Prevalence, risk factors, and survival associated with pulmonary hypertension and heart failure among patients with underlying coronary artery disease: a national prospective, multicenter registry study in China

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Abstract

Background: Coronary artery disease (CAD) is the commonest cause of heart failure (HF), whereas pulmonary hypertension (PH) has not been established or reported in this patient population. Therefore, we assessed the prevalence, risk factors, and survival in CAD-associated HF (CAD-HF) complicated with PH.

Methods: Symptomatic CAD-HF patients were continuously enrolled in this prospective, multicenter registry study. Echocardiography, coronary arteriography, left and right heart catheterization (RHC), and other baseline clinical data were recorded. Patients were followed up and their survival was recorded.

Results: One hundred and eighty-two CAD-HF patients were enrolled, including 142 with HF with a preserved ejection fraction (heart failure with preserved ejection fraction [HFpEF]; left ventricular ejection fraction [LVEF] ≥50%) and 40 with a reduced ejection fraction (heart failure with reduced ejection fraction [HFrEF]; LVEF < 50%). PH was diagnosed with RHC in 77.5% of patients. Patients with PH showed worse hemodynamic parameters and higher mortality. HFrEF-PH patients had worse survival than HFpEF-PH patients. CAD-HF patients with an enlarged left ventricular end-diastolic diameter and reduced hemoglobin were at higher risk of PH. Nitrate treatment reduced the risk of PH. Elevated creatinine and mean pulmonary arterial pressure (mPAP), diastolic pressure gradient (DPG) ≥7 mmHg, and previous myocardial infarction (MI) entailed a higher risk of mortality in CAD-HF patients with PH.

Conclusions: PH is common in CAD-HF and worsens the hemodynamics and survival in these patients. Left ventricle enlargement and anemia increase the risk of PH in CAD-HF. Patients may benefit from nitrate medications. Renal impairment, elevated mPAP, DPG ≥7 mmHg, and previous MI are strong predictors of mortality in CAD-HF-PH patients.

Trial Registration: ClinicalTrials.gov, NCT02164526.

Keywords: Coronary artery disease; Heart failure; Pulmonary hypertension; Registry study

Introduction

Pulmonary hypertension (PH) arising from left heart disease (LHD), classified as group 2 PH, is believed to be

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the commonest type of PH,[1] accounting for 65% to 80% of cases.[2] PH is common in heart failure (HF) with a preserved ejection fraction (HFpEF) or a reduced ejection fraction (HFrEF) resulting from LHD,[3,4] with an overall prevalence of 23% to 73% when diagnosed with right heart catheterization (RHC). The prevalence of PH in HFrEF was 47% to 73% when assessed with RHC.[5,6] A study of HFpEF evaluated with RHC reported that the prevalence of PH was 52.5%.[7] An increase in the left ventricle (LV) filling pressure in HF causes elevated pulmonary venous pressure, leading to post-capillary PH. Continuously elevated pulmonary arterial pressure (PAP) may result in structural and functional abnormalities of the pulmonary vascular bed. HF patients with PH present with more severe symptoms, abnormal hemodynamics, and higher mortality.[2,4,8]

Although recent studies had reported some about HF-PH, the results may be weak in specificity. HF results from different etiology may have different progression of HF, which may further influence the development of PH. Coronary artery disease (CAD), the main cause of HF, is common in both HFpEF and HFrEF patients.[9] In nearly two-thirds of patients, HF is attributable to underlying CAD.[10] However, the prevalence of PH in CAD-associated HF (CAD-HF) is unknown, and the clinical characteristics, risk factors, prognosis, and prognostic predictors of CAD-HF have not yet been reported. Therefore, in this prospective multicenter registry study, we comprehensively assessed the prevalence, clinical characteristics, and survival of PH in CAD-HF patients, and examined the potential risk factors for and predictors of mortality from PH in CAD-HF patients with either HFpEF or HFrEF.

Methods

Ethical approval

This study complied with the *Declaration of Helsinki* and was approved by the Institutional Review Board of Fuwai Hospital (Beijing, China) (No. 2012-401). All patients enrolled provided written informed consent.

Patients and enrolment

Inpatients with symptomatic CAD-HF who complied with the inclusion and exclusion criteria were continuously enrolled in the study between October 2012 and November 2016. These patients were studied as part of a prospective, multicenter registry study of LHD-associated PH (LHD-PH) in China. The inclusion criteria were (1) diagnosis of CAD, with coronary stenosis ≥50% on coronary arteriography; (2) symptomatic HF (New York Heart Association functional classification [NYHA-FC] II-IV) with left ventricular end-diastolic pressure (LVEDP) ≥16 mmHg on left heart catheterization or pulmonary capillary wedge pressure (PCWP) ≥15 mmHg on RHC; (3) echocardiography with an assessment of the left ventricular ejection fraction (LVEF); (4) invasive hemodynamic test conducted within the month before enrolment; and (5) informed consent. The exclusion criteria were valvular disease; other myocardiopathy (dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy); congenital or acquired left heart inflow/outflow tract obstruction; congenital or acquired pulmonary vein stenosis; pericardial disease; non-cardiac disease that limited the life expectancy (eg, malignancy); chronic lung disease; or PH with another etiology.

Definitions and diagnosis

Symptomatic HF was diagnosed according to the 2012 European Society of Cardiology guideline on HF.[11] HFpEF or HFrEF was defined as LVEF ≥50% or <50% on echocardiography, respectively. PH was diagnosed with RHC as a resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg.[1] Diastolic pressure gradient (DPG) ≥7 was considered an indicator of combined post-capillary and pre-capillary PH according to the guideline for PH.

Data collection

Patients enrolled all had two-dimensional echocardiography, left heart catheterization, and RHC (details of the tests were referred to the Supplementary Materials, http://links.lww.com/CM9/B16). The baseline data were collected from the medical record system by a researcher and checked by another staff, all of them were with a medical background. The baseline data included basic demographic data (gender, age, and others), signs, the NYHA-FC, diagnostic information, accompanying diseases, treatment, laboratory data, echocardiography, coronary arteriography, and hemodynamic parameters.

Follow-up and endpoint

The enrolled patients were followed-up every 6 months by telephone, at an out-patient clinic, or upon hospital admission. Patients who could not be reached through neither telephone, clinic, hospital system, nor other possible ways for more than three times and last for >6 months were identified as lost to follow-up. The endpoint was all-cause mortality. Survival information on the patients and the follow-up times were censored to the last contact date.

Statistical analysis

The patients were classified into the HFpEF or HFrEF group and into the PH or non-PH group. Continuous data are presented as means ± standard deviations for normally distributed variables and as medians with interquartile ranges for variables with abnormal distributions. Categorical data are presented as numbers and percentages. Comparisons between groups were made with a *t*-test or the Mann-Whitney test for continuous variables, and with the χ^2 statistic or Fisher's exact test for categorical variables. Univariate and multivariate logistic regression analyses were used to identify potential risk factors for the occurrence of PH in CAD-HF patients. Kaplan-Meier survival analyses with a log-rank test were used to evaluate the cumulative occurrence of death in the groups. Univariate and multivariate Cox proportional hazards regression

analyses were used to identify independent predictors of mortality in CAD-HF patients with PH. Candidate variables with a P value <0.2 on univariate analyses were included in multivariate Cox proportional hazards models. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 23.0 (IBM Corp, Armonk, NY, USA). Random effect models were used to verify the risk factors for PH in CAD-HF and predictors of mortality in CAD-HF-PH as sensitivity analyses.

Results

Baseline demographic, clinical, and hemodynamic characteristics of CAD-HF patients with PH

In total, 182 symptomatic CAD-HF patients were enrolled. Among them, 142 (78.0%) patients presented with HFpEF and 40 (22.0%) with HFrEF. The enrolment and research procedures are described in the supplementary materials [Supplementary Figure 1, http://links.lww.com/CM9/B16].

Among all the CAD-HF patients enrolled, 141 patients had PH, accounting for 77.5% of the overall cohort. A total of 108 (76.1%) patients in the HFpEF group and 33 (82.5%) patients in the HFrEF group presented with PH. The proportions of patients with PH in the two groups were similar ($P = 0.389$).

The CAD-HF patients with PH showed lower diastolic blood pressure, red blood cell (RBC) counts, and hemoglobin levels than the non-PH patients. Echocardiography indicated a significantly larger left ventricular end-diastolic diameter (LVEDD) in PH patients than in non-PH patients. The hemodynamic parameters were worse in PH patients than in non-PH patients, with significantly higher mean right atrial pressure (mRAP), systolic pulmonary artery pressure, mPAP, right ventricle systolic pressure, right ventricular end-diastolic pressure, and DPG (all, $P < 0.001$). Medicinal treatment with nitrates was less common in PH patients. The NYHA-FC, the kinds of CAD, and extension of CAD (measured with coronary arteriography) were similar in the PH and non-PH patients. The ratio of patients who received percutaneous coronary intervention (PCI) treatment at enrolment showed no difference between PH and non-PH patients. No patients received coronary artery bypass grafting [Supplementary Table 1, http://links.lww.com/CM9/B16].

Comparisons of PH and non-PH patients in the HFpEF and HFrEF groups

Among the HFpEF patients, those with PH also showed lower RBC and hemoglobin levels, larger LVEDD on echocardiography, and a greater proportion of nitrate use than non-PH patients. Among the HFrEF patients, the PH and non-PH patients did not differ greatly, except in their hemodynamic parameters. Both HFpEF and HFrEF patients with PH presented worse hemodynamics, with elevated mRAP, right ventricle pressure, and pulmonary circulation pressure [Table 1].

Comparison of the HFpEF-PH and HFrEF-PH patients showed that sodium was lower in the HFrEF-PH patients. More HFrEF-PH patients than HFpEF-PH patients had a history of previous myocardial infarction (MI). Echocardiography indicated more significant enlargement of the left atrial diameter, LVEDD, and right ventricular diameter in HFrEF-PH patients than in HFpEF-PH patients, whereas the hemodynamic parameters did not differ greatly between the groups, except for the higher pulmonary circulation pressure in HFrEF-PH patients [Table 1].

Risk factors for PH in patients with CAD-HF

A univariate analysis of the risk factors for PH in CAD-HF patients showed significant associations with lower hemoglobin levels, larger LVEDD, and less use of nitrate. Age, body mass index, LVEF, the combination of hypertension and diabetes, and diuretic use were identified as possible risk factors of PH in HF. After multivariate adjustment, hemoglobin, LVEDD, and nitrate use remained independent predictors of PH. Each 10 mm increase in LVEDD was associated with a 2.77-fold increased risk of PH in CAD-HF (95% confidence interval [CI]: 1.431–5.374, $P = 0.003$). Reduced hemoglobin was an independent risk factor for PH (odds ratio [OR] = 0.965, 95% CI: 0.939–0.992, $P = 0.012$), and treatment with nitrate was a significant protective factor for CAD-HF, clearly reducing the risk of PH (OR = 0.246, 95% CI: 0.095–0.637, $P = 0.004$) [Table 2]. Other factors associated with CAD, including previous MI, previous PCI, coronary artery multiple-vessel lesion, a diagnosis of MI and PCI at enrolment were not significantly associated with the risk of PH in CAD-HF in univariate and adjusted multivariate analysis. Results about the risk factors for PH development in CAD-HF remained stable in the random effect model, except for factor of treatment with nitrate which showed marginally non-significant ($P = 0.075$; Supplementary Table 2, http://links.lww.com/CM9/B16).

Analysis of the risk factors for PH in the HFpEF group confirmed findings similar to those in the total group of CAD-HF patients. Hemoglobin, LVEDD, and the use of nitrate remained predictive of PH. No statistically significant factors were associated with PH development in the HFrEF group, which we attributed to the limited sample size in this group [Supplementary Table 3, http://links.lww.com/CM9/B16].

Survival prognosis in CAD-HF patients with PH

After a mean follow-up time of 31.2 ± 11.3 months, 35 patients had died, including 23 HFpEF patients (22 PH patients and one non-PH patient) and 12 HFrEF patients (12 PH patients and zero non-PH patient). Nine patients were lost to follow-up. The overall loss rate throughout follow-up was 4.9%.

A Kaplan-Meier survival analysis showed that the overall survival rate was distinctly lower in the PH patients than in the non-PH patients (log-rank $P = 0.009$) [Figure 1A]. The HFpEF-PH patients showed worse survival than the non-PH patients (log-rank $P = 0.027$). The HFrEF-PH patients had a significantly higher mortality rate than

Table 1: Comparisons about the baseline demographic, clinical, and hemodynamic characteristics between PH and non-PH patients in HFpEF and HFrEF subgroup.

Variables	HFpEF			HFrEF			
	PH ($n = 108$)	Non-PH ($n = 34$)	*P* value	PH ($n = 33$)	Non-PH ($n = 7$)	*P* value	*P* value*
Age (years)	66.6 ± 12.0	63.4 ± 12.4	0.175	64.8 ± 11.6	64.0 ± 13.7	0.880	0.433
Females	34 (31.5)	6 (17.6)	0.118	5 (15.2)	1 (14.3)	NA	0.066
BMI (kg/m^2)	22.6 ± 2.6	22.4 ± 2.4	0.746	23.6 ± 2.5	22.4 ± 3.0	0.288	0.058
SBP (mmHg)	133.0 ± 22.4	138.2 ± 27.4	0.269	135.7 ± 21.0	137.3 ± 20.2	0.859	0.536
DBP (mmHg)	74.8 ± 11.2	79.7 ± 17.9	0.137	77.6 ± 11.0	83.4 ± 7.3	0.189	0.208
NYHA-FC			0.249			0.146	0.054
II	73 (67.6)	28 (82.4)		15 (45.5)	3 (42.9)		
III	30 (27.8)	5 (14.7)		14 (42.4)	1 (14.3)		
IV	5 (4.6)	1 (2.9)		4 (12.1)	3 (42.9)		
Kinds of CAD			0.240			0.418	0.846
Stable CAD	27 (25.0)	9 (26.5)		9 (27.3)	1 (14.3)		
STEMI	27 (25.0)	14 (41.2)		11 (33.3)	1 (14.3)		
Non-STEMI	17 (15.7)	4 (11.8)		3 (9.1)	2 (28.6)		
Unstable angina	37 (34.3)	7 (20.6)		10 (30.3)	3 (42.9)		
Prior MI	16 (14.8)	8 (23.5)	0.237	10 (30.3)	2 (28.6)	NA	0.045
Prior PCI	12 (11.1)	3 (8.8)	0.766	2 (6.1)	1 (14.3)	NA	0.520
Follow-up time (months)	32.8 ± 9.8	30.3 ± 12.3	0.283	27.3 ± 13.9	28.7 ± 11.1	0.809	0.041
Laboratory tests							
RBC ($\times 10^{12}$/L)	4.4 ± 0.7	4.7 ± 0.7	0.038	4.7 ± 0.5	5.1 ± 0.7	0.092	0.033
RDW (%)	13.9 ± 3.6	13.7 ± 1.3	0.746	13.9 ± 1.8	14.7 ± 1.2	0.316	0.958
Hemoglobin (g/L)	130.2 ± 18.2	138.2 ± 11.8	0.018	135.2 ± 16.5	139.4 ± 12.5	0.534	0.164
PLT ($\times 10^9$/L)	226.9 ± 72.4	225.8 ± 59.5	0.938	230.1 ± 65.7	240.8 ± 75.9	0.704	0.821
PDW (%)	15.6 ± 2.1	16.8 ± 6.3	0.086	16.1 ± 2.1	14.4 ± 3.6	0.309	0.239
ALT (IU/L) (Q1, Q3)	22.0 (15.5, 34.3)	27.0 (15.8, 45.3)	0.371	23.0 (15.5, 38.1)	31.0 (14.0, 48.3)	0.972	0.256
AST (IU/L) (Q1, Q3)	22.0 (15.0, 38.4)	26.1 (16.0, 39.2)	0.362	25.0 (17.3, 38.9)	34.0 (27.0, 54.0)	0.084	0.513
Albumin (g/L)	39.1 ± 5.4	41.0 ± 5.3	0.077	38.9 ± 4.4	36.9 ± 4.4	0.294	0.823
Sodium (mmol/L)	140.5 ± 3.7	140.7 ± 2.8	0.769	137.8 ± 4.8	139.0 ± 2.6	0.533	0.001
Creatinine (μmol/L)	85.2 ± 39.2	85.7 ± 23.6	0.944	96.9 ± 57.5	95.5 ± 38.5	0.949	0.182
BUN (mmol/L)	5.7 ± 2.6	5.7 ± 2.2	NA	5.5 ± 2.0	6.4 ± 3.2	0.466	0.657
Uric acid (mmol/L)	362.7 ± 117.1	372.5 ± 98.0	0.660	408.9 ± 130.1	438.3 ± 110.3	0.582	0.056
Triglyceride (mmol/L)	1.5 (1.1, 2.4)	1.5 (1.1, 2.0)	0.973	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	0.845	0.707
Cholesterol (mmol/L)	4.5 (3.6, 5.7)	4.8 (4.0, 5.6)	0.487	4.5 (3.5, 5.1)	5.1 (3.3, 7.6)	0.160	0.613
Glucose (mmol/L)	6.1 ± 3.0	6.1 ± 2.3	0.919	6.4 ± 2.6	5.6 ± 0.9	0.213	0.611
Echocardiogram							
LAD (mm)	33.9 ± 3.7	33.2 ± 5.1	0.369	38.1 ± 6.8	42.3 ± 6.0	0.164	0.001
LVEDD (mm)	47.5 ± 4.8	44.7 ± 5.1	0.004	58.1 ± 10.0	57.3 ± 9.9	0.860	<0.001
LVEF (%)	58.6 ± 4.9	57.3 ± 3.7	0.161	42.4 ± 6.4	39.0 ± 8.3	0.266	<0.001
RVD (mm)	18.9 ± 2.4	18.8 ± 3.5	0.790	20.8 ± 4.6	23.0 ± 6.7	0.331	0.027
Hemodynamic							
LVEDP (mmHg)	17.9 ± 3.8	20.0 ± 6.0	0.101	18.0 ± 2.5	19.5 ± 2.1	0.246	0.440
RAP (mmHg)	15.2 ± 3.3	11.7 ± 3.0	<0.001	14.0 ± 4.1	7.7 ± 6.2	0.002	0.108
sPAP (mmHg)	44.9 ± 8.4	31.4 ± 9.6	<0.001	50.0 ± 12.1	29.0 ± 5.7	<0.001	0.029
dPAP (mmHg)	22.8 ± 4.5	16.1 ± 3.9	<0.001	23.2 ± 7.1	14.3 ± 2.8	0.003	0.775
mPAP (mmHg)	30.3 ± 5.2	20.3 ± 3.5	<0.001	33.6 ± 7.1	19.6 ± 3.1	<0.001	0.018
RVSP (mmHg)	45.0 ± 9.3	30.7 ± 7.7	<0.001	49.2 ± 14.7	26.0 ± 7.8	<0.001	0.128
RVEDP (mmHg)	14.5 ± 4.5	10.4 ± 3.8	<0.001	14.4 ± 5.8	7.7 ± 6.6	0.011	0.910
PCWP (mmHg)	18.6 ± 4.3	20.5 ± 5.8	0.075	18.3 ± 2.7	18.0 ± 2.4	0.784	0.744
DPG (mmHg)	7.0 (4.0, 11.0)	–1.0 (–3.5, 2.0)	<0.001	5.0 (2.0, 9.0)	– 1.0 (–8.0, – 1.0)	0.003	0.665
CAD extension			0.975			0.503	0.806
Single-vessel	39 (36.1)	13 (38.2)		14 (42.4)	2 (28.6)		
Two-vessel	33 (30.6)	10 (29.4)		9 (27.3)	1 (14.3)		
Multiple-vessel	36 (33.3)	11 (32.4)		10 (30.3)	4 (57.1)		
Comorbidities							
Hypertension	54 (50.0)	19 (55.9)	0.550	16 (48.5)	3 (42.9)	NA	0.879
Diabetes	27 (25.0)	13 (38.2)	0.135	11 (33.3)	2 (28.6)	NA	0.345

(*continued*)

Table 1
(continued).

Variables	HFpEF			HFrEF			
	PH ($n=108$)	Non-PH ($n=34$)	*P* value	PH ($n=33$)	Non-PH ($n=7$)	*P* value	*P* value*
Hyperlipidemia	34 (31.5)	9 (26.5)	0.579	10 (30.3)	2 (28.6)	NA	0.898
Atrial fibrillation	4 (3.7)	0 (0.0)	0.572	3 (9.1)	1 (14.3)	NA	0.354
Medication							
ACEI	41 (38.0)	17 (50.0)	0.213	18 (54.5)	5 (71.4)	0.677	0.091
ARB	32 (30.2)	7 (21.2)	0.316	5 (16.1)	1 (14.3)	NA	0.121
Aldosterone inhibitor	54 (50.0)	12 (35.3)	0.134	26 (78.8)	6 (85.7)	NA	0.003
β-blocker	74 (68.5)	26 (76.5)	0.376	26 (78.8)	7 (100.0)	0.317	0.256
CCB	20 (18.5)	6 (17.6)	0.909	6 (18.2)	1 (14.3)	NA	0.965
Diuretic	37 (34.3)	10 (29.4)	0.600	25 (75.8)	6 (85.7)	0.672	<0.001
Nitrate	15 (13.9)	12 (35.3)	0.006	7 (21.2)	2 (28.6)	NA	0.310
Interventional therapy							
PCI at enrolment	77 (71.3)	20 (58.8)	0.173	18 (54.5)	2 (28.6)	0.407	0.072

Data are presented as *n* (%), mean ± standard deviation or median (interquartile range). NA: Data not available as for the limited sample size. * Comparison between HFpEF-PH and HFrEF-PH group. ACEI: Angiotensin-converting enzyme inhibitors; ALT: Alanine aminotransferase; ARB: Angiotensin receptor blocker; AST: Aspartate transaminase; BMI: Body mass index; BUN: Blood urea nitrogen; CAD: Coronary artery disease; CCB: Calcium channel blocker; DBP: Diastolic blood pressure; dPAP: Dystolic pulmonary artery pressure; DPG: Diastolic pressure gradient; HFpEF: Heart failure with a preserved ejection fraction; HFrEF: Heart failure with a reduced ejection fraction; LAD: Left atrial diameter; LVEDD: Left ventricular end-diastolic diameter; LVEDP: Left ventricular end-diastolic pressure; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; mPAP: Mean pulmonary arterial pressure; NYHA-FC: New York Heart Association functional classification; PCI: Percutaneous transluminal coronary intervention; PCWP: Pulmonary capillary wedge pressure; PDW: Platelet volume distribution width; PH: Pulmonary hypertension; PLT: Platelet count; RAP: Right atrial pressure; RBC: Red blood cell; RDW: Red blood cell distribution width; RVD: Right ventricular diameter; RVEDP: Right ventricular end-diastolic pressure; RVSP: Right ventricle systolic pressure; SBP: Systolic blood pressure; sPAP: Systolic pulmonary artery pressure; STEMI: ST-segment elevation myocardial infarction.

either the HFpEF-PH or non-PH patients (log-rank $P < 0.001$ and $P = 0.027$, respectively) [Figure 1B]. The 1-year, 2-year, and 3-year survival rates of all the CAD-HF patients with PH were 93.6%, 86.2%, and 75.9%, respectively. The 1-year, 2-year, and 3-year survival rates of the CAD-HFpEF patients with PH were 97.2%, 89.6%, and 79.5%, respectively. The 1-year, 2-year, and 3-year survival rates of the CAD-HFrEF patients with PH were 81.8%, 75.4%, and 64.4%, respectively.

Predictors of mortality in patients with CAD-HF with PH

A univariate Cox proportional hazards regression analysis showed that older age, NYHA-FC III–IV, increased creatinine, elevated mPAP, DPG ≥7, and combined hypertension and previous MI, were significant predictors of mortality in CAD-HF patients with PH. DPG ≥7 and mPAP were included in two separate models in the multivariate analysis to test for the presence of multicollinearity. After adjustment in model 1, a 50 μmol/L in increased creatinine (hazard ratio [HR] = 1.937, 95% CI: 1.377–2.725, $P < 0.001$), DPG ≥7mmHg (HR = 2.198, 95% CI: 1.038–4.653, $P = 0.040$), and previous MI (HR = 3.366, 95% CI: 1.525–7.430, $P = 0.003$) remained independent predictors of mortality. After adjustment in model 2, an increase in mPAP of 5 mmHg was associated with a 1.426-fold increased risk of mortality in patients with CAD-HF with PH (95% CI: 1.095–1.857, $P = 0.008$), and elevated creatinine and previous MI remained strong predictive factors for mortality [Table 3].

Previous PCI, coronary artery multiple-vessel lesion, a diagnosis of MI, and PCI at enrolment were not predictive of mortality in CAD-HF patients with PH in the univariate and multivariate analyses. Predictors of mortality for CAD-HF with PH in Cox proportional hazards regression analysis also remained significant in the random effect models [Supplementary Table 4, http://links.lww.com/CM9/B16].

Elevated creatinine, increased mPAP, and previous MI were confirmed to be strong predictors of mortality in a subgroup analysis of HFpEF-PH with multivariate Cox proportional hazards regression. The HFpEF-PH patients with previous MI had a 5-fold greater risk of death than those without previous MI. Age remained predictive of mortality in this group of patients. No significant valuable predictors of mortality were identified in the HFrEF-PH patients, which may be attributable to the limited sample size [Supplementary Table 5, http://links.lww.com/CM9/B16].

Discussion

As far as we know, this is a rare report of a prospective registry study of PH resulting from CAD-HF. In this study, we investigated the prevalence, clinical characteristics, risk factors, survival, and predictors of mortality in patients with PH arising from CAD-HF. The diagnoses of PH, CAD, and HF in all the enrolled patients were confirmed with the "gold standard" hemodynamic technique, with the appropriate invasive test, which ensures the credibility of our results.

The reported prevalence of PH in LHD varies with the patient population studied, the definition of PH used, and the progression of HF.[8] When PH was diagnosed with RHC, it showed a prevalence of 52.5% in HFpEF

Table 2: Risk factors for PH development in CAD-HF patients in univariate and multivariate logistic regression analysis.

	Univariate		Multivariate	
Variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age	1.019 (0.990–1.048)	0.208	1.033 (0.996–1.073)	0.082
BMI	1.064 (0.924–1.224)	0.388	1.168 (0.981 –1.391)	0.080
Hemoglobin	0.974 (0.953–0.996)	0.021	0.965 (0.939–0.992)	0.012
LVEF	1.003 (0.963–1.045)	0.882	1.059 (0.998–1.124)	0.058
LVEDD per + 10	2.341 (1.142–4.798)	0.020	2.773 (1.431–5.374)	0.003
Hypertension	0.851 (0.424–1.709)	0.651	0.576 (0.249–1.332)	0.197
Diabetes	0.639 (0.306–1.335)	0.234	0.831 (0.360–1.920)	0.664
Diuretic	1.226 (0.603–2.495)	0.573	1.120 (0.482–2.600)	0.793
Nitrate	0.357 (0.162–0.785)	0.010	0.246 (0.095–0.637)	0.004

BMI: Body mass index; CAD: Coronary artery disease; CI: Confidence interval; HF: Heart failure; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; OR: Odds ratio; PH: Pulmonary hypertension.

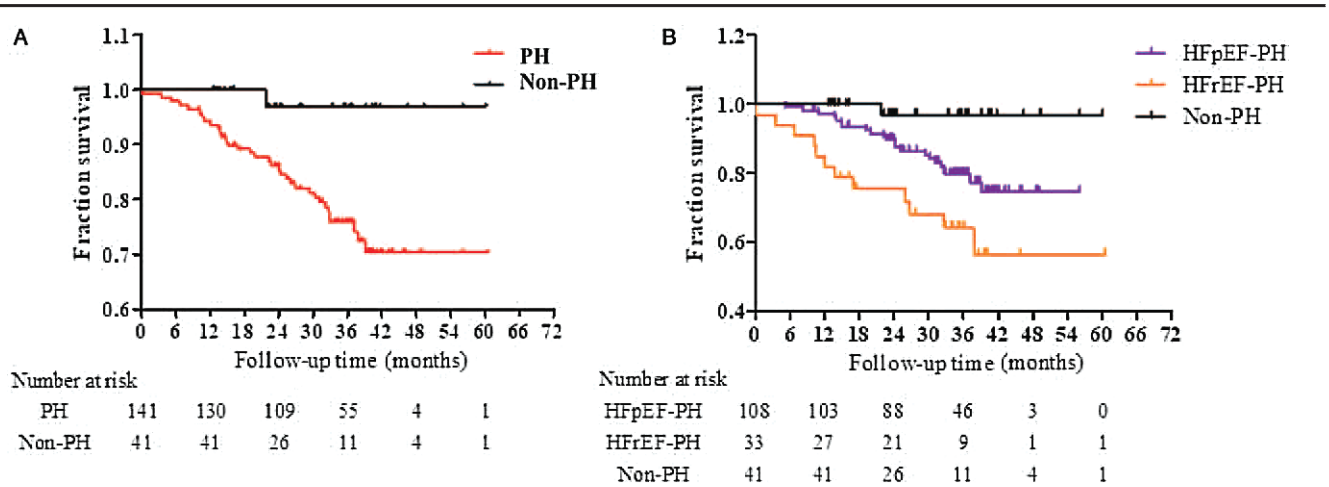

Figure 1: Kaplan–Meier survival analyses for HF-PH and non-PH patients with underlying CAD. (A) Overall survival for CAD-HF-PH and non-PH group (log-rank P = 0.009). (B) Survival for HFpEF-PH and HFrEF-PH subgroup (HFpEF-PH *vs.* non-PH, log-rank $P = 0.027$; HFrEF-PH *vs.* non-PH, log-rank $P < 0.001$; HFpEF-PH *vs.* HFrEF-PH, log-rank $P = 0.027$). CAD: Coronary artery disease; HF: Heart failure; HFpEF: HF with a preserved ejection fraction; HFrEF: HF with a reduced ejection fraction; PH: Pulmonary hypertension.

Table 3: Predictors of mortality for CAD-HF patients with PH in Cox proportional hazards regression analysis.

	Univariate		Multivariate (model 1)		Multivariate (model 2)	
Variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age	1.046 (1.012–1.080)	0.007	1.026 (0.991–1.061)	0.148	1.035 (0.998–1.073)	0.062
NYHA-FC III-IV	2.083 (1.060–4.091)	0.033	1.394 (0.672–2.892)	0.373	1.141 (0.526–2.475)	0.738
Creatinine per + 50	2.349 (1.712–3.224)	<0.001	1.937 (1.377–2.725)	<0.001	1.866 (1.320–2.638)	<0.001
LVEF	0.967 (0.933–1.002)	0.060	0.989 (0.949–1.031)	0.607	0.991 (0.951–1.033)	0.682
DPG ≥ 7	3.216 (1.378–7.508)	0.007	2.198 (1.038–4.653)	0.040	-	-
mPAP per + 5	1.557 (1.241–1.953)	<0.001	-	-	1.426 (1.095–1.857)	0.008
Hypertension	2.173 (1.059–4.460)	0.034	1.498 (0.706–3.180)	0.293	1.359 (0.634–2.912)	0.431
Prior MI	3.135 (1.542–6.373)	0.002	3.366 (1.525–7.430)	0.003	2.841 (1.329–6.072)	0.007

CAD: Coronary artery disease; CI: Confidence interval; DPG: Diastolic pressure gradient; HF: Heart failure; HR: Hazard ratio; LVEF: Left ventricular ejection fraction; mPAP: Mean pulmonary arterial pressure; PH: Pulmonary hypertension; MI: Myocardial infarction; NYHA-FC: New York Heart Association functional classification.

patients,[7] and a higher prevalence of 73% in HFrEF patients (LVEF ≤40%)[6] in the cohort of patients with multiple-cause HF. PH diagnosed with RHC in our study showed a higher overall proportion of 77.5% in CAD-HF patients, accounting for 76.1% in HFpEF patients and 82.5% in HFrEF patients. The different etiologies, pathogenesis, and severity of HF may affect the proportion of patients with PH, and HF patients with underlying CAD seem most likely to develop PH.

Characteristics and risk factors for PH in CAD-HF patients

In this study, CAD-HF patients with PH presented with more severe pulmonary hemodynamics, consistent with previous studies. The increase in LVEDD was associated with a clearly higher risk of PH in CAD-HF patients. Elevated LVEDD indicated the greater enlargement of the LV in PH patients, which might have resulted from more severe impairment of the LV function and a higher LV filling pressure, and got a higher probability of PH development. Also, we noticed that majority of the patients in this study had acute coronary syndrome (ACS), and multivessel lesion on angiogram. Higher risk CAD patients were supposed to be more likely to have elevated LVEDP or PCWP and meet the inclusion criteria.

The HFrEF-PH patients presented with more obvious structural changes in left atrial, LV, and right ventricular than the HFpEF-PH patients under similar filling pressures in this study. A previous study reported a stiffer pulmonary circulation in HFpEF-PH patients than in HFrEF-PH patients under similar levels of PCWP,[12] which might indicate a disparate evolving remodeling with a pre-capillary component in HFpEF-PH, independent of the initial PCWP. Our study demonstrated the opposite phenomenon, mPAP was higher in the HFrEF-PH patients than in the HFpEF-PH patients, which might be resulted from severer congestion of systemic and pulmonary circulation in CAD-HFrEF patients. The response of pulmonary circulation to elevated left ventricular filling pressure in CAD-HF patients seemed to be more involved with a post-capillary effect, especially in patients with HFrEF.

Hemoglobin was significantly reduced in the HF-PH patients, especially those in the HFpEF group. This may indicate a more common anemic condition in HF patients with PH than those without PH. Anemia as a common complication of HF and reportedly occurs in about one-third of HF patients.[13] Anemia can increase the risk of structural and functional heart abnormalities, including cardiac hypertrophy, such as LV dilatation and hypertrophy.[14] A reduction in hemoglobin of 1 g/dL was associated with a 6% increase in LV hypertrophy,[15] and cardiac hypertrophy can aggravate HF. In the present study, the reduction in hemoglobin was accompanied by a significantly increased risk of PH in CAD-HF patients. We speculate that chronic anemia in HF induced LV dilatation and hypertrophy, which may aggravate cardiac dysfunction and abnormal pulmonary hemodynamics, ultimately promoting the development of PH.

Nitrate has been used clinically as a treatment for CAD for years. Nitrate activates the nitric oxide (NO)-cyclic guanosine-3′-5′-monophosphate signaling pathway within smooth muscle cells, resulting in the dilatation of the systemic and coronary vasculature.[16] The nitrate-nitrite-NO pathway is a potential therapeutic target for HFpEF because it allows the modification of exercise intolerance.[17] In this study, nitrate was shown to be protective against the development of PH in CAD-HF, and in the HFpEF subgroup. It is well-known that the NO signaling pathway plays an important role in PH development. Medication targeting the NO signaling pathway activates it, dilates the remolded pulmonary arterioles, reduces PAP and pulmonary vascular resistance, and ultimately improves the condition and survival of patients with pulmonary arterial hypertension (PAH). We speculate that the potential benefit of nitrate in patients with CAD-HF-PH may be largely attributable to the activation of the NO pathway. Approved PAH therapies are not recommended for patients with LHD-PH because the therapeutic effect is ambiguous, but some patients may benefit from nonspecific vasodilators, such as nitrates.[1] Nitrates may benefit CAD-HF patients, especially HFpEF patients, reducing the occurrence of PH, but more clinical research is required.

Survival and predictors of mortality in CAD-HF patients with PH

Previous studies demonstrated that PH was associated with increased short- andlong-termmortality in both HFpEF and HFrEF.[6,18] Similarly, the overall mortality was significantly higher in CAD-HF patients with PH than in non-PH patients. Agarwal *et al*[19] reported 1-year and 2-year survival rates of 81.1% and 73.8%, respectively, in HF-PH patients, which included patients with different HF etiologies. In this single disease study, CAD-HF-PH patients had higher 1-year and 2-year survival rates of 93.6% and 86.2%, respectively. This indicated that patients with CAD-induced HF-PH may have a better survival prognosis than those with other HF etiologies. Previous studies have reported that HFpEF is associated with a lower risk of death than HFrEF.[20] In this study, HFpEF-PH group had higher survival rates than HFrEF-PH group, while the proportions of ACS and multivessel lesion in these groups were similar as well as the non-PH group. Even though we cannot exclude the possible influence of higher risk profiles and the revascularization process after enrolment on the prognosis in this study as the limited following-up information. The occurrence of PH worsened the prognosis for both the HFpEF and HFrEF patients.

Age is a common risk or predictive factor for PH, reportedly increasing its development and consequent mortality in LHD patients.[6] In this study, age was also associated with increased mortality from HFpEF-PH in CAD patients. Renal dysfunction has also been shown to be a prognostic factor in patients with PH due to LHD.[21] Similarly, in this study, increased creatinine, a marker of renal impairment, was related to a higher risk of mortality in CAD-HF-PH patients.

MI is a frequent cause of HF and is independently associated with a worse outcome after HF.[22,23] In this study, previous MI was associated with a mortality rate

more than 3-fold higher in CAD-HF patients with PH than in non-PH patients, and in the CAD-HFpEF-PH subgroup, the risk was five times higher. The mechanism underlying in this phenomenon may be complex. After acute MI, the loss of myocyte function causes myocardial fibrosis and LV dilatation, resulting in neurohormonal activation and LV remodeling, which lead to the progressive deterioration of the remaining viable myocardium.[24] All these factors may worsen the condition and increase the risk of death.

DPG is considered a reliable indicator with which to differentiate post-capillary PH from combined post-capillary and pre-capillary PH in the new guideline for PH,[1] although the prognostic value of DPG for LHD-PH is controversial. The prognostic value of DPG seemed to vary across the LHD-PH population studied. Yamabe *et al*[21] reported a lower survival rate for LHD-PH patients with DPG ≥7mmHg, and DPG ≥7mmHg was associated with a higher risk of mortality in LHD-PH. Adir *et al*[12] showed that DPG ≥7 mmHg negatively predicted mortality in both HFrEF-PH and HFpEF-PH patients. However, in the study by Tampakakis *et al*,[25] DPG was not significantly associated with mortality in LHD-PH patients who were predominantly diagnosed with dilated cardiomyopathy. In this prospective study, in which we focused on CAD-HF patients, DPG ≥7 mmHg was found to be associated with increased mortality in CAD-HF patients with PH. Because of the limited size of the subgroups, DPG showed no significant prognostic value in the HFpEF-PH and HFrEF-PH patients. Further research with a larger sample is required to verify this finding.

Although some studies identified a negative predictive value of mPAP for mortality in patients with HFpEF-PH,[26] we found that an increase in mPAP was associated with a higher mortality rate in CAD-HF patients with PH. The underlying CAD (eg, CAD type, CAD extension) and PCI treatment seemed to have little effect on PH development and the survival of PH patients with CAD-HF.

Strengths and limitations

To the best of our knowledge, the current study was a rare report focusing solely on CAD-HF patients, instead of regarding all etiologies of HF as a single study group, which could enable the detection of specific characteristics in patients with PH arising from CAD-HF. Besides, the current study was a prospective multicenter report, with a relatively large sample size of patients who underwent both left heart catheterization and RHC to confirm the diagnosis of HF and PH, which could help provide reliable data on the topics. Furthermore, a long-term follow-up period and the relatively tolerable lost rate ensured sufficient analyses for long-term prognosis.

This study had several limitations. First, because of the strict inclusion and exclusion criteria, the sample size in the HFrEF group of patients was relatively small. Further clinical research with a larger sample of CAD-HFrEF patients is required. Second, we collected no following-up information other than the survival status, which might have allowed us to evaluate the prognoses of patients more comprehensively.

Conclusions

In this prospective study, we have provided the insight into the prevalence of, risk factors for, and survival after PH attributable to CAD-HF. We have demonstrated that PH was relatively common in patients with CAD-HF, occurring in >70% of patients. The occurrence of PH worsened the clinical condition and hemodynamic status of CAD-HF patients and increased their mortality rate. Our results suggested that CAD-HF patients with more obvious LV enlargement and anemia are at greater risk of PH, but should benefit from treatment with nitrates. Nitrates may be a potentially effective therapy for CAD-HF rather than PCI treatment, reducing the development of PH. Renal impairment, elevated mPAP, DPG ≥7 mmHg, and previous MI were closely associated with the survival of CAD-HF-PH patients and could be strong predictors of mortality in these patients.

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Conflicts of interest

None.

References

1. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, *et al*. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37:67–119. doi: 10.1093/eurheartj/ehv317.
2. Rosenkranz S, Gibbs JSR, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016;37:942–954. doi:10.1093/eurheartj/ehv512.
3. Fang JC, DeMarco T, Givertz MM, Borlaug BA, Lewis GD, Rame JE, *et al*. World Health Organization Pulmonary Hypertension Group 2: pulmonary hypertension due to left heart disease in the adult — a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation. J Hear Lung Transplant 2012;31:913–933. doi: 10.1016/j.hea-lun.2012.06.002.
4. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation 2012;126:975–990. doi: 10.1161/CIRCULATIONAHA.111.085761.
5. Khush KK, Tasissa G, Butler J, McGlothlin D, De Marco T. ESCAPE Investigators. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. Am Heart J 2009;157:1026–1034. doi: 10.1016/j.ahj.2009.02.022.
6. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. JACC Hear Fail 2013;1:290–299. doi: 10.1016/j.jchf.2013.05.001.

7. Leung CC, Moondra V, Catherwood E, Andrus BW. Prevalence and risk factors of pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved ejection fraction. Am J Cardiol 2010;106:284–286. doi: 10.1016/j.amjcard.2010.02.039.
8. Georgiopoulou VV, Kalogeropoulos AP, Borlaug BA, Gheorghiade M, Butler J. Left ventricular dysfunction with pulmonary hypertension part 1: epidemiology, pathophysiology, and definitions. Circ Hear Fail 2013;6:344–354. doi: 10.1161/CIRCHEARTFAI-LURE.112.000095.
9. Lala A, Desai AS. The role of coronary artery disease in heart failure. Heart Fail Clin 2014;10:353–365. doi: 10.1016/j.hfc.2013.10.002.
10. Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, *et al*. Navigating the crossroads of coronary artery disease and heart failure. Circulation 2006;114:1202–1213. doi: 10.1161/CIRCULATIONAHA.106.623199.
11. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al*. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur J Heart Fail 2012;14:803–869. doi: 10.1093/eurjhf/hfs105.
12. Adir Y, Guazzi M, Offer A, Temporelli PL, Cannito A, Ghio S. Pulmonary hemodynamics in heart failure patients with reduced or preserved ejection fraction and pulmonary hypertension: similarities and disparities. Am Heart J 2017;192:120–127. doi: 10.1016/j.ahj.2017.06.006.
13. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. Nat Rev Cardiol 2011;8:485. doi: 10.1038/nrcardio.2011.77.
14. Hayashi T, Joki N, Tanaka Y, Hase H. Anaemia and early phase cardiovascular events on haemodialysis. Nephrology (Carlton) 2015;20 (Suppl 4):1–6. doi: 10.1111/nep.12642.
15. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, *et al*. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am JKidney Dis 1999;34:125–134. doi: 10.1016/s0272-6386(99)70118-6.
16. Tarkin JM, Kaski JC. Vasodilator therapy: nitrates and nicorandil. Cardiovasc Drugs Ther 2016;30:367–378. doi: 10.1007/s10557-016-6668-z.
17. Russi AE, Brown MA. The nitrate-nitrite-NO pathway and its implications for heart failure and preserved ejection fraction. Curr Heart Fail Rep 2016;13:47–59. doi: 10.1007/s11897-016-0277-9.
18. Kjaergaard J, Akkan D, Iversen KK, Kjoller E, Køber L, Torp-Pedersen C, *et al*. Prognostic importance of pulmonary hypertension in patients with heart failure. Am J Cardiol 2007;99:1146–1150. doi: 10.1016/j.amjcard.2006.11.052.
19. Agarwal R, Shah SJ, Foreman AJ, Glassner C, Bartolome SD, Safdar Z, *et al*. Risk assessment in pulmonary hypertension associated with heart failure and preserved ejection fraction. J Hear Lung Transplant 2012;31:467–477. doi: 10.1016/j.healun.2011.11.017.
20. Gupta DK, Shah AM, Castagno D, Takeuchi M, Loehr LR, Fox ER, *et al*. Heart failure with preserved ejection fraction in African Americans. The ARIC (Atherosclerosis Risk In Communities) study. JACC Hear Fail 2013;1:156–163. doi: 10.1016/j.jchf.2013.01.003.
21. Yamabe S, Dohi Y, Fujisaki S, Higashi A, Kinoshita H, Sada Y, *et al*. Prognostic factors for survival in pulmonary hypertension due to left heart disease. Circ J 2016;80:243–249. doi: 10.1253/circj.CJ-15-0708.
22. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN, Investigators SOLVD. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302. doi: 10.1056/NEJM199108013250501.
23. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, *et al*. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669–677. doi: 10.1056/NEJM199209033271001.
24. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 2000;101:2981–2988. doi: 10.1161/01.cir.101.25.2981.
25. Tampakakis E, Leary PJ, Selby VN, De Marco T, Cappola TP, Felker GM, *et al*. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. JACC Hear Fail 2015;3:9–16. doi: 10.1016/j.jchf.2014.07.010.
26. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. JACC Hear Fail 2015;3:467–474. doi: 10.1016/j.jchf.2015.01.013.

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