Research Square

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Prevalence, characteristics and survival of pulmonary hypertension due to chronic heart failure: a national multicenter prospective registry study

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Abstract

Background The prevalence, characteristics and survival of pulmonary hypertension due to left heart disease (PH-LHD) in heart failure with reduced and preserved ejection fraction (HFrEF, HFpEF) has yet to be explored.

Methods Consecutive patients with chronic heart failure undergoing first right heart catheterization (RHC) were prospectively enrolled from October 2012 to August 2016 in 11 participating medical centers. Follow-up was performed every 6 months ± 2 weeks. The primary endpoint was all-cause mortality.

Results A total of 500 patients were enrolled. The prevalence of PH was 67.2% in HFrEF and 40.2% in HFpEF, respectively. Predictors of PH differed between PH etiologies, but left ventricular end diastolic diameter (LVEDD) was a consistent both in HFrEF (P=0.031) and HFpEF (P=0.003). During a median follow-up time of 33.39 months, 69 patients (13.8%) met the primary endpoint. The survival of PH patients was significantly worse than that of patients without PH (P=0.001). Diastolic pressure gradient (DPG) was a significant prognostic variable both in HFrEF (HR=1.057, 95% CI=1.007-1.108, P=0.024) and HFpEF (HR=1.094, 95% CI=1.009-1.187, P=0.030). Patients with a DPG ≥ 7 mmHg had a worse survival compared to those whose DPG < 7 mmHg both in HFrEF (log rank test, P=0.047) and in HFpEF (P=0.016).

Conclusion Though the prevalence, characteristics and prognosis of PH differ between HFrEF and HFpEF, PH-LHD is a common complication and has an adverse effect on the prognosis. Study registration NCT02164526.

Background

Pulmonary hypertension due to left heart disease (PH-LHD), typically characterized by a passive increase in pulmonary artery wedge pressure (PAWP) in response to a backward transmission of elevated left-sided filling pressures, is the most frequent cause of pulmonary hypertension (PH)[1–3]. PH-LHD can result from a variety of etiology, but it is most common in left ventricular systolic or diastolic dysfunction, which is also referred to as heart failure with reduced or preserved ejection fraction (HFrEF or HFpEF)[4, 5]. Independent of the left ventricular ejection fraction (LVEF) and stage of heart failure (HF), PH is associated with increased hospitalization and mortality, which emphasizes the importance of the identification of PH to achieve a better management[6]. However, the prevalence of PH-LHD in HF has yet to be explored, with estimates ranging from 40–81% in HFrEF and from 23–83% in HFpEF[7, 8]. The inconsistency can be attributed to several reasons, such as the diverse study designs, the heterogeneous study cohorts, and the different diagnostic modalities[7–15]. The similar disparity also exists in the data with regard to not only the survival of PH-LHD, but also the outcome correlates[6–12, 15–21]

Though right heart catheterization (RHC) is recommended as the gold standard to confirm the diagnosis of PH, its usage remains limited in the setting of LHD due to its invasive nature, leading to few studies using RHC as diagnositc criteria. Therefore, yet several studies have tried to utilize a combination of clinical characteristics, comorbid conditions, laboratory results and noninvasive tests to help the

identification of PH-LHD[9, 21–25]. However, the majority of the studies have focused on the differentiation between PH-LHD and pulmonary arterial hypertension (PAH)[22–25]. In a HF cohort, how to identify patients at high risk of PH with noninvasive methods remains to be explored.

On the other hand, several hemodynamic parameters obtained from RHC have proven to be prognostic predictors for survival and/or other outcomes, such as transpulmonary pressure gradient (TPG), diastolic pressure gradient (DPG) and pulmonary vascular pressure (PVR)[26]. However, as none of them are free from limitations, their prognostic value are still controversial[26].

Accordingly, the objectives of our study were: 1) to illustrate the prevalence and characteristics of PH-LHD in two well-defined etiology groups: HFrEF and HFpEF; 2) to explore risk factors of PH-LHD; and 3) to assess the survival and outcome correlates of PH-LHD.

Methods

Patient enrollment

In this national multicenter prospective registry study, patients with symptomatic chronic heart failure undergoing first right heart catheterization (RHC) during hospitalization were consecutively enrolled from October 2012 to August 2016 in 11 participating medical centers throughout China. The study has been registered on ClinicalTrials.gov (Identifier: NCT02164526). Patients were included if: 1) their age was between 18 and 80; 2) they were diagnosed with chronic heart failure with NYHA □-□; 3) the etiology of their heart failure was ischemic heart disease, hypertension or idiopathic cardiomyopathy; 4) they underwent RHC. Patients were excluded if they: 1) had pulmonary hypertension of other types; 2) had organic valvular heart disease; 3) had right ventricular outflow tract obstruction; 4) had pericardial disease, including pericarditis, a thickened or calcified pericardium; 5) had chronic pulmonary diseases such as interstitial fibrosis, chronic obstructive pulmonary disease or primary parenchymal lung disease; and 6) had hypertrophic obstructive cardiomyopathy. Written informed consent was obtained from all enrolled patients. This study complied with the Declaration of Helsinki. The study protocol was approved by the ethics committee of Fuwai hospital (Approval No.2012-401).

Definitions

Symptomatic heart failure was diagnosed according to the 2012 HF guidelines, which differentiates HFpEF from HFrEF by echocardiographically estimated LVEF, with a cut-off value of ≥ 50% or < 50% respectively[5]. Post-capillary pulmonary hypertension, also referred to as PH-LHD, was hemodynamically defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg and PAWP□15 mmHg[4].

Measurements and data collection

Electrocardiogram (ECG), chest X ray, transthoracic echocardiography, pulmonary function test, high-resolution computed tomography of the chest, ventilation/perfusion scintigraphy lung scan (if necessary) and pulmonary angiography (if necessary) were performed to evaluate the severity of heart failure,

exclude pulmonary hypertension due to other causes and conditions in the exclusion criteria, such as lung diseases or chronic thromboembolism pulmonary hypertension.

The indications of RHC were based upon referring physicians, mostly for the diagnosis of suspected pulmonary hypertension with an elevated systolic pulmonary arterial systolic pressure (PASP) at echocardiography. Catheterizations were also performed for transplantation eligibility assessments, or prior to percutaneous interventions or surgical procedures. Catheterizations were performed in stable, non-acute clinical conditions.

For patients who met the inclusion and exclusion criteria, the following data were collected: 1) demographics, medical history, clinical symptoms and vital signs; 2) results of laboratory tests, echocardiography and catheterizations; and 3) drug treatments (patients were optimally managed by HF treatments, with no usage of PH-targeted drugs).

RHC

RHC was centralized using a standard protocol across all the participating centers. During the procedure, patients were positioned supine with legs flat. A 7F Swan-Ganz catheter (Edwards Lifesciences World Trade Co. Ltd, Irvine, CA, USA) was inserted from a femoral or jugular approach, with zeroing calibration in the mid-axillary line to atmospheric pressure. Correct positioning of the catheter was verified by chest fluoroscopy. Hemodynamics, including right atrial pressure (RAP), diastolic pulmonary arterial pressure (dPAP), systolic pulmonary arterial pressure (sPAP), mPAP and PAWP, were obtained during spontaneous breathing. All pressures were recorded after at least 6 stable cardiac cycles during several respiratory cycles. Cardiac output (CO) was measured by the thermodilution method (the mean value of three-time measurements). The DPG was assessed as the difference between dPAP and PAWP. TPG was calculated by subtracting PAWP from mPAP. PVR was obtained by the equation: PVR= (mPAP-PAWP)/ CO. Pulmonary arterial compliance (PAC) was calculated as stroke volume divided by the difference between sPAP and dPAP. In 428 (85.6%) of 500 patients, RHC was combined with a left heart catheterization for coronary angiography, and we substituted left ventricular end diastolic pressure (LVEDP) for PAWP in those patients.

Primary endpoint and follow-up

The primary endpoint of this study was all-cause mortality. Overall survival was measured from the date of RHC to the date of death from any cause. Follow-up was performed by telephone calls, outpatient visits or inpatient admissions every 6 months ± 2 weeks. In each follow-up, it was confirmed whether patients died or received transplantations and whether they had received any surgical or intervention treatments or had any instances of cardiac hospitalization. Patients were followed until death or until the end of the study (July 2017).

Statistical analysis

Continuous variables are presented as the mean ± standard deviations. For normally distributed variables, the differences between groups were compared by the Student's t test, while for non-normally distributed variables, the analyses were carried out by the Mann-Whitney test. Categorical variables are shown as frequencies and percentages, and chi-square tests were used to compare the differences between two subgroups. Univariate and multivariate logistic regression models were performed to identify variables associated with the presence of PH. To identify the association between variables and primary endpoint, univariate and multivariate Cox proportional hazards models were conducted, and the effects were estimated by the hazard ratio (HR) and 95% confidence interval (CI). Variables were included in the multivariate logistic or Cox models on the basis of previous literature, clinical expertise and univariate analyses. Survival was estimated by means of Kaplan-Meier analysis and the difference was compared by the log-rank test. Receiver operating characteristic (ROC) curve was used to identify an optimized cut-off value, which was determined by maximizing the Youden index (sum of sensitivity and specificity minus one). Differences were considered statistically significant when the two-sided P value was 0.05. All the statistical analyses were performed by SPSS Statistics (version 22.0, IBM).

Results

Baseline characteristics

A total of 500 patients who met the inclusion and exclusion criteria were enrolled, patients dispositions are presented in Fig. 1. In the study cohort, 122 (24.4%) patients were classified as HFrEF, with 378 (75.6%) patients diagnosed as HFpEF. As shown in Table 1, the baseline characteristics significantly differed between the two groups.

Table 1

Baseline characteristics of the study cohort.

Characteristics	All (N = 500)	HFrEF (N = 122)	HFpEF (N = 378)	P value†
Age (years)	62.59 ± 12.32	61.38 ± 13.97	62.98 ± 11.73	0.716
Males, n (%)	373 (74.6)	96 (78.7)	277 (73.3)	0.233
BMI (kg/m2)	22.69 ± 2.70	23.05 ± 2.99	22.57 ± 2.59	0.073
NYHA-FC, n (%)				< 0.001
	344 (68.8)	49 (40.2)	295 (78.0)	
	123 (24.6)	51 (41.8)	72 (19.0)	
	33 (6.6)	22 (18.0)	11 (2.9)	
Arterial hypertension, n (%)	191 (38.2)	35 (28.7)	156 (41.3)	0.015
Stable coronary artery disease, n (%)	386 (77.2)	72 (59.0)	314 (83.1)	< 0.001
Diabetes mellitus, n (%)	117 (23.4)	26 (21.3)	91 (24.1)	0.531
Atrial fibrillation, n (%)	13 (2.6)	6 (4.9)	7 (1.9)	0.064
Creatinine clearance < 60 mL/min, n (%)	153 (30.6)	41 (33.6)	112 (29.6)	0.407
Hyperlipidemia, n (%)	127 (25.4)	27 (22.1)	100 (26.5)	0.340
Laboratory tests				
NT-proBNP (fmol/mL)	1412.42 ± 1873.78	2512.64 ± 2320.18	969.81 ± 1448.37	< 0.001
Echocardiography				

† HFrEF versus HFpEF.

HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction; BMI: body mass index; NYHA-FC: New York Heart Association-Functional Class; NT-proBNP: N-terminal pro-brain natriuretic peptide; LAAPD: left atrial anteroposterior diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; RVAPD: right ventricular anteroposterior diameter; PASP: pulmonary arterial systolic pressure; HR: heart rate; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; DPG: diastolic pressure gradient; TPG: transpulmonary pressure gradient; CI: cardiac index; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist.

Characteristics	All (N = 500)	HFrEF (N = 122)	HFpEF (N = 378)	P value†
LAAPD (mm)	35.07 ± 6.47	39.90 ± 7.60	33.54 ± 5.21	< 0.001
LVEDD (mm)	48.99 ± 8.45	57.96 ± 10.40	46.14 ± 5.12	< 0.001
LVEF (%)	54.26 ± 11.04	38.21 ± 8.94	59.39 ± 5.15	< 0.001
RVAPD (mm)	19.77 ± 5.17	22.51 ± 6.50	18.91 ± 4.34	< 0.001
Tricuspid regurgitaion velocity	3.32 ± 0.65	3.56 ± 0.68	3.15 ± 0.58	0.021
PASP	47.55 ± 13.59	53.90 ± 13.19	42.90 ± 12.03	< 0.001
Right heart catheterization				
HR(beats/min)	75.90 ± 14.11	79.13 ± 16.78	74.86 ± 12.99	0.002
RAP (mmHg)	12.89 ± 4.36	11.53 ± 5.58	13.32 ± 3.81	0.017
sPAP (mmHg)	40.76 ± 12.41	46.83 ± 15.84	38.80 ± 10.38	< 0.001
dPAP (mmHg)	20.20 ± 6.84	22.25 ± 9.36	19.54 ± 5.66	< 0.001
mPAP (mmHg)	27.29 ± 8.51	31.43 ± 11.24	25.95 ± 6.93	< 0.001
PAWP (mmHg)	17.16 ± 4.70	18.70 ± 5.62	16.66 ± 4.25	< 0.001
DPG (mmHg)	3.04 ± 6.30	3.55 ± 8.35	2.88 ± 5.48	0.383
TPG (mmHg)	10.13 ± 7.70	12.73 ± 10.22	9.29 ± 6.49	0.001
CI (L/min/m2)	2.44 ± 0.56	2.22 ± 0.51	2.59 ± 0.55	0.809

† HFrEF versus HFpEF.

HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction; BMI: body mass index; NYHA-FC: New York Heart Association-Functional Class; NT-proBNP: N-terminal pro-brain natriuretic peptide; LAAPD: left atrial anteroposterior diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; RVAPD: right ventricular anteroposterior diameter; PASP: pulmonary arterial systolic pressure; HR: heart rate; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; DPG: diastolic pressure gradient; TPG: transpulmonary pressure gradient; CI: cardiac index; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist.

Characteristics	All (N = 500)	HFrEF (N = 122)	HFpEF (N = 378)	P value†
PVR (WU)	2.96 ± 3.24	4.12 ± 3.51	1.97 ± 2.75	0.012
PAC (mL/mmHg)	3.22 ± 2.55	2.35 ± 1.55	3.83 ± 2.94	0.004
Drug therapy				
ACEI/ARB, n (%)	320 (64.0)	86 (70.5)	234 (61.9)	0.086
Beta blocker, n (%)	340 (68.0)	98 (80.3)	242 (64.0)	0.001
Ca^{2+} channel blockers, n (%)	92 (18.4)	15 (12.3)	77 (20.4)	0.045
Diuretics, n (%)	203 (40.6)	91 (74.6)	112 (29.6)	< 0.001
Digoxin, n (%)	98 (19.6)	64 (52.5)	34 (9.0)	< 0.001
MRA, n (%)	218 (43.6)	91 (74.6)	127 (33.6)	< 0.001
Antiplatelet/anticoagulant, n (%)	388 (77.6)	78 (64.0)	310 (82.0)	< 0.001

† HFrEF versus HFpEF.

HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction; BMI: body mass index; NYHA-FC: New York Heart Association-Functional Class; NT-proBNP: N-terminal pro-brain natriuretic peptide; LAAPD: left atrial anteroposterior diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; RVAPD: right ventricular anteroposterior diameter; PASP: pulmonary arterial systolic pressure; HR: heart rate; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; DPG: diastolic pressure gradient; TPG: transpulmonary pressure gradient; CI: cardiac index; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist.

Prevalence and characteristics of PH-LHD

PH-LHD was identified in 82 (67.2%) patients with HFrEF and in 152 (40.2%) patients with HFpEF (Fig. 1). As shown in Table 2, patients with PH-LHD presented significantly worse echocardiographic and invasive hemodynamic parameters regardless of HF etiology.

Table 2

Baseline characteristics of Non-PH and PH-LHD.

Characteristics	HFrEF			HFpEF		
	Non-PH (N = 40)	PH-LHD (N = 82)	P value	Non-PH N = 226)	PH-LHD (N = 152)	P value†
Age (years)	62.78 ± 14.23	60.70 ± 13.88	0.355	62.28 ± 11.21	64.03 ± 12.42	0.149
Males, n (%)	29 (72.5)	67 (81.7)	0.244	179 (79.2)	98 (64.5)	0.002
BMI (kg/m2)	22.19 ± 2.78	23.47 ± 3.02	0.063	22.35 ± 2.16	22.90 ± 3.10	0.120
NYHA-FC, n (%)			0.120			< 0.001
	21 (52.5)	28 (34.1)		194 (85.8)	101 (66.4)	
	12 (30.0)	39 (47.6)		30 (13.3)	42 (27.6)	
	7 (17.5)	15 (18.3)		2 (0.9)	9 (5.9)	
Arterial hypertension, n(%)	13 (32.5)	22 (26.8)	0.542	93 (41.2)	63 (41.4)	0.954
Stable coronary artery disease, n(%)	30 (75.0)	42 (51.2)	0.015	196 (86.7)	118 (77.6)	0.021

Non-PH versus PH-LHD in HFrEF; † Non-PH versus PH-LHD in HFpEF.

HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction; Non-PH: patients without pulmonary hypertension; PH-LHD: pulmonary hypertension due to left heart disease; BMI: body mass index; NYHA-FC: New York Heart Association-Functional Class; NT-proBNP: N-terminal pro-brain natriuretic peptide; LAAPD: left atrial anteroposterior diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; RVAPD: right ventricular anteroposterior diameter; PASP: pulmonary arterial systolic pressure; HR: heart rate; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; DPG: diastolic pressure gradient; TPG: transpulmonary pressure gradient. CI: cardiac index; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance.

Characteristics	HFrEF			HFpEF		
	Non-PH (N = 40)	PH-LHD (N = 82)	P value[]	Non-PH N = 226)	PH-LHD (N = 152)	P value[†]
Diabetes mellitus, n(%)	6 (15.0)	20 (24.4)	0.234	50 (22.1)	41 (27.0)	0.280
Atrial fibrillation, n(%)	2 (5.0)	4 (4.9)	0.977	2 (0.9)	5 (3.3)	0.089
Creatinine clearance < 60 mL/min, n(%)	13 (32.5)	28 (34.1)	0.857	61 (27.0)	51 (33.6)	0.171
Hyperlipidemia, n(%)	9 (22.5)	18 (22.0)	0.945	55 (24.3)	45 (29.6)	0.255
Laboratory tests						
NT-proBNP (fmol/mL)	1777.74 ± 1853.55	2872.27 ± 2455.51	0.063	825.67 ± 1140.30	1290.12 ± 1943.30	0.139
Echocardiography						
LAAPD (mm)	37.76 ± 6.13	40.89 ± 8.04	0.025	32.34 ± 3.44	35.33 ± 6.69	< 0.001
LVEDD (mm)	54.58 ± 8.25	59.52 ± 10.96	0.018	45.26 ± 4.83	47.45 ± 5.28	< 0.001
LVEF (%)	39.13 ± 8.06	37.78 ± 9.35	0.466	59.30 ± 4.73	59.53 ± 5.73	0.656
RVAPD (mm)	21.61 ± 7.19	22.97 ± 6.12	0.024	18.01 ± 1.78	20.34 ± 6.38	< 0.001

[]Non-PH versus PH-LHD in HFrEF; [†] Non-PH versus PH-LHD in HFpEF.

HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction; Non-PH: patients without pulmonary hypertension; PH-LHD: pulmonary hypertension due to left heart disease; BMI: body mass index; NYHA-FC: New York Heart Association-Functional Class; NT-proBNP: N-terminal pro-brain natriuretic peptide; LAAPD: left atrial anteroposterior diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; RVAPD: right ventricular anteroposterior diameter; PASP: pulmonary arterial systolic pressure; HR: heart rate; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; DPG: diastolic pressure gradient; TPG: transpulmonary pressure gradient. CI: cardiac index; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance.

Characteristics	HFrEF			HFpEF		
	Non-PH (N = 40)	PH-LHD (N = 82)	P value[]	Non-PH N = 226)	PH-LHD (N = 152)	P value[†]
Tricuspid regurgitaion velocity	3.11 ± 0.43	3.72 ± 0.69	0.041	2.98 ± 0.59	3.28 ± 0.55	0.031
PASP	44.88 ± 9.89	57.18 ± 12.85	0.007	37.29 ± 11.16	46.88 ± 11.20	0.008
Right heart catheterization						
HR(beats/min)	77.03 ± 14.53	80.16 ± 17.77	0.366	74.21 ± 12.54	75.82 ± 13.63	0.203
RAP (mmHg)	10.08 ± 6.13	12.26 ± 5.16	0.047	12.12 ± 3.24	15.13 ± 3.91	< 0.001
sPAP (mmHg)	35.45 ± 12.79	52.38 ± 14.18	< 0.001	34.00 ± 7.30	45.95 ± 10.16	< 0.001
dPAP (mmHg)	16.38 ± 7.43	25.12 ± 8.88	< 0.001	16.92 ± 4.11	23.43 ± 5.41	< 0.001
mPAP (mmHg)	23.08 ± 9.44	35.51 ± 9.72	< 0.001	22.36 ± 4.44	31.28 ± 6.54	< 0.001
PAWP (mmHg)	15.58 ± 2.10	20.23 ± 6.15	< 0.001	15.14 ± 3.39	18.93 ± 4.41	< 0.001
DPG (mmHg)	0.80 ± 7.82	4.89 ± 8.32	0.001	1.78 ± 5.23	4.51 ± 5.44	< 0.001

[]Non-PH versus PH-LHD in HFrEF; [†] Non-PH versus PH-LHD in HFpEF.

HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction; Non-PH: patients without pulmonary hypertension; PH-LHD: pulmonary hypertension due to left heart disease; BMI: body mass index; NYHA-FC: New York Heart Association-Functional Class; NT-proBNP: N-terminal pro-brain natriuretic peptide; LAAPD: left atrial anteroposterior diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; RVAPD: right ventricular anteroposterior diameter; PASP: pulmonary arterial systolic pressure; HR: heart rate; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; DPG: diastolic pressure gradient; TPG: transpulmonary pressure gradient. CI: cardiac index; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance.

Characteristics	HFrEF			HFpEF		
	Non-PH (N = 40)	PH-LHD (N = 82)	P value[]	Non-PH N = 226)	PH-LHD (N = 152)	P value[†]
TPG (mmHg)	6.72 ± 8.68	15.88 ± 9.30	< 0.001	7.24 ± 5.72	12.24 ± 6.27	< 0.001
CI (L/min/m2)	2.90 ± 0.28	2.16 ± 0.48	0.345	2.69 ± 0.64	2.52 ± 0.49	0.395
PVR (WU)	0.24 ± 0.62	4.53 ± 3.40	0.032	0.03 ± 2.03	3.64 ± 2.04	< 0.001
PAC (mL/mmHg)	4.35 ± 0.79	2.16 ± 1.47	0.047	4.63 ± 1.43	3.31 ± 3.54	0.002

[]Non-PH versus PH-LHD in HFrEF; [†] Non-PH versus PH-LHD in HFpEF.

HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction; Non-PH: patients without pulmonary hypertension; PH-LHD: pulmonary hypertension due to left heart disease; BMI: body mass index; NYHA-FC: New York Heart Association-Functional Class; NT-proBNP: N-terminal pro-brain natriuretic peptide; LAAPD: left atrial anteroposterior diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; RVAPD: right ventricular anteroposterior diameter; PASP: pulmonary arterial systolic pressure; HR: heart rate; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; DPG: diastolic pressure gradient; TPG: transpulmonary pressure gradient. CI: cardiac index; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance.

Predictors of PH-LHD

By multivariate logistic regression model conducted for HFrEF patients, increasing body mass index (BMI) (Odds ratio, OR: 1.187; 95% CI: 1.010–1.394; P = 0.037) and left ventricular end diastolic diameter (LVEDD) (OR: 1.051, 95% CI: 1.005–1.099, P = 0.031) were identified as independent predictors for PH (Table 3). Furthermore, by performing ROC analysis, a LVEDD > 62.5 mm was identified to be the best cut-off value to differentiate PH-LHD from non-PH patients (area under the curve, AUC: 0.617, sensitivity: 36.59%, specificity: 86.84%). As for BMI, a cut-off value of 22.23 kg/m^2 was identified (AUC: 0.586, sensitivity: 65.85%, specificity: 52.50%).

Table 3
Predictors of pulmonary hypertension.

Variables	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
HFrEF				
Age (years)	0.989 (0.962–1.017)	0.440	1.002 (0.970–1.035)	0.907
BMI (kg/m2)	1.171 (1.015–1.350)	0.030	1.187 (1.010–1.394)	0.037
Glucose (mmol/L)	1.222 (0.967–1.543)	0.093	1.267 (0.970–1.655)	0.082
LVEDD (mm)	1.051 (1.009–1.096)	0.018	1.051 (1.005–1.099)	0.031
HFpEF				
Age (years)	1.013 (0.995–1.031)	0.154	1.013 (0.994–1.032)	0.185
Females, n (%)	2.099 (1.322–3.331)	0.002	2.157 (1.331–3.497)	0.00
BMI (kg/m2)	1.086 (1.002–1.178)	0.045	1.090 (0.998–1.192)	0.055
LVEDD (mm)	1.092 (1.045–1.140)	< 0.001	1.090 (1.043–1.139)	< 0.001
RVAPD (mm)	1.366 (1.183–1.577)	< 0.001	1.300 (1.131–1.494)	< 0.001*

OR: odds ratio; CI: confidence interval; HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction; BMI: body mass index; LVEDD: left ventricular end diastolic diameter; RVAPD: right ventricular anteroposterior diameter.

Regarding patients with HFpEF, it revealed that female sex (OR: 1.742, 95% CI: 1.033–2.938, P = 0.038), increasing LVEDD (OR: 1.077, 95% CI: 1.026–1.131, P = 0.003) and increasing right ventricular anteroposterior diameter (RVAPD) (OR: 1.300, 95% CI: 1.131–1.494, P < 0.001) were significant predictors for PH-LHD (Table 3). Furthermore, a cut-off value of 45.50 mm and 18.50 mm was identified respectively for LVEDD and RVAPD to best distinguish PH-LHD patients from non-PH patients (AUC: 0.598, sensitivity: 67.76%, specificity: 51.77%; AUC: 0.627, sensitivity: 52.86%, specificity: 72.52%, respectively).

Survival

During a median follow-up time of 33.39 months (range from 0.13 to 60.50 months), 69 patients (13.8%) met the primary endpoint. 5 patients underwent heart transplantations. Overall survival of HFrEF was significantly worse than that of HFpEF (P = 0.032, Fig. 2A). Patients with PH-LHD had a higher mortality rate than those without PH (P = 0.001, Fig. 2B). Because of the mortality rate of non-PH was low (21/266), we did not conduct a subgroup analysis, analyzing HFrEF and HFpEF separately.

Outcome correlates of PH-LHD

In the multivariate Cox proportional hazards model conducted for HFrEF, NYHA class (HR: 5.773; 95% CI: 1.860-17.921; P = 0.002) and DPG (HR: 1.057, 95% CI: 1.007–1.108, P = 0.024) were found out to be significant predictors for mortality. Besides, DPG was further substituted as a dichotomous variable divided by 7 mmHg, and the significance remained (HR: 2.695, 95% CI: 1.169–6.211, P = 0.020). In PH-HFpEF, we found that only DPG remained a significant predictor for mortality after adjusted (Continuous: HR = 1.094, 95% CI = 1.009–1.187, P = 0.030; binary: HR = 2.149, 95% CI = 1.156–3.997, P = 0.016) (Table 4). By Kaplan-Meier analysis, a significant worse survival was observed in HFrEF patients with a DPG ≥ 7 mmHg compared to those whose DPG < 7 mmHg (log rank test, P = 0.047, Fig. 3A). The difference was also identified in patients with HFpEF (P = 0.016, Fig. 3B).

Table 4

Univariate and multivariate Cox proportional hazards model of all-cause mortality.

Variables	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
HFrEF				
Age (years)	1.019 (0.981–1.058)	0.341	1.031 (0.992–1.070)	0.118
Females, n (%)	0.652 (0.193–2.207)	0.492	0.849 (0.233–3.097)	0.804
NYHA □	4.717 (1.663–13.381)	0.004	5.773 (1.860-17.921)	0.002
Diabetes mellitus, n(%)	2.080 (0.889–4.868)	0.091	1.253 (0.499–3.149)	0.632
DPG (mmHg)	1.053 (1.008-1.100)	0.020	1.057 (1.007–1.108)	0.024
HFpEF				
Age (years)	1.056 (1.019–1.094)	0.003	1.035 (0.994–1.076)	0.094
Females, n (%)	0.696 (0.292–1.656)	0.412	0.466 (0.178–1.218)	0.119
NYHA □	4.018 (1.309–12.329)	0.015	3.614 (0.993–13.150)	0.051
Arterial hypertension, n(%)	1.970 (0.904–4.290)	0.088	1.763 (0.733–4.240)	0.205
Stable coronary artery disease, n(%)	3.398 (0.803–14.387)	0.097	2.606 (0.562–12.090)	0.221
DPG (mmHg)	1.081 (1.018–1.147)	0.011	1.094 (1.009–1.187)	0.030

HR: hazard ratio; CI: confidence interval; HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction; NYHA □: New York Heart Association Functional Class □; DPG: diastolic pressure gradient.

Discussion

The objective of this study was to investigate the prevalence, characteristics and survival of pulmonary hypertension due to chronic heart failure, with HFrEF and HFpEF analyzed separately, in a prospective multicenter setting. We demonstrated that: 1) the prevalence of PH was 67.2% in HFrEF and 40.2% in HFpEF, respectively; 2) patients with PH-LHD presented significantly worse echocardiographic and

invasive hemodynamic parameters regardless of HF etiology; 3) predictors of PH differed between PH etiologies, but LVEDD could be a consistent predictor of PH both in HFrEF and in HFpEF; 4) the survival of PH patients was significantly worse than patients without PH; and 5) DPG was a significant prognostic variable both in HFrEF and HFpEF.

The true prevalence of PH due to HF is unknown, which can be attributed to the heterogeneity of epidemiological studies based on different study designs, study cohorts, diagnostic modalities, or various definitions and thresholds of PH. It is estimated that the prevalence of PH-LHD in HF ranges from 25–83%[7–15].The prevalence of PH-LHD reported in this study is accordance with what have reported before, indicating PH is a common complication in HF regardless of etiology. However, it should be noted that, compared to Group I PH, RHC was not common or of routine practice in patients with heart failure. Usually, catheterization is performed for suspected PH or for evaluation prior to surgical procedures such as transplantations. It is also true in our institutes, which implies the actual prevalence of PH can be overestimated in literatures and in our study as not all HF patients would undergo RHC in daily practice. It can also explain why we only enrolled 500 patients in our study period despite the large HF population in China[27]. The relatively small sample size could be attributed to our inclusion criteria, as we only enrolled patients undergoing RHC.

It should be noted that ischemic heart disease accounted for the most prevalent etiology in our study (77.2%), and RHC was combined with a left heart catheterization for coronary angiography in 85.6% of all patients, whose PAWPs were substituted by LVEDPs. It is recognized that when measured properly, the PAWPs should closely approximate LVEDPs[26, 28]. However, the accurate measurement of PAWPs has been a challenge in many clinical circumstances, such as the respiratory status of measurement, the existence of a larger left atrial diameter and atrial fibrillation[28]. Therefore, when LVEDPs could be attained in our study, we used LVEDPs to classify PH-LHD.

In our cohort, males accounted for 74.6% of the cohort, with a similar distribution between HFrEF and HFpEF, which was higher than the data reported by China-HF Registry[27], and opposite to the knowledge that HFpEF is thought to be more prevalent in women[8]. The paucity of women with this condition could be explained by the inherent sex inequality in the patient population, as the majority of the patients in the study was patients with coronary artery disease. Besides, It is reported that in heart failure treatment, barriers exist for seeking optimal quality care between men and women, with women less frequently receiving advanced treatments[29, 30]. It is also noteworthy that we cannot ignore the influence of sex inequality on the results reported by this study.

Besides, our data showed that patients with PH had worse hemodynamics and a significant worse survival than patients without PH. However, although the adverse effects of PH on the prognosis have been more and more recognized, the management of PH-LHD is still restricted to the treatments of HF, without sufficient evidence on the benefit of PH-targeted drugs in this patient population[26]. Nevertheless, as we reported, a large proportion of patients in our study were not on optimal therapy of HF, evidenced by the low usage of HF medications. The data was similar to China-HF Registry[27],

reporting the usage of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs),β-Blockers and mineralocorticoid receptor antagonists (MRAs) were more common in HFrEF than HFpEF, and less implemented in China compared to the data of HF registries in developed countries, such as ATTEND, ADHERE and EHFS [31–33]. Our data has provided insights into the gaps in clinical practice of the HF management in China, indicating efforts are needed to improve the compliance to recommended guidelines.

Various risk factors, from clinical presentation to parameters obtained from echocardiography or other tests, have been reported to be related to the presence of PH-LHD[4]. Despite several risk stratification strategies has been proposed to help differentiate PH-LHD from pre-capillary PH[22–25], predictors of PH in HF patients still lack demonstrations. In a HFrEF cohort, Miller et al. [21]found that the presence of PH was associated with older age, diuretic use, atrial fibrillation, and lower PAC. Besides, Gerges et al.[9] demonstrated that chronic obstructive pulmonary disease and the tricuspid annular plane systolic excursion to systolic pulmonary artery pressure ratio predicted combined post- and pre-capillary PH (Cpc-PH) in HFrEF, while in HFpEF, younger age, valvular heart disease, and the tricuspid annular plane systolic excursion to systolic pulmonary artery pressure ratio predicted Cpc-PH. In our cohort, BMI and LVEDD were found to be predictors of PH in HFrEF, and the female gender, LVEDD and RVAPD were associated with the presence of PH in HFpEF. As we discussed above, though as the gold standard to diagnose PH, RHC remains less utilized in HF. Consequently, demographics, clinical presentation and results of noninvasive tests, especially echocardiography, are still more helpful references to identify PH in HF population. As none of risk factors can consistently predict PH in different study cohorts, a comprehensive evaluation is needed for every patient with their relevant data fully considered. Meanwhile, further studies are still required to investigate how different HF etiologies, including hypertensive heart disease, ischemic heart disease or cardiomyopathy would affect the hemodynamic phenotypes of PH-LHD due to HF.

Till now, none of the hemodynamic parameters are free from limitations. The most debated point of DPG is its conflicted prognostic value[9]. Therefore, PVR, considered as a better reflection of pre-capillary component, was then reintroduced to define Cpc-PH incorporating with DPG[8]. However, reported by Gerges M et al.[9], PVR alone was a predictor of outcome only in HFrEF but not in HFpEF, while DPG retained significant in both etiologies. In our cohort, we found increasing DPG was a significant predictor for mortality, and patients whose DPG $\geq$ 7 mmHg had a worse survival both in HFrEF and in HFpEF, which can provide extra prognostic information about the hemodynamics of PH-LHD in a prospective multicenter study setting. The optimal combination of variables is still under debate, and it could be better to use those variables in combination rather than focus on an isolated value[26].

Our study has several limitations. First, the proportion of patients who met primary endpoint was relatively small, which might had a potential effect on the differentiation power regarding the comparisons of survival curves, as well as the Cox regression analyses. In addition, data about right cardiac function, or right ventricular to pulmonary vascular coupling were not available in the present study. Besides, as only baseline characteristics were included in the analysis, with the absence of follow-

up data, further studies are needed to explore the the effect of changing hemodynamics and medical interventions.

Conclusion

In conclusion, our study shows that though the prevalence, characteristics and prognosis of PH differ between HFrEF and HFpEF, PH-LHD is a common complication in HF and has an adverse effect on the prognosis.

Abbreviations

ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; AUC: area under the curve; CO: Cardiac output; CI: confidence interval; dPAP: diastolic pulmonary arterial pressure; DPG: diastolic pressure gradient; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio; LVEDD: left ventricular end diastolic diameter; LVEDP: left ventricular end diastolic pressure; LVEF: left ventricular ejection fraction; MRAs: mineralocorticoid receptor antagonists; PAC: Pulmonary arterial compliance; PAH: pulmonary arterial hypertension; PASP: pulmonary arterial systolic pressure; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; PH-LHD: Pulmonary hypertension due to left heart disease; PVR: pulmonary vascular pressure; RAP: right atrial pressure; RHC: right heart catheterization; ROC: receiver operating characteristic; RVAPD: right ventricular anteroposterior diameter; sPAP: systolic pulmonary arterial pressure; TPG: transpulmonary pressure gradient.

Declarations

Ethics approval and consent to participate

This study complied with the Declaration of Helsinki. The study protocol was approved by the ethics committee of Fuwai hospital (Approval No.2012-401).

Consent for publication

Written informed consent was obtained from all patients in this study.

Availability of data and materials

All data generated or analyzed during this study are included in this manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Contributing to the conception and design: Ruilin Quan, Changming Xiong and Jianguo He. Patient enrollment and data collection: Ruilin Quan, Shian Huang, Jieyan Shen, Weifeng Wu, Fangming Tang, Xiulong Zhu, Weiqing Su, Jingzhi Sun, Zaixin Yu, Lemin Wang, Xianyang Zhu. Data analysis, interpretation: Ruilin Quan and Changming Xiong. Drafting the article: Ruilin Quan. Revising the article: Jianguo He. Approving the final version to be published: All authors.

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None

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Figures

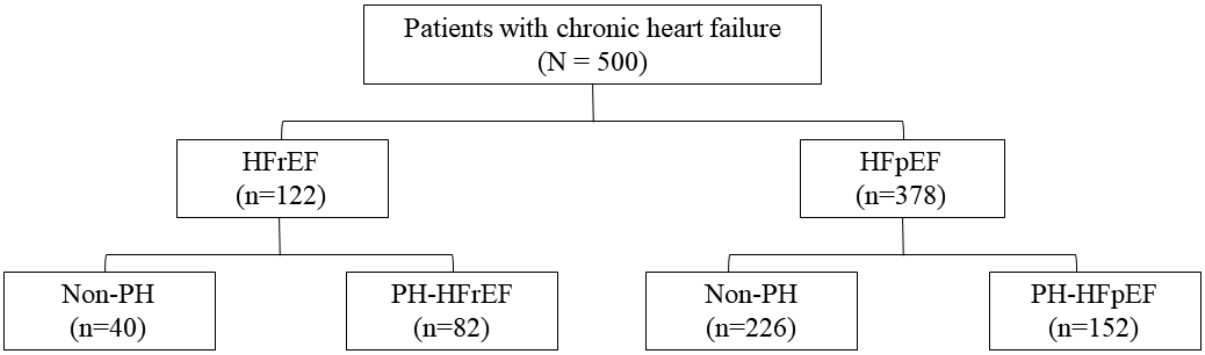

Figure 1

Patient dispositions. HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction. PH: pulmonary hypertension;

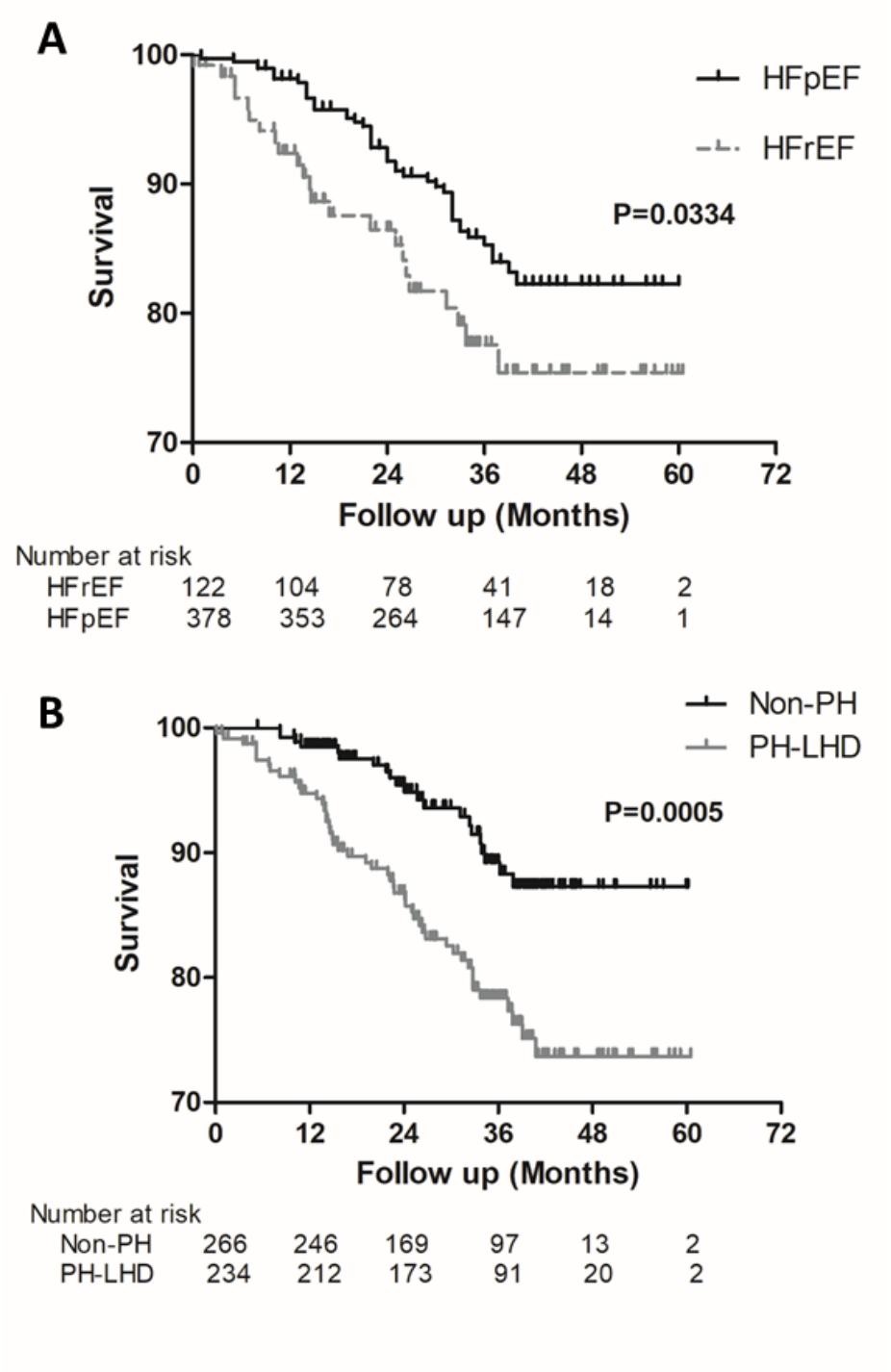

Figure 2

Comparison of Kaplan–Meier survival curves according to etiology (A, HFrEF versus HFpEF) and the presence of PH (B, Non-PH versus PH-LHD). HFrEF: heart failure with reduced ejection fraction; HRpEF: heart failure with preserved ejection fraction. Non-PH: patients without pulmonary hypertension; PH-LHD: pulmonary hypertension due to left heart disease;

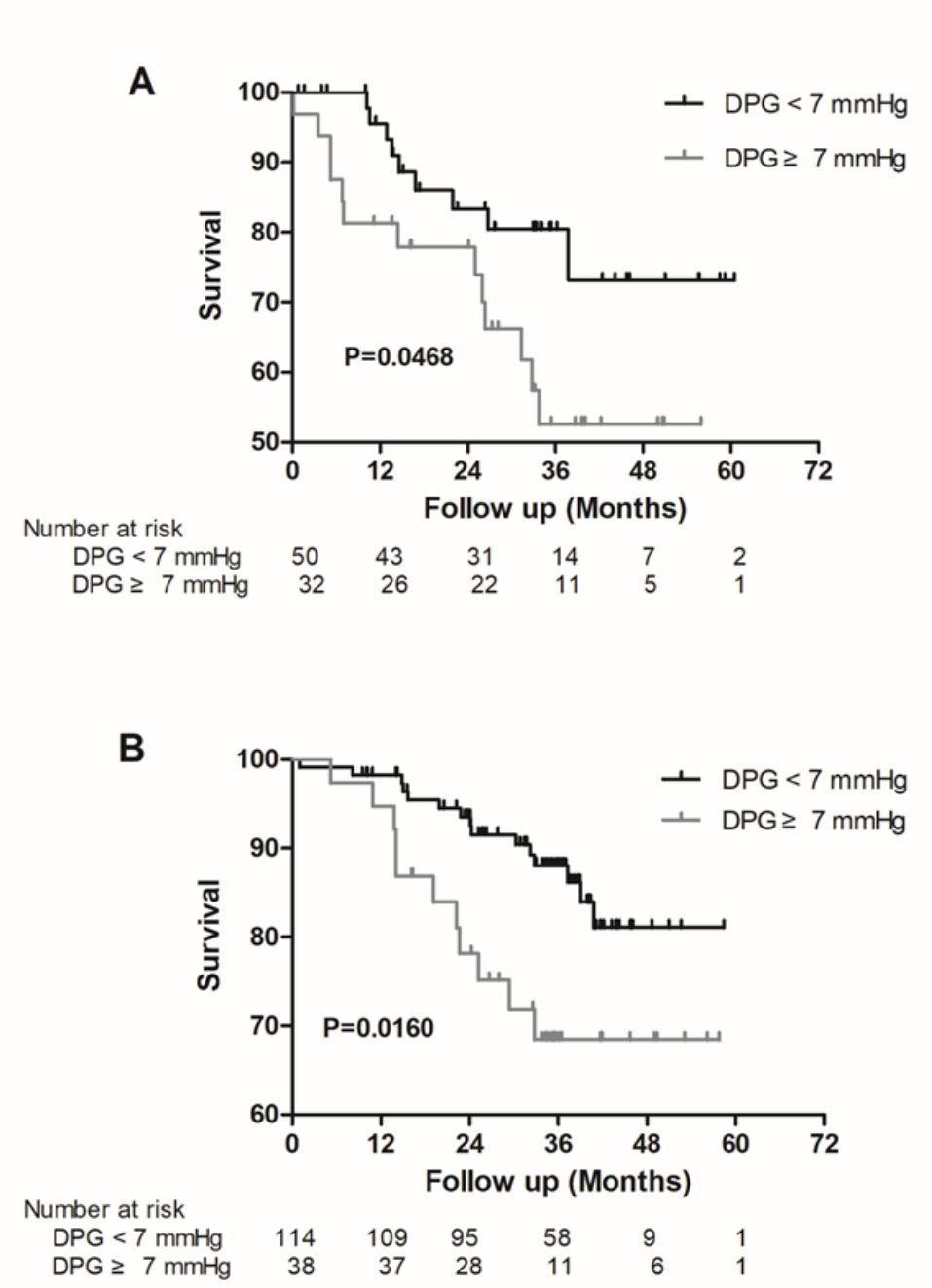

Figure 3

Comparison of Kaplan–Meier survival curves according to DPG (< 7 or ≥ 7 mmHg) in HFrEF (A) and in HFpEF (B). DPG: diastolic pressure gradient; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction.