Artery Pulsatility Index

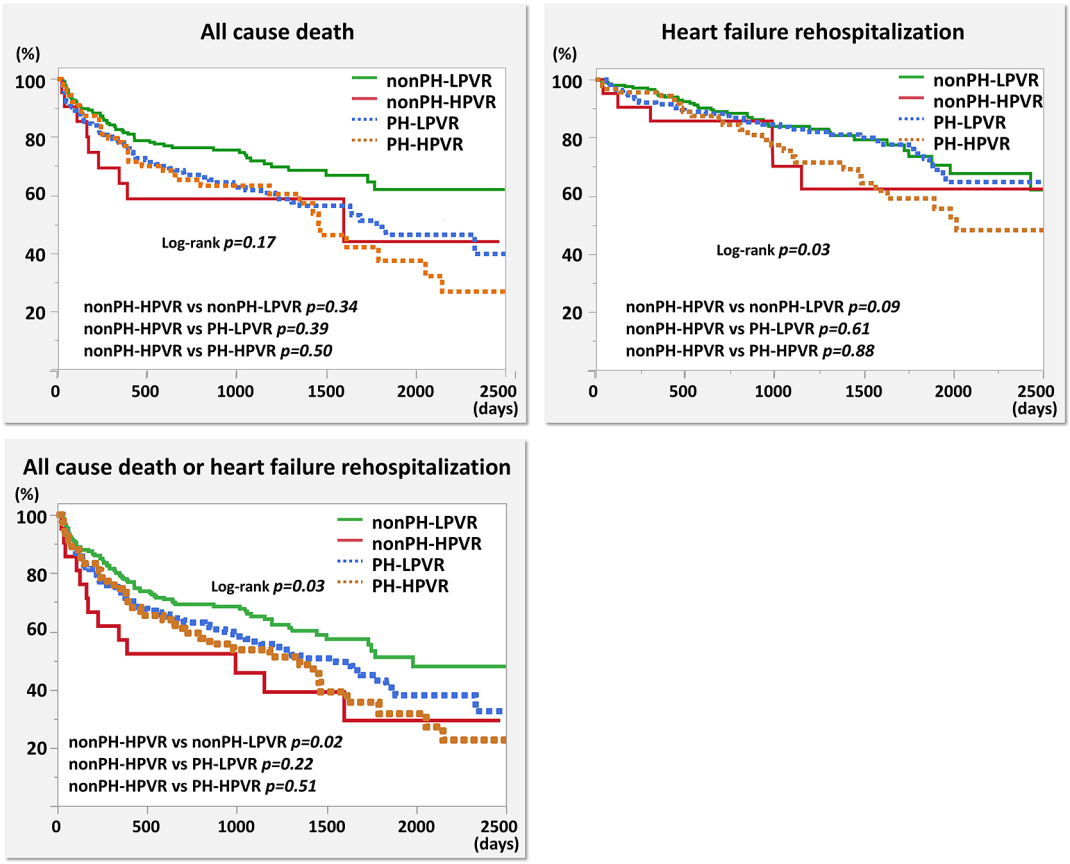

Figure 2 **Kaplan–Meier analysis for all-cause death, heart failure rehospitalization, and all-cause death or heart failure rehospitalization between the four groups**

PH, pulmonary hypertension (pulmonary artery pressure > 20 mmHg); PVR, pulmonary vascular resistance; HPVR, high PVR (PVR > 3.0 WU); LPVR, low PVR (PVR ≤ 3.0 WU).

Table 5 **Independent predictor for mortality or HF rehospitalization in nonPH patients**

Variables	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
age, yrs	1.02	1.00–1.05	0.08	1.01	0.99–1.05	0.32
male	0.66	0.38–1.15	0.14	0.44	0.23–0.85	0.02
BMI < 18 kg/m^2	1.48	0.37–5.88	0.58	1.22	0.28–5.38	0.79
estimated GFR, mL/min/1.73 m^2	0.99	0.97–1.00	0.02	0.99	0.98–1.01	0.21
BNP, pg/mL	1.00	1.00–1.00	0.11	1.00	1.00–1.00	0.18
HCT, %	0.96	0.92–1.00	0.06	0.95	0.90–1.01	0.09
LVEF, %	0.99	0.98–1.01	0.57	0.99	0.97–1.02	0.52
PVR > 3.0 WU	2.57	1.05–6.29	0.04	4.56	1.56–13.32	0.01

HF, heaert failure; PH, pulmonary hypertension; BMI, body mass index; GFR, GFR, glomerular filtration rate; BNP, B-type natriuretic peptide; HCT, hematocrit; LVEF, left ventricular ejection fraction; PVR, pulmonary vascular resistance; WU, wood units; OR, odds ratio; CI, confidense interval.

right heart function, was not. This suggests that, in many cases, left HF rather than right HF may be related to decreased CO. Considering that the nonPH-HPVR group had a lower PAWP despite a lower LVEF when compared to

the nonPH-LPVR group, this supports the hypothesis that PVR might be increased to protect the left ventricle. Furthermore, it has been reported that in patients with interstitial lung disease, elevated PVR without PH is also associated with low CO [27].

Previous reports have suggested that PH may be underestimated in patients with right heart dysfunction [28, 29]. However, the results of this study indicate that PH may also be underestimated in patients with left heart dysfunction. Even in the absence of PH, it is important to evaluate PVR using right heart catheterization, especially in patients with decreased CO, to differentiate between various conditions such as pulmonary arterial hypertension, including connective tissue diseases, comorbid pulmonary diseases, and pulmonary embolism, to guide individualized treatment strategies.

Clinical Implications

The patients with HF frequently exhibit elevated PVR with various underlying pathophysiological causes. Additionally, many HF patients have reduced CO levels, which may lead to an underestimation of PH because of decreased pulmonary blood flow [28, 30]. Furthermore, PAP often decreases with treatment in HF patients [31]. Therefore, PVR assessment after HF treatment may be useful for the accurate evaluation. It is well known that reduced CO due to right heart dysfunction can lead to an underestimation of PH. It is also important to note that PH may also be underestimated in patients with reduced CO due to left heart dysfunction, and attention is needed in such situations. There are no evidence of pulmonary vasodilators improving prognosis in PH with left HF. Further research is needed to determine whether treatments targeting PVR contribute to improved prognosis in HF patients with elevated PVR without PH.

Limitations

This study was retrospective, which limited our ability to determine the causal relationships between elevated PVR and reduced CO. Whether elevated PVR leads to decreased CO, decreased CO results in elevated PVR, or the association between elevated PVR and reduced CO is incidental remained unclear. Additionally, the evaluation of right heart function was not sufficiently detailed to assess the mechanisms underlying the reduced CO. The study also lacked adequate evaluation of pulmonary diseases, such as connective tissue diseases leading to pulmonary arterial hypertension, or pulmonary embolism.

In the nonPH-HPVR group, there was a higher proportion of women and more severe dyspnea symptoms (higher proportion of NYHA class IV), suggesting the possibility of concurrent diseases with sex differences, such as connective tissue diseases, or a higher prevalence of pulmonary diseases or pulmonary artery disease, which may have influenced the results. Furthermore, the nonPH-HPVR group comprised only 22 patients, limiting the statistical power of the analysis. Nevertheless, even with this small sample size, the nonPH-HPVR group clearly demonstrated a poor prognosis. Future studies should include a larger number of cases to further investigate these findings.

CONCLUSION

In patients with HF, approximately 10 % exhibited elevated PVR without PH, which was associated with a poorer prognosis even in the absence of PH. PH may also be underestimated in patients with reduced LVEF and CO. PVR assessment might be useful for accurate evaluation, even in HF patients even without PH.

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AUTHOR DISCLOSURES

The authors declare that they have no conflicts of interest.

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