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Clinical Significance of Reactive Post-Capillary Pulmonary Hypertension in Patients With Left Heart Disease

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Background: Post-capillary pulmonary hypertension (pc-PH) is a disorder with elevated pulmonary arterial pressure and pulmonary vascular resistance (PVR) because of left heart disease (LHD), and is classified as reactive (PVR >2.5 WU) or passive (PVR ≤2.5 WU). However, the clinical significance of these pc-PH subtypes remains to be elucidated.

Methods and Results: We examined 676 consecutive patients with chronic heart failure (CHF) (NYHA ≥2), and found that 158 (23%) had pc-PH: reactive pc-PH in 58 and passive pc-PH in 100. Univariate analysis showed that 4 factors were significantly associated with reactive pc-PH and multivariate analysis showed that female sex was the only independent predictor of reactive pc-PH (odds ratio 2.12, 95% confidence interval (CI) 1.05–4.30, P=0.03). During the mean follow-up period of 2.6 years, 125 CHF patients (18%) died, including 22 with reactive pc-PH and 24 with passive pc-PH (P<0.001). Multivariate Cox regression analysis showed that elevated PVR was independently associated with higher mortality (hazard ratio 1.18, 95%CI 1.03–1.35, P=0.02). Kaplan-Meier analysis demonstrated that the prognosis of patients with reactive pc-PH was significantly worse than for those with no PH or passive pc-PH. Reactive pc-PH was a significant prognostic factor regardless of CHF etiology (ischemic vs. non-ischemic) or reduced/preserved LV ejection fraction (HFrEF vs. HFpEF).

Conclusions: Reactive pc-PH is characterized by predominant female sex and is a significant prognostic factor of LHD with PH. (*Circ J* 2012; **76:** 1235–1244)

Key Words: Left heart disease; Post-capillary pulmonary hypertension; Prognosis; Pulmonary vascular resistance

The classification of pulmonary hypertension (PH) has been recently updated[1] to present 5 major classes of the disorder. Of them, pulmonary arterial hypertension (class 1) is a fatal disorder of precapillary PH, caused by small pulmonary artery obstruction because of vascular proliferation and remodeling.[2–4] PH because of left heart disease (LHD) [post-capillary PH (pc-PH), class 2] usually develops as a result of increased left ventricular (LV) filling pressure and is thought to be the most common cause of PH.[1] Indeed, pc-PH is a risk factor for poor prognosis in patients with chronic heart failure (CHF).[5]

pc-PH is defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg and mean pulmonary capillary wedge pressure (mPCWP) >15 mmHg, and is classified into 2 types, depending on the elevation of pulmonary vascular resistance (PVR) or the transpulmonary pressure gradient (TPPG): reactive pc-PH with elevated PVR (>2.5 Wood units [WU]) and/or TPPG (>12 mmHg), and passive pc-PH with normal PVR (≤2.5 WU) and TPPG (≤12 mmHg).[6–8] The mechanism of passive pc-PH is a simple backward transmission of elevated left atrial (LA) pressure, whereas reactive pc-PH is caused by functional and/or structural changes of the pulmonary arteries as a result of chronic elevation of pulmonary venous pressure.[9]

Although patients with reactive pc-PH have an increased risk of postoperative right ventricular heart failure (HF) after heart transplantation,[10] the clinical significance of pc-PH, especially that of the pc-PH subclasses, remains to be fully elucidated. Furthermore, the clinical determinants of reactive pc-PH remains unclear because the severity and/or duration of venous pressure elevation does not correlate with the development of reactive pc-PH.[11]

In the present study, we thus examined the clinical significance of reactive pc-PH in patients with CHF.

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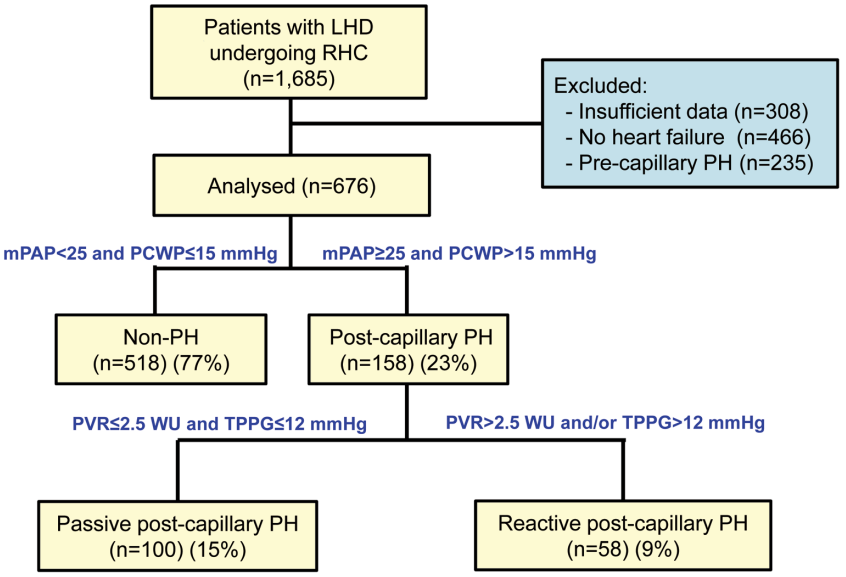

Figure 1. Patient enrollment. Of the 1685 consecutive patients with left heart disease (LHD) and suspected pulmonary hypertension (PH), 676 who had NYHA ≥2 heart failure symptoms were analyzed in the present study. Of these, 158 patients had post-capillary PH, among whom 58 had reactive post-capillary PH. mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; TPPG, transpulmonary pressure gradient.

Methods

The present study was approved by the Ethical Committee of Tohoku University Graduate School of Medicine and written informed consent was obtained from all patients.

Study Population

Our cohort consisted of 1,685 consecutive patients who underwent right heart catheterization for suspected PH in our hospital from January 2000 to December 2010 (Figure 1).[12–14] Of these, 308 patients were excluded because of insufficient data, 466 who did not have symptoms or signs of HF, and 235 because of precapillary PH (Figure 1). Thus, the remaining 676 consecutive patients with HF symptoms of NYHA ≥2 because of LHD were included in the present study (Figure 1).

Diagnosis and Classification of HF

HF is a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or to eject blood. In the present study, we included symptomatic HF patients in stages C/D as defined by the 2005 ACC/AHA Guidelines (≥NYHA ≥2).[15] We divided the etiology of HF into 5 subgroups: ischemic heart disease (IHD), cardiomyopathy, valvular heart disease (VHD), hypertensive heart disease, and other/unknown.

According to the 2007 ESC Guidelines, we also divided the 676 patients into 3 groups: HF with reduced ejection fraction without VHD (HFrEF, systolic dysfunction, LVEF <50%, n=369), HF with preserved EF without VHD (HFpEF, diastolic dysfunction, LVEF ≥50%, n=153), and VHD (n=154).[16]

Diagnosis of PH

pc-PH was defined as mPAP ≥25 mmHg and mPCWP >15 mmHg (Figure 1).[17] PVR was calculated as the TPPG (defined as mPAP−PCWP, mmHg) divided by cardiac output (CO, L/min). Vascular compliance (ml/mmHg) was estimated by stroke volume devided by pulse pressure (systolic pressure−diastolic pressure). We defined patients who had PH with PVR >2.5 WU as reactive pc-PH (n=58), and those with PVR ≤2.5 WU as passive pc-PH (n=100) (Figure 1).[8] When PVR data were unavailable, TPPG >12 mmHg was used as the cutoff value.[8]

Data Collection

Baseline demographic information were collected from the medical records, including age, sex, height, body weight, body mass index (BMI), underlying heart disease, type of LV dysfunction, CHF stage, risk factors [eg, hypertension, dyslipidemia, diabetes mellitus, smoking, anemia, chronic kidney disease (CKD), hemodialysis, and atrial fibrillation (AF)], medications [eg, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, β-blocker, calcium channel blocker (CCB) and statins], blood pressure, pulse rate, and laboratory data [hemoglobin, red cell distribution width, creatinine, uric acid, and brain natriuretic peptide (BNP)] (Table 1). Anemia was defined as hemoglobin concentration <12 g/dl for women and <13 g/dl for men, using the WHO criteria. CKD stage was determined by the estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula modified for Japanese.[18] Echocardiography and cardiac catheterization data were also collected (Table 1).

Statistical Analysis

Results are expressed as the median (interquartile range) or the number (%). Differences among the 3 groups were analyzed by 1-way analysis of variance. Logistic regression model was used to determine which variables were independently associated with the presence of reactive PH among post-capillary PH patients. After univariate analysis, variables with P<0.05, including female sex, BMI, hypertension and CCB, were used in the adjusted model. Age was also adjusted because increased age is known to be associated with elevated mPAP. On the other hand, hemodynamic data, on which the PH classification is based, were not used in the final model. For survival analysis, follow-up time was calculated from the date of catheterization until the date of the last clinical visit or contact by telephone or death. The correlation between elevated PVR and survival was assessed using Kaplan-Meier survival curves. The result of the log-rank test for all 3 groups is shown as "P value for all 3 groups". Cox hazard regression was used to determine inde-

Table 1. Clinical Characteristics of the Patients in the 3 Groups

	No PH (n=518)	Passive pc-PH (n=100)	Reactive pc-PH (n=58)	ANOVA P value
Age (years)	64 (51–72)	63 (53–71)	64 (54–70)	0.99
Female (n, %)	189 (37)	34 (34)	30 (52)*,†	0.06
BMI (kg/m², range)	22.2 (19.9–24.4)	23.2 (20.5–25.7)	21.4 (19.3–24.1)††	0.02
Underlying heart disease (n, %)				
VHD	97 (19)	39 (39)	18 (31)*	<0.001
Aortic valve disease	56 (11)	15 (15)	4 (7)	0.27
Mitral valve disease	43 (8)	24 (24)	15 (26)**	<0.001
CM	222 (43)	34 (34)	20 (35)*	0.16
IHD	120 (23)	19 (19)	16 (28)	0.45
HHD	32 (6)	5 (5)	3 (5)	0.63
Other/unknown	47 (9)	3 (3)	1 (2)	
Type of LV dysfunction (n, %)				
Systolic	291 (56)	48 (48)	30 (52)*	0.29
Diastolic	130 (25)	13 (13)	10 (17)	0.01
Valvular disease	97 (19)	39 (39)	18 (31)*	<0.001
NYHA ≥3/4 (n, %)	227 (44)	56 (56)	35 (60)*	0.009
Hypertension (n, %)	331 (64)	67 (67)	28 (48)*,†	0.048
Dyslipidemia (n, %)	199 (38)	31 (31)	18 (31)	0.23
Diabetes mellitus (n, %)	133 (26)	33 (33)	17 (29)	0.31
Smoking (n,%)				
Current	34 (10)	15 (15)	5 (9)	0.39
History	71 (22)	25 (25)	15 (26)	
None	225 (68)	56 (56)	37 (65)	
Anemia (n, %)	194 (38)	53 (53)	29 (50)	0.006
CKD ≥stage 3 (n, %)	203 (39)	52 (52)	29 (50)	0.03
Hemodialysis (n, %)	18 (3)	8 (8)	5 (9)	0.06
AF (n, %)	130 (25)	49 (49)	27 (47)**	<0.001
Laboratory data				
BNP (pg/ml)	191 (77–477)	450 (214–802)	483 (191–1,190)**	<0.001
Hemoglobin (g/dl)	13.1 (11.7–14.6)	12.3 (10.5–14.0)	12.7 (10.5–14.8)	<0.001
RDW	13.3 (12.7–14.3)	14.8 (13.7–16.4)	15.5 (13.9–17.9)**	<0.001
Creatinine (mg/dl)	0.8 (0.7–1.1)	1.0 (0.7–1.5)	0.9 (0.7–1.1)	0.004
eGFR (ml/min/1.73 m²)	67 (51–81)	57 (38–74)	60 (45–71)*	<0.001
Uric acid (mg/dl)	6.2 (5.0–7.8)	6.8 (5.4–8.0)	7.3 (5.8–8.5)**	0.02
Echocardiography				
LAD (mm)	41 (36–47)	46 (41–52)	46 (41–51)**	<0.001
LVDD (mm)	56 (48–64)	57 (47–64)	57 (44–64)	0.70
LVEF (%)	43 (30–57)	49 (35–64)	50 (28–61)	0.09
LVMI (g/m²)	200 (153–250)	211 (155–254)	172 (141–222)†	0.046
RWT	0.36 (0.31–0.44)	0.40 (0.31–0.49)	0.39 (0.29–0.50)	0.20
Cardiac catheterization data				
mRAP (mmHg)	4 (3–6)	9 (6–12)	9 (6–12)**	<0.001
sPAP (mmHg)	27 (23–31)	43 (39–50)	54 (48–59)**,††	<0.001
dPAP (mmHg)	11 (9–13)	20 (18–24)	24 (21–28)**,††	<0.001
mPAP (mmHg)	17 (14–19)	30 (27–33)	35 (31–40)**,††	<0.001
mPCWP (mmHg)	9 (7–12)	21 (18–26)	21 (18–24)**	<0.001
TPPG (mmHg)	7 (6–9)	8 (6–10)	14 (11–17)**,††	<0.001
dPAP-PCWP (mmHg)	1 (0–3)	–1 ((–4)–1)	3 (1–5)**,††	<0.001
sAoP (mmHg)	123 (107–143)	132 (105–152)	115 (95–142)	0.10
dAoP (mmHg)	68 (59–76)	70 (60–80)	68 (58–77)	0.20
mAoP (mmHg)	90 (80–101)	94 (82–110)	88 (76–99)	0.10
PVR (Wood unit)	1.7 (1.2–2.1)	1.8 (1.4–2.2)	3.7 (3.0–4.7)**,††	<0.001
SVR (Wood unit)	19.9 (16.5–23.8)	19.4 (16.1–24.0)	22.0 (18.2–26.2)*†	0.047
PAC (ml/mmHg)	3.9 (3.1–5.0)	2.7 (2.1–3.3)	1.6 (1.4–2.1)**,††	<0.001

(Table 1 continued the next page.)

	No PH (n=518)	Passive pc-PH (n=100)	Reactive pc-PH (n=58)	ANOVA P value
AoC (ml/mmHg)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	0.9 (0.7–1.4)*	0.12
SvO_2 (%)	71 (67–75)	68 (62–72)	65 (59–70)**†	<0.001
Cardiac index (L/min/m^2)	2.7 (2.3–3.1)	2.6 (2.2–2.7)	2.4 (2.0–2.7)**,††	0.002
Heart rate (beats/min)	70 (61–80)	78 (65–87)	77 (71–86)**	<0.001
LVEF (%)	49 (35–65)	52 (30–64)	45 (23–71)	0.89
Medications				
Digoxin	83 (16)	30 (30)	18 (31)**	<0.001
ACEI/ARB	318 (61)	63 (63)	35 (60)	0.94
β-blocker	210 (41)	32 (32)	17 (29)	0.09
Diuretics	260 (50)	62 (62)	42 (72)**	0.001
AA	142 (27)	26 (26)	23 (40)	0.14
CCB	128 (25)	34 (34)	11 (19)†	0.08
Statin	116 (22)	22 (22)	9 (16)*	0.46
Warfarin	166 (32)	43 (43)	18 (31)	0.10
Aspirin	178 (34)	31 (31)	22 (38)	0.66

Results are expressed as median (interquartile range) or n (%).
*P<0.05, **P<0.01 vs. no PH group. †P<0.05, ††P<0.01 vs. passive pc-PH group.
AA, aldosterone antagonist; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AoC, aortic compliance; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium-channel blocker; CKD, chronic kidney disease; CM, cardiomyopathy; dAoP, diastolic aortic pressure; dPAP, diastolic pulmonary arterial pressure; eGFR, estimated gromellular filtration rate; HHD, hypertensive heart disease; IHD, ischemic heart disease; LAD, left atrial diameter; LV, left ventricular; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; mAoP, mean aortic pressure; mPAP, mean pulmonary arterial pressure; mPCWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; PAC, pulmonary arterial compliance; PH, pulmonary hypertension; pc-PH, post-capillary pulmonary hypertension; PVR, pulmonary vascular resistance; RDW, red cell distribution width; RWT, relative wall thickness; sAoP, systolic aortic pressure; sPAP, systolic pulmonary arterial pressure; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance; TPPG, transpulmonary pressure gradient; VHD, valvular heart disease.

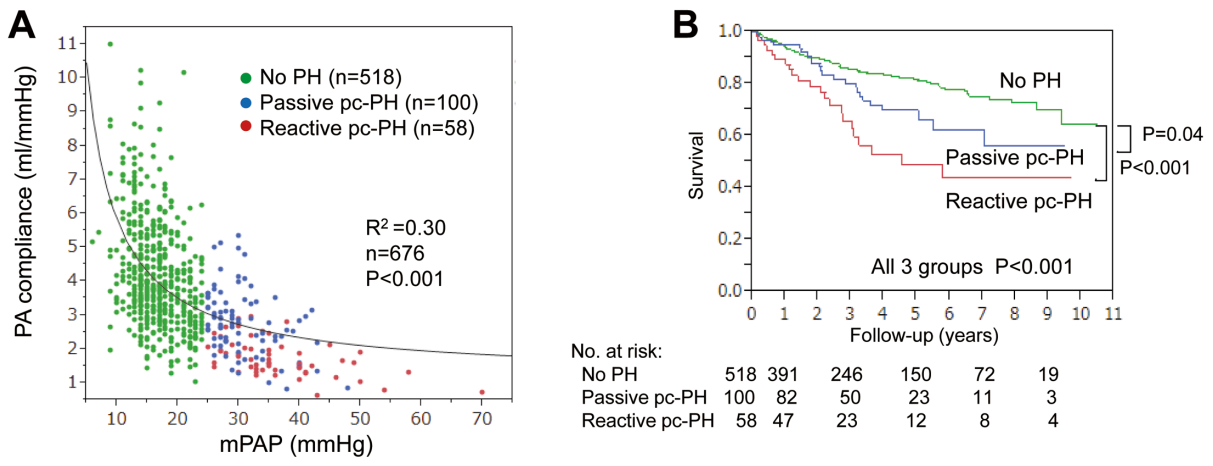

Figure 2. Pulmonary hemodynamics and long-term survival. (**A**) Pulmonary arterial compliance inversely correlated with mean pulmonary artery pressure (mPAP) (solid line). (**B**) Survival curve according to the subtypes of post-capillary pulmonary hypertension (pc-PH).

pendent risk factors for mortality. In the final model, variables with P<0.05 in the univariate analysis were adjusted, including age, female sex, BMI, NYHA ≥3, VHD, anemia, CKD ≥stage 3, AF, BNP, mean right atrial pressure (mRAP), RVR, and β-blocker. P<0.05 was considered statistically significant. All analyses were performed with JMP® Pro 9.0.2 (SAS Institute Inc, Cary, NC, USA).

Results

Among the 676 patients with LHD of NYHA ≥2 HF symptoms, 158 (23%) had pc-PH, comprising reactive pc-PH in 58 and passive pc-PH in 100 (Figure 1). Patients were followed up for a median period of 2.6 years.

Characteristics of Patients With Post-Capillary PH

Baseline characteristics of the 3 groups (no PH, passive pc-

Table 2. Risk Factors for Reactive Post-Capillary PH

	Non-adjusted		Adjusted	
	OR (95%CI)	P value	OR (95%CI)	P value
Age (years)	1.00 (0.98–1.03)	0.77	1.01 (0.98–1.04)	0.52
Female	2.08 (1.08–4.05)	0.03	2.12 (1.05–4.30)	0.03
BMI (kg/m^2)	0.91 (0.83–0.98)	0.02	0.93 (0.85–1.01)	0.07
Hypertension	0.46 (0.24–0.89)	0.02	0.59 (0.25–1.33)	0.20
CCB	0.45 (0.20–0.96)	0.046	0.55 (0.21–1.38)	0.20

Results are expressed as median (interquartile range) or number (%).
OR, odds ratio; CI, confidence interval. Other abbreviations see in Table 1.

PH, and reactive pc-PH) are shown in Table 1. The prevalence of VHD was significantly higher in patients with pc-PH than in those with no PH, whereas mitral valve disease was more often observed in patients with pc-PH, but not aortic valve disease (Table 1). More than half of the pc-PH patients had NYHA functional class ≥3/4. Compared with the no PH patients, the pc-PH patients had more complications, including anemia, CKD and Af, had higher levels of BNP, red blood cell distribution width and uric acid, and took more digoxin and diuretics and less statins (Table 1). Reactive pc-PH patients had the significantly higher prevalence of being female and less hypertension compared with no PH or passive pc-PH patients.

Hemodynamic measurements revealed that the pc-PH patients had significantly higher mRAP, increased heart rate, and lower cardiac index than non-PH patients (Table 1). According to the hemodynamic definition of pulmonary vascular disease, the reactive pc-PH patients had significantly higher TPPG and PVR than the passive pc-PH patients, although mPCWP was comparable between the 2 groups. Furthermore, the patients with reactive pc-PH had elevated pulmonary pulse pressure with a resultant reduced pulmonary artery compliance, which reciprocally correlated with mPAP (Figure 2A). Moreover, Kaplan-Meier analysis showed that both subgroups of post-capillary PH had a significantly worse prognosis than the non-PH group (Figure 2B).

Risk Factors for Reactive Post-Capillary PH

More than one-third of the pc-PH patients were identified as having reactive pc-PH (Table 1). Univariate logistic regression analysis for the risk of reactive pc-PH showed significant associations with female sex, lower BMI, absence of systemic hypertension, and no use of CCB (Table 2). However, multiple regression analysis after adjusting for age showed that female sex was the only independent predictor of reactive pc-PH (odds ratio 2.12, 95% confidence interval (CI) 1.05–4.30, P=0.03) (Table 2).

Prognosis of Patients With Post-Capillary PH

During the follow-up period, 125 (18%) of the 676 CHF patients died, including 22 (38%) in the reactive pc-PH and 24 in the passive pc-PH group. Overall, the pc-PH patients had significantly higher mortality rate (P<0.001) than those with no PH (Figure 3A). Although there was no significant difference in mortality rate among HFpEF, HFrEF, and VHD with and without pc-PH (Figure 3B), the presence of pc-PH worsened the prognosis in the patients with VHD and those with HFrEF (Figures 3C,D), but not in those with HFpEF (Figure 3E).

In the pc-PH patients, the presence of reactive pc-PH significantly worsened the prognosis for all-cause death and a composite endpoint of all-cause death and HF re-admission (Figures 4A,B), which also was the case for non-VHD, but not VHD (Figures 4C–F).

In the patients with IHD-CHF, the prevalence of pc-PH tended to be higher in patients with HFrEF than in those with HFpEF (27% vs. 13%, P=0.06). Kaplan-Meier analysis showed that the IHD-CHF patients with reactive pc-PH had a significantly higher mortality than the IHD-CHF patients with no PH and those with passive pc-PH (P<0.001 and P=0.03, respectively) (Figure 5A). Although there was no significant difference in mortality among the patients with IHD-HFpEF in terms of pc-PH subtype (Figure 5B), the presence of reactive pc-PH was associated with a significantly worse prognosis in IHD-HFrEF patients (P=0.02) (Figure 5C). Similarly, the non-IHD patients with reactive pc-PH had a significantly higher mortality than those with no PH (P=0.003) (Figure 5D). In the subgroup of non-IHD and HFpEF, both the reactive and the passive pc-PH patients had worse prognosis compared with those with no PH (P<0.001 and P=0.045, respectively) (Figure 5E), which was not the case for those with non-IHD and HFrEF (Figure 5F).

Cox Hazard Analysis

In the non-adjusted univariate model, elevated PVR was significantly associated with poor outcome (hazard ratio (HR) 1.28, 95%CI 1.14–1.42, P<0.001), in addition to age, BMI, anemia, CKD stage ≥3, serum BNP level, mRAP and use of β-blockers (Table 3). Multivariate Cox regression analysis showed that elevated PVR was an independent risk factor for mortality (adjusted HR 1.18, 95%CI 1.03–1.35, P=0.02) after the adjustment for age, sex, BMI, NYHA functional class, group 2 PH subcategory (VHD and HFrEF), anemia, CKD ≥stage 3, AF, BNP, mRAP, and use of β-blockers (Table 3). Higher age, the presence of anemia, the advanced CKD stage, elevated BNP level, and no use of β-blockers were also significant poor predictors of adverse outcome (Table 3).

Discussion

The novel findings of the present study are: (1) female sex was the only significant risk factor for reactive pc-PH after adjustment of covariates, (2) patients with reactive pc-PH had a worse prognosis than those with no PH or passive pc-PH, and (3) elevated PVR was an independent risk factor for poor prognosis in patients with LHD and NYHA ≥2 HF symptoms.

Characteristics of Reactive Post-Capillary PH

LHD is one of the most common etiologies of PH.[11] Indeed, a high prevalence of pc-PH has been reported in patients with advanced systolic HF,[19] diastolic HF,[20] VHD including mitral valve diseases, and advanced HF referred for heart transplantation.[8,21] In addition, systolic PAP also increases with age in

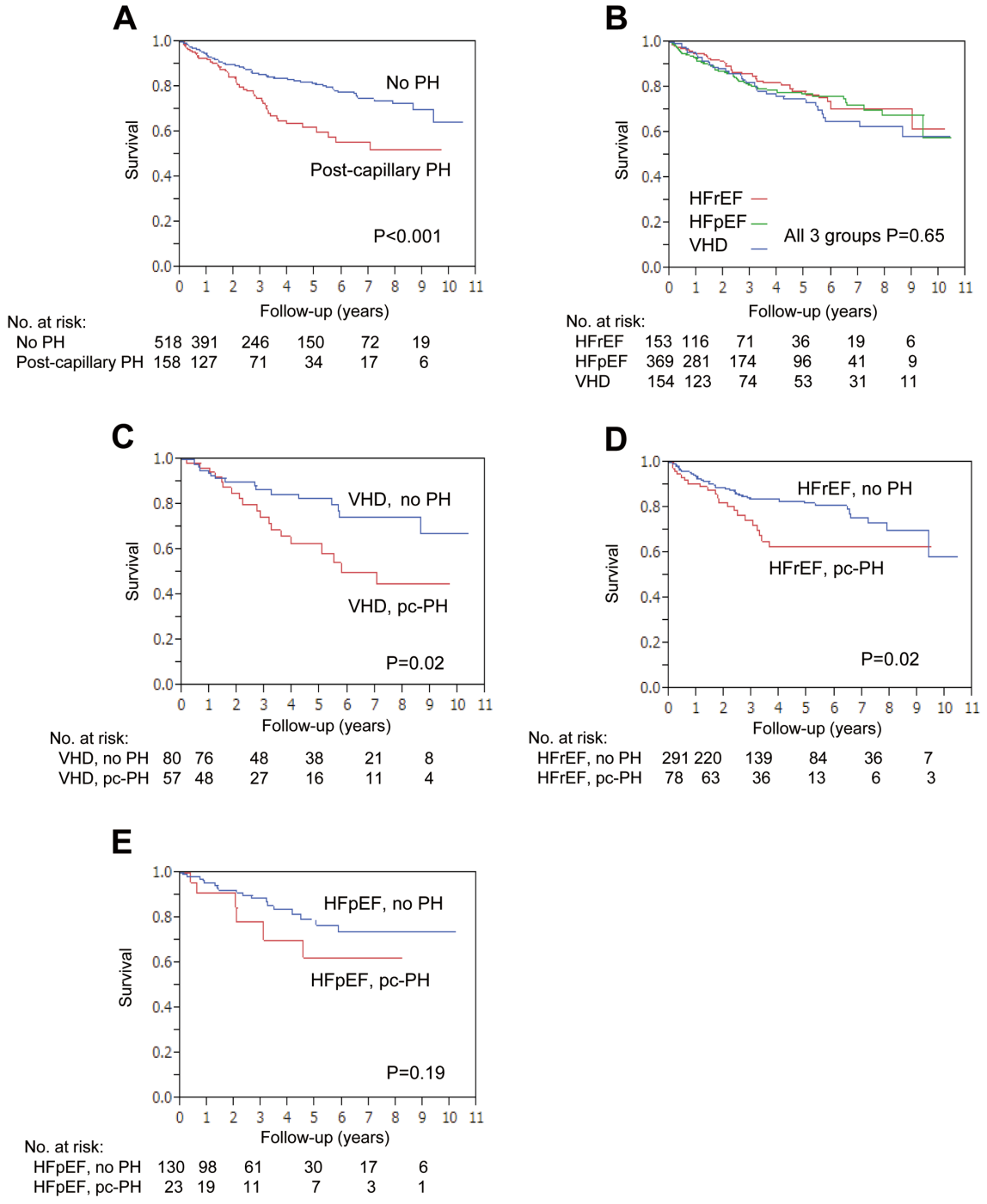

Figure 3. Kaplan-Meier analysis for all-cause death in all patients. (**A**) Survival curve according to the presence of post-capillary pulmonary hypertension (pc-PH). (**B**) Survival curve stratified by Dana point group 2 PH subcategories. (**C**) Survival curve of VHD patients with and without pc-PH. (**D**) Survival curve of HFrREF patients with and without pc-PH. (**E**) Survival curve of HFpEF patients with and without pc-PH. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; VHD, valvular heart disease.

the general population.[22] Several risk factors have been suggested for PH in patients with diastolic LV dysfunction, such as increased age, presence of atrial arrhythmias, hypertension and metabolic syndrome.[20,23,24] However, no mechanism has yet been identified for the development of the pulmonary vascular involvement that causes PVR elevation in a proportion of PH cases.

In the present study, female sex was identified as the only independent risk factor for reactive pc-PH, suggesting that menopause may be a potential mechanism of reactive pc-PH.

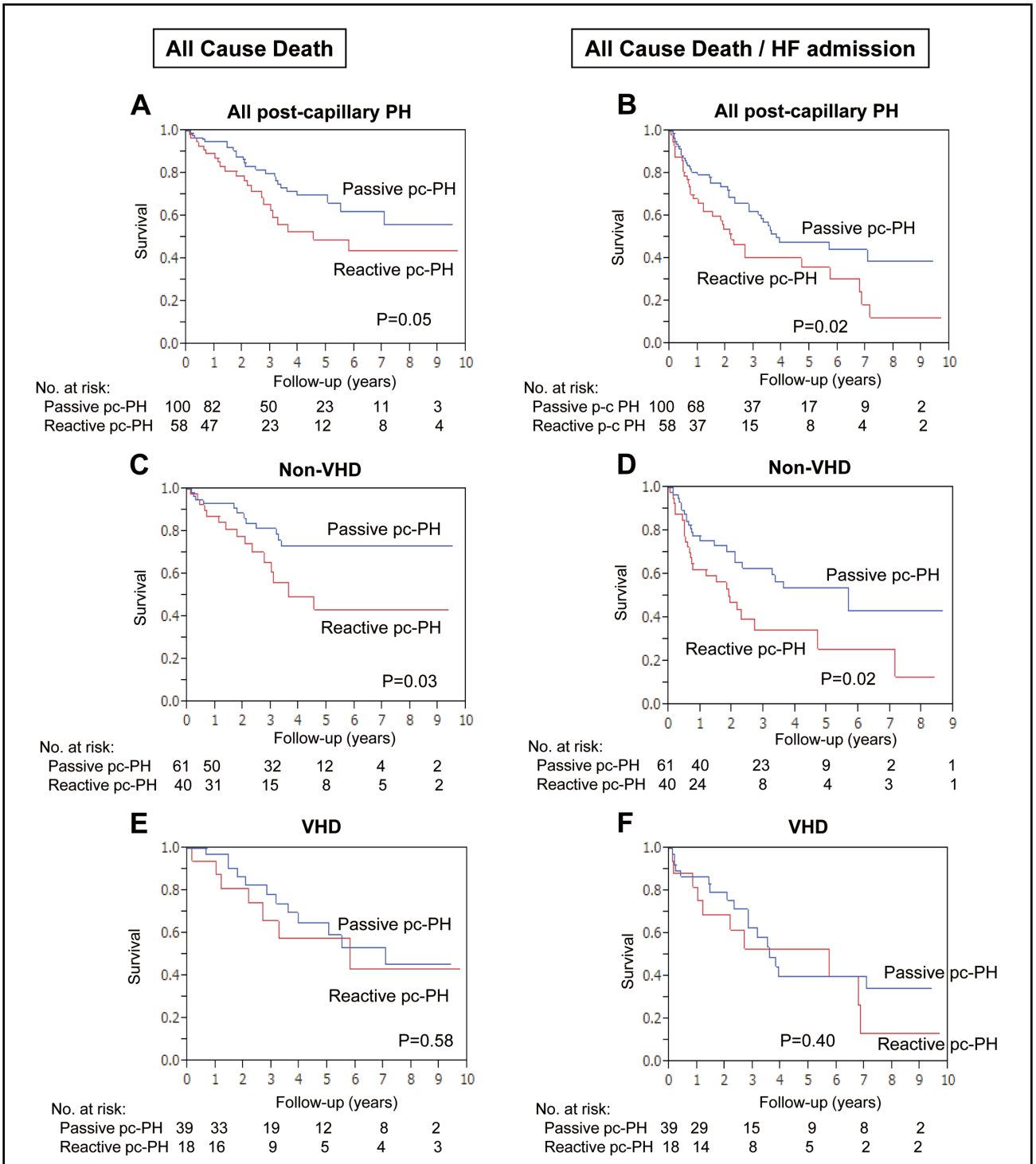

Figure 4. Kaplan-Meier analysis for all-cause death and composite endpoint in patients with post-capillary pulmonary hypertension (PH). (**A**,**C**,**E**) All-cause death, (**B**,**D**,**F**) Heart failure admission/all-cause death. Survival curve of patients with post-capillary PH (**A**,**B**), with non-VHD (**C**,**D**), and with VHD (**E**,**F**). VHD, valvular heart disease.

Because female sex hormones, especially estrogen, are protective for the development of cardiovascular diseases, menopause causes endothelial dysfunction and decreases flow-mediated dilatation,[25,26] which may affect pulmonary vascular tone, resulting in the sex difference in the prevalence of reactive pc-PH. In addition to the vascular impairment, age-related ventricular dysfunction is more likely to develop into HFpEF in postmenopausal women compared with men, and worsening of ventricular function and functional reserve is more dramatic in women.[27] Indeed, 70% of reactive pc-PH patients

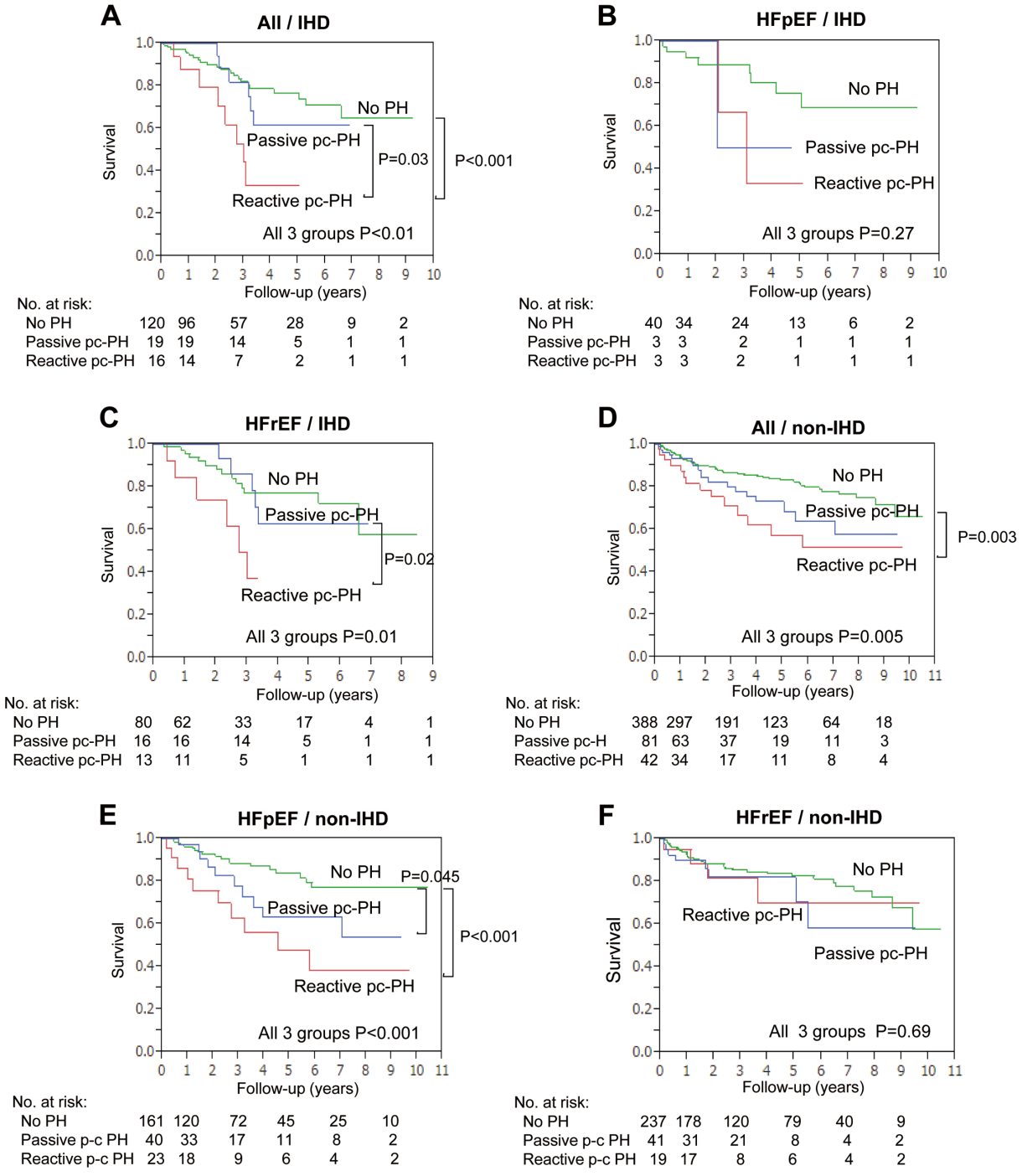

Figure 5. Kaplan-Meier analysis for all-cause death according to the presence of ischemic heart disease (IHD) and the subtypes of post-capillary pulmonary hypertension (PH). Survival curves of patients with IHD (**A**), IHD and HFpPEF (**B**), IHD and HFrREF (**C**), non-IHD (**D**), non-IHD and HFpPEF (**E**), and IHD and HFrEF (**F**). HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; VHD, valvular heart disease.

with HFpEF in the present study were female.

Prognosis of Patients With Reactive Post-Capillary PH

It has been repeatedly demonstrated that the presence of PH in patients with HF is a predictor of all-cause death and HF admission for both systolic and diastolic dysfunction.[5,19,20,28,29] In addition, elevated PVR has been reported as associated with early death and RV dysfunction after heart transplantation.[10,30] However, convincing evidence is lacking that elevated PVR or TPPG is a risk factor for adverse outcome in patients with LHD-HF, especially those with pc-PH. It was reported that the degree of PH and RV systolic pressure are risk factors for poor

Table 3. Risk Factors for All-Cause Mortality in All Patients of the 3 Groups

	Non-adjusted		Adjusted	
	HR (95%CI)	P value	HR (95%CI)	P value
Age (years)	1.03 (1.02–1.05)	<0.001	1.02 (1.00–1.04)	0.02
Female	0.88 (0.60–1.28)	0.52	0.76 (0.50–1.15)	0.20
BMI (kg/m^2)	0.95 (0.90–0.99)	0.02	0.96 (0.90–1.01)	0.11
NYHA ≥3	1.25 (0.88–1.78)	0.22	0.91 (0.61–1.35)	0.62
VHD	1.19 (0.80–1.75)	0.38	0.96 (0.58–1.55)	0.86
HFrEF	1.00 (0.70–1.44)	0.98	1.04 (0.67–1.63)	0.85
Anemia	2.13 (1.49–3.04)	<0.001	1.62 (1.08–2.37)	0.02
CKD ≥stage 3	2.06 (1.45–2.95)	<0.001	1.54 (1.01–2.37)	0.05
AF	1.33 (0.92–1.90)	0.13	0.98 (0.64–1.49)	0.92
BNP (pg/ml)	1.00 (1.00–1.001)	<0.001	1.00 (1.00–1.001)	0.04
mRAP (mmHg)	1.06 (1.02–1.10)	0.004	1.03 (0.98–1.08)	0.26
PVR (Wood unit)	1.28 (1.14–1.42)	<0.001	1.18 (1.03–1.35)	0.02
β-blocker	0.59 (0.38–0.89)	0.01	0.49 (0.30–0.78)	0.002

HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio. Other abbreviations see in Tables 1,2.

outcome,[20,31] but those studies only estimated PAP by Doppler echocardiography and thus were unable to differentiate reactive and passive pc-PH.[32] Recently, it was reported that reactive pc-PH correlates with increased mortality among patients with acute decompensated HF after initial treatment; however, the follow-up period in that study (6 months) was relatively short.[33] In the present study, we used reliable and invasive hemodynamic data to classify pc-PH, and assessed the long-term outcome with a mean follow-up of 3 years. Our results showed that elevated PVR was a strong predictor for all-cause death in patients with chronic HF in all subgroups of HFrEF, HFpEF and VHD. Furthermore, the presence of reactive pc-PH was associated with increased mortality and HF re-admission in patients with pc-PH and HF, even if in a stable condition. These results suggest that reactive pc-PH is an important therapeutic target to optimize medical therapy for HF, such as phosphodiesterase 5 inhibitors (ie, sildenafil)[34] and soluble guanylate cyclase stimulators. However, further studies are required to develop the optimized medical therapy for pc-PH.

Influences of LVEF and Etiology of HF on the Prognosis of Patients With pc-PH

It has been demonstrated that LV remodeling is associated with both systolic dysfunction after acute myocardial infarction and mortality.[35] Furthermore, a restrictive LV filling pattern on echocardiography, which indicates elevated LA pressure, has been identified as an independent prognostic factor.[36] In the present study, pc-PH was more prevalent in IHD patients with HFrEF compared with those with HFpEF. Moreover, reactive pc-PH was associated with poor outcome in patients with IHD-HFrEF but not in those with IHD-HFpEF, suggesting that the extent of LV remodeling is a potential mechanism to explain the difference. Future studies are required to clarify this issue and to develop a new therapeutic target for HFpEF.[37]

Study Limitations

First, this was a retrospective study in a single center with a relatively small sample size. Thus, we were unable to divide mitral valve disease into mitral stenosis and mitral regurgitation (Table 1). Second, time-dependent variables (ie, valve surgery for VHD, percutaneous coronary intervention and/or coronary artery bypass surgery), which could affect clinical course of pc-PH, were not included in the Cox model. Third, hemodynamic diagnosis by challenge tests such as exercise and the acute pulmonary vasoreactivity test, were not performed in all patients. Fourth, reactive pc-PH was associated with poor outcome in patients with non-IHD-HFpEF but not in those with non-IHD-HFrEF, probably because of the small number of patients in each group.

Conclusions

In the present study, we were able to demonstrate that reactive pc-PH is characterized by predominant female sex and a significantly worse prognosis compared with passive pc-PH.

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Disclosures

None.

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