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Prognosis of pulmonary hypertension in patients with hypertrophic cardiomyopathy: A multicenter propensity score matching study

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ABSTRACT

Objectives: Pulmonary hypertension (PH) is known to be associated with increased mortality in patients suffering from left ventricular disease. The aim of this study was to assess the incidence of PH among patients diagnosed with hypertrophic cardiomyopath (HCM) and to evaluate its prognostic significance.
Methods: The study cohort consisted of 2781 patients with HCM. Among them, 226 patients had PH (8.1%), and 2555 patients did not have PH (91.8%). The fourteen demographic and clinical variables were matched between the two groups using a 1:3 propensity score matching (PSM) method. Kaplan–Meier survival curves and Cox proportional hazard regression models were used to evaluate the correlation between PH and mortality. Moreover, a competing risk regression analysis was conducted to assess the competing risk.
Results: Before matching, there were 519 (18.7 %) patients with all-cause mortality, including 292 (10.5 %) patients who experienced cardiovascular mortality and 128 (4.6 %) patients who experienced SCD. There was a significant difference in the Kaplan–Meier survival curves for all-cause mortality (log-rank $P < 0.0001$), cardiovascular mortality (log-rank $P < 0.0001$) and SCD (log-rank $P = 0.0005$). After matching, there were also significant differences in cardiovascular mortality (log-rank $P = 0.011$) and SCD (log-rank $P = 0.042$), but only a similar trend was observed for all-cause mortality (log-rank $P = 0.052$). Cox regression analyses suggested that PH was an independent risk predictor for cardiovascular mortality [HR: 1.666; 95 % CI: 1.145–2.424; $P = 0.008$].
Conclusion: HCM patients with PH characterized by increased cardiovascular mortality and SCD, as well as a similar trend in all-cause mortality. Moreover, PH is an independent risk factor for cardiovascular mortality.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a potentially inherited cardiomyopathy characterized by myocardial hypertrophy in the absence of another etiology, affecting approximately 0.2–0.5 % of the population [1,2]. While the majority of patients with HCM have a relatively favorable outcomes, some individuals are at increased risk of experiencing adverse events, even sudden cardiac death (SCD) [2]. Pulmonary hypertension (PH) is characterized by a mean pulmonary arterial pressure (mPAP) of 20 mm Hg or higher while at rest, a diagnosis that is confirmed through right heart catheterization (RHC) [3]. It can also be detected non-invasively on Doppler echocardiography, which allows for the estimation of the pulmonary artery systolic pressure (PASP) on the basis of the peak velocity of tricuspid regurgitation (TRV) [4]. A PASP greater than 40 mmHg is used to define pulmonary arterial hypertension (PAH) [5]. PH is generally classified into five clinical subgroups: PAH,

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PH due to left-sided heart disease (PH-LHD), PH due to chronic lung disease, chronic thromboembolic PH (CTEPH), and PH with unclear and/or multifactorial mechanisms [6]. And PH associated with HCM belong to PH-LHD [7].

Although there are numerous causes of PH, it is typically linked to worsening symptoms and a higher risk of mortality, irrespective of the underlying condition [8]. PH is present in at least 50 % of patients with heart failure (HF) [8]. PH registries indicate that survival rates range from 68 % to 93 % at 1 year and from 39 % to 77 % at 3 years [6,8,9]. The 12-month mortality rate for patients with PH-LHD may reach as high as 32 % [10]. The reported incidence of pH in patients with HCM is approximately 1.0 % per year [11]. PH in patients with HCM is associated with several significant complications, including thromboembolic events, atrial fibrillation (AF), and HF [12]. Furthermore, PH in patients with HCM has been linked to an increased risk of ischemic stroke during long-term follow-up compared the risk in patients without PH[13].

In recent years, the latest advancements in HCM management have provided new perspectives for the treatment strategies of PH. Mavacamten, a novel cardiac myosin inhibitor, has demonstrated significant efficacy in multiple studies for symptomatic obstructive HCM [14]. The research indicated that drugs like mavacamten not only improve the symptoms and quality of life of HCM patients but may also indirectly influence the management of PH by reducing the pressure gradient in the left ventricular outflow tract (LVOT)[14,15]. The introduction of this drug offers a disease-specific treatment option for HCM patients, potentially intersecting with PH treatment strategies to provide a more comprehensive treatment plan for patients. Studies have shown that the prevalence of PH varies significantly among different clinical groups, gradually increasing from patients without left ventricular outflow tract obstruction (LVOTO) to those with end-stage HCM, and it is an independent predictor of HCM-related morbidity[11]. The aim of this study is to investigate the impact of PH on the prognosis of HCM patients by employing propensity score matching. This approach seeks to provide evidence regarding the effects of PH on outcomes for individuals with HCM.

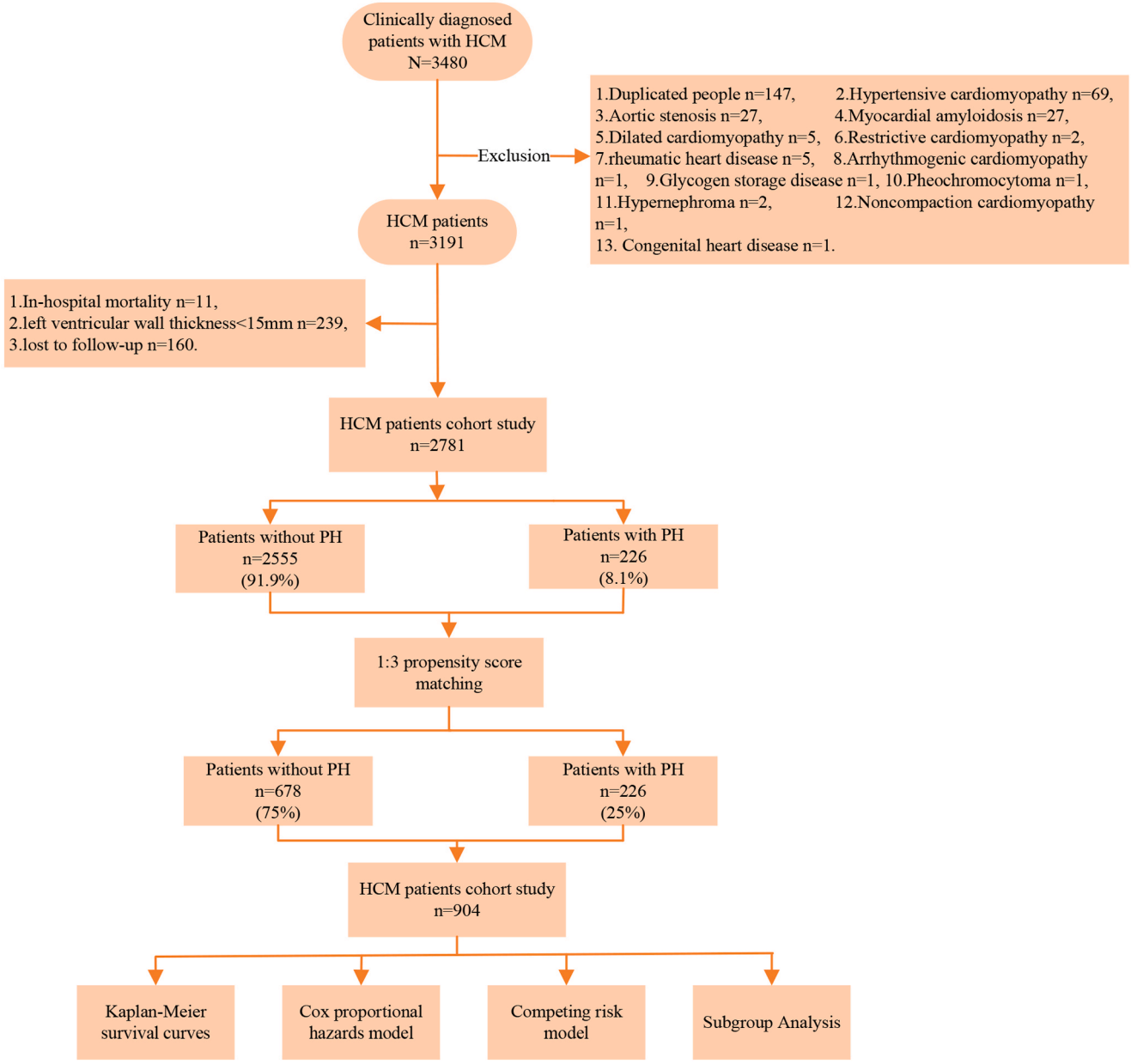

Fig. 1. Patient flow diagram.

2. Methods

2.1. Ethics statement

Ethic approval was obtained from the Sichuan Provincial People's Hospital Research Ethics Committees (No. 2022424). The Institutional Review Board approved the study protocol.

2.2. Study population

We conducted a multicenter cohort study of 2781 patients with HCM, who were hospitalized at 13 tertiary hospitals from 1996 to 2021. In addition, we performed propensity score matching for patients with and without PH at a 1:3 ratio. Ultimately, 226 patients with PH and 678 patients without PH were enrolled after matching. Patients with cardiac or systemic diseases capable of producing similar magnitudes of hypertrophy, such as cardiac amyloidosis, Fabry disease, Noonan syndrome and amyloidosis cardiomyopathy, were excluded (Fig. 1).

2.3. Diagnostic criteria and definitions

HCM is defined as a wall thickness of the left ventricular myocardium $\geq$ 15 mm in one or more left segments, as measured on any imaging modality (echocardiography, cardiac magnetic resonance imaging (CMR), or computed tomography (CT)), rather than as explained by the loading conditions alone[1,16]. The existence of first-degree relatives with a history of HCM or SCD, and a left ventricular wall thickness of 13 mm or greater in one or more regions can be used to diagnose HCM[16]. Since the apex is typically the thinnest part of the left ventricle, a lower threshold of 13–14 mm may be applied for diagnosing apical HCM (AHCM), particularly when clinical manifestations and other imaging features, such as electrocardiography, family history, genotyping, CMR imaging, and echocardiography, support the diagnosis of AHCM[16,17].

The PASP was calculated by adding the estimated right atrial pressure to the *trans*-tricuspid gradient, which was determined with the modified Bernoulli equation $4v^2$, where v is the peak tricuspid regurgitation velocity (TRV)[18]. In general, a TRV greater than 2.8 to 2.9 m/s, which corresponds to a PASP of approximately 36 mmHg, assuming a right atrial pressure of 3–5 mm Hg, indicates elevated right ventricular systolic pressure and pulmonary artery pressure (39–41 mmHg)[5]. In the present study, we defined PH as a PASP $\geq$ 40 mmHg.

2.4. Follow-up and endpoints

The follow-up period commenced in October 2011 and ended in April 2024. The study endpoints included all-cause mortality, cardiovascular mortality, and SCD. All-cause mortality encompasses deaths from various causes, whereas cardiovascular mortality is specifically defined as death resulting from cardiac transplantation, stroke, heart failure (HF), and appropriate discharges from implantable cardioverter-defibrillators (ICDs). SCD was characterized as an unexpected death occurring in the absence of, or within one hour of, symptom onset in patients who had previously experienced a relatively stable or uneventful clinical course[19]. Data on all-cause mortality, cardiovascular mortality, and SCD during the follow-up period were collected through a review of medical records (including outpatient clinic visits and hospitalizations), telephone interviews, and verification of survival status through national police records. Patients who were lost to follow-up within six months of discharge were classified as lost to follow-up.

2.5. Statistical analysis

Continuous variables are presented as the means $\pm$ standard deviations (SDs) or medians with interquartile ranges, and differences between groups were analyzed via the unpaired Student's *t*-test and the Mann-Whitney test (Wilcoxon rank test). Categorical variables are expressed as proportions, with group differences assessed via the Pearson chi-square test. A logistic regression model was performed on the basis of 33 baseline variables, and those with a P-value $\leq$ 0.15 were subsequently included in the propensity score matching. The variables considered included sex, age, non-sustained ventricular tachycardia (NSVT), familial hypertrophic cardiomyopathy (FHCM), coronary artery disease (CAD), alcohol septal ablation or septal myectomy (ASA or SM), QTc duration, interventricular septal (IVS) thickness, left atrial (LA) diameter, right atrial (RA) diameter, left ventricular ejection fraction (LVEF), logarithm of N-terminal pro-B-type natriuretic peptide (Log NT-proBNP), the aspartate aminotransferase to alanine aminotransferase ratio (AST/ALT), and the triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-C).

Cox proportional hazards modeling was employed to identify the factors independently associated with mortality. Hazard ratios (HRs), 95 % confidence intervals (CIs), and *P* values are reported. All-cause mortality, cardiovascular mortality and SCD were treated as endpoints, whereas non-cardiovascular mortality and non-SCD were treated as competing events. The cumulative incidence function was used to evaluate the cumulative risk of combined PH group and non-combined PH group, and the Gray test was used to analyze the difference in cumulative risk between the two groups. In addition, the competing risk Fine-Gray regression was used for univariate and multivariate analyses to explore the influencing factors. Analyses were performed with R Version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria), with P values $\leq$ 0.05 considered statistically significant.

3. Results

3.1. Baseline clinical characteristics

Table 1 shows the baseline characteristics of patients with and without PH before and after matching. Before matching, a total of 2781 patients with HCM were included in the study. In terms of demographic characteristics, the patients with PH were generally older than those without PH, and among those with combined PH, there was a predominance of females. In terms of clinical features, the incidence of AF and stroke greater in patients with PH than in patients without PH, and the thrombolysis in myocardial infarction (TRI) index was elevated in patients with PH. In echocardiography, patients with PH had larger LA diameters and the obstruction of the left ventricular outflow (LVOTO) was lower. Additionally, log (NT-pro-BNP) levels were significantly higher in patients with PH than in patients without PH according to the laboratory assessments. After matching, 226 patients with PH, and 678 patients without PH were included, and only the RA diameters diameter was significantly different.

3.2. Follow-up results in the unmatched cohort

Before matching, the median follow-up time for the unmatched cohort was 4.54 years (IQR: 2.13–7.99 years). A total of 519 patients (18.7 %) experienced all-cause mortality, including 457 patients (17.9 %) without PH and 62 patients (27.4 %) with PH. In terms of cardiovascular mortality, 292 patients (10.5 %) were affected, including 251 patients (9.8 %) without PH and 41 patients (18.1 %) with PH. Additionally, 128 patients (4.6 %) had SCD, of whom 112 (4.4 %) did not have PH and 16 (7.1 %) had PH.

Statistical analysis revealed that all-cause mortality (log-rank $P <$ 0.0001), cardiovascular mortality (log-rank $P <$ 0.0001), and SCD (log-rank $P =$ 0.0005) were significantly more common in patients with PH than in those without PH (Figure2. a-c). Cox regression analysis indicated that PH was an independent risk predictor for cardiovascular mortality [HR: 1.712; 95 % CI: 1.203–2.437; $P =$ 0.003] and a univariate risk predictor for all-cause mortality [HR: 2.39; 95 % CI: 1.83–3.13; $P <$ 0.001] and SCD [HR: 2.48; 95 % CI: 1.46–4.2; $P =$ 0.001] (Table2).

Table 1
Baseline demographic and clinical characteristics of before and after matching cohort.

	Before matching					After matching				
	Overall N = 2781	Without PH n = 2555	With PH n = 226	P value	SMD	Overall N = 904	Without PH n = 678	With PH n = 226	P value	SMD
Age, years (mean (SD))	57.00 ± 15.39	56.45 ± 15.22	63.21 ± 15.99	<0.001	0.433	63.12 ± 14.04	63.09 ± 13.34	63.21 ± 15.99	0.91	0.008
Age ≥ 60 years, n (%)	1275 (45.8)	1128 (44.1)	147 (65.0)	<0.001	0.429	578 (63.9)	431 (63.6)	147 (65.0)	0.749	0.031
Female, n (%)	1064 (38.3)	944 (36.9)	120 (53.1)	<0.001	0.329	503 (55.6)	383 (56.5)	120 (53.1)	0.417	0.068
NYHA III-IV class, n (%)	925 (33.3)	858 (33.6)	67 (29.6)	0.259	0.085	281 (31.1)	214 (31.6)	67 (29.6)	0.648	0.042
Course of disease, month (median [IQR])	12.00 [0.13—60.00]	12.00 [0.20—60.00]	12.00 [0.10—60.00]	0.221	0.091	12.00 [0.10—60.00]	12.00 [0.10—60.00]	12.00 [0.10—60.00]	0.808	0.03
Syncope, n (%)	321 (11.5)	292 (11.4)	29 (12.8)	0.6	0.043	96 (10.6)	67 (9.9)	29 (12.8)	0.262	0.093
FHCM, n (%)	191 (6.9)	166 (6.5)	25 (11.1)	0.014	0.162	95 (10.5)	70 (10.3)	25 (11.1)	0.851	0.024
FSCD, n (%)	36 (1.3)	33 (1.3)	3 (1.3)	1	0.003	19 (2.1)	16 (2.4)	3 (1.3)	0.503	0.077
Stroke, n (%)	345 (12.4)	305 (11.9)	40 (17.7)	0.016	0.163	146 (16.2)	106 (15.6)	40 (17.7)	0.531	0.055
Ventricular arrhythmia, n (%)	402 (14.5)	366 (14.3)	36 (15.9)	0.576	0.045	130 (14.4)	94 (13.9)	36 (15.9)	0.511	0.058
VT, n (%))	236 (8.5)	215 (8.4)	21 (9.3)	0.742	0.031	70 (7.7)	49 (7.2)	21 (9.3)	0.389	0.075
NSVT, n (%)	141 (5.1)	134 (5.2)	7 (3.1)	0.211	0.108	28 (3.1)	21 (3.1)	7 (3.1)	1	<0.001
AF, n (%)	495 (17.8)	417 (16.3)	78 (34.5)	<0.001	0.427	267 (29.5)	189 (27.9)	78 (34.5)	0.07	0.144
LBBB, n (%)	123 (4.4)	118 (4.6)	5 (2.2)	0.129	0.133	29 (3.2)	24 (3.5)	5 (2.2)	0.446	0.079
RBBB, n (%)	147 (5.3)	139 (5.4)	8 (3.5)	0.285	0.092	34 (3.8)	26 (3.8)	8 (3.5)	1	0.016
IVCD, n (%)	88 (3.2)	82 (3.2)	6 (2.7)	0.796	0.033	15 (1.7)	9 (1.3)	6 (2.7)	0.293	0.095
AVB, n (%)	113 (4.1)	100 (3.9)	13 (5.8)	0.244	0.086	44 (4.9)	31 (4.6)	13 (5.8)	0.592	0.053
CAD, n (%)	558 (20.1)	507 (19.8)	51 (22.6)	0.372	0.067	202 (22.3)	151 (22.3)	51 (22.6)	1	0.007
ICD, n (%)	58 (2.1)	51 (2.0)	7 (3.1)	0.386	0.07	16 (1.8)	9 (1.3)	7 (3.1)	0.145	0.121
ASA&SM, n (%)	464 (16.7)	451 (17.7)	13 (5.8)	<0.001	0.377	48 (5.3)	35 (5.2)	13 (5.8)	0.864	0.026
MSI (mean (SD))	0.84 ± 0.24	0.83 ± 0.23	0.88 ± 0.35	0.003	0.167	0.87 ± 0.29	0.86 ± 0.27	0.88 ± 0.35	0.391	0.062
Electrocardiogram										
QRS, ms (mean (SD))	106.10 ± 27.14	106.12 ± 27.11	105.78 ± 27.61	0.854	0.013	104.08 ± 23.97	103.52 ± 22.62	105.78 ± 27.61	0.22	0.09
QT, ms (mean (SD))	416.04 ± 51.78	416.35 ± 51.29	412.49 ± 56.98	0.283	0.071	412.18 ± 53.66	412.08 ± 52.55	412.49 ± 56.98	0.921	0.008
QTc, ms (mean (SD))	453.66 ± 48.76	454.33 ± 48.40	446.05 ± 52.15	0.014	0.165	446.34 ± 48.04	446.44 ± 46.63	446.05 ± 52.15	0.916	0.008
PR, ms (mean (SD))	168.98 ± 37.89	168.62 ± 36.87	173.03 ± 47.86	0.094	0.103	171.57 ± 44.40	171.09 ± 43.21	173.03 ± 47.86	0.569	0.043
Echocardiogram										
LVD, mm (mean (SD))	43.79 ± 6.63	43.78 ± 6.58	43.85 ± 7.21	0.885	0.01	43.64 ± 6.61	43.56 ± 6.40	43.85 ± 7.21	0.575	0.042
RVD, mm (mean (SD))	20.07 ± 3.36	20.04 ± 3.34	20.37 ± 3.57	0.16	0.095	20.23 ± 3.51	20.18 ± 3.49	20.37 ± 3.57	0.494	0.052
LAD, mm (mean (SD))	40.48 ± 7.34	40.12 ± 7.18	44.55 ± 7.92	<0.001	0.586	43.77 ± 7.82	43.51 ± 7.78	44.55 ± 7.92	0.085	0.132
RA, n (%)	206 (7.4)	128 (5.0)	78 (34.5)	<0.001	0.798	204 (22.6)	126 (18.6)	78 (34.5)	<0.001	0.367
LVEF, % (mean (SD))	66.37 ± 9.80	66.44 ± 9.63	65.58 ± 11.54	0.209	0.08	65.89 ± 10.68	66.00 ± 10.38	65.58 ± 11.54	0.612	0.038
IVS, mm (mean (SD))	18.22 ± 4.87	18.26 ± 4.91	17.82 ± 4.40	0.193	0.094	17.99 ± 4.41	18.04 ± 4.41	17.82 ± 4.40	0.511	0.051
Maximal LV wall thickness, mm (mean (SD))	19.70 ± 4.49	19.73 ± 4.53	19.31 ± 4.03	0.173	0.099	19.19 ± 4.07	19.15 ± 4.08	19.31 ± 4.03	0.621	0.038
LVPW (mean (SD))	11.97 ± 3.02	11.94 ± 2.96	12.23 ± 3.64	0.169	0.087	12.23 ± 3.19	12.23 ± 3.02	12.23 ± 3.64	0.988	0.001
AHCM, n (%)	290 (10.4)	259 (10.1)	31 (13.7)	0.115	0.111	91(10.1)	60 (8.8)	31 (13.7)	0.048	0.154
HOCM, n (%)	1259 (45.3)	1174 (45.9)	85 (37.6)	0.019	0.17	376 (41.6)	291 (42.9)	85 (37.6)	0.185	0.108
Laboratory examination										
AST/ALT (mean (SD))	1.31 ± 1.25	1.27 ± 0.99	1.78 ± 2.78	<0.001	0.244	1.60 ± 1.89	1.55 ± 1.48	1.78 ± 2.78	0.106	0.106
TG/HDL-C (mean (SD))	1.61 ± 1.74	1.64 ± 1.80	1.22 ± 0.81	<0.001	0.303	1.22 ± 0.83	1.22 ± 0.84	1.22 ± 0.81	0.916	0.008
TyG (mean (SD))	8.78 ± 0.66	8.79 ± 0.66	8.67 ± 0.65	0.009	0.182	8.64 ± 0.61	8.63 ± 0.59	8.67 ± 0.65	0.492	0.052
Log (NT-proBNP) (mean (SD))	3.10 ± 0.55	3.07 ± 0.54	3.41 ± 0.50	<0.001	0.645	3.41 ± 0.53	3.41 ± 0.54	3.41 ± 0.50	0.901	0.01
Creatinine (mean (SD))	87.29 ± 65.98	87.29 ± 67.30	87.25 ± 48.83	0.994	0.001	90.81 ± 56.69	92.00 ± 59.06	87.25 ± 48.83	0.276	0.088
Betablocker, n (%)	2037 (73.2)	1882 (73.7)	155 (68.6)	0.116	0.112	636 (70.4)	481 (70.9)	155 (68.6)	0.556	0.051
Ca^{2+} antagonist, n (%)	612 (22.0)	581 (22.7)	31 (13.7)	0.002	0.235	160 (17.7)	129 (19.0)	31 (13.7)	0.087	0.144
Follow-up										

(*continued on next page*)

Table 1 (*continued*)

	Before matching					After matching				
	Overall N = 2781	Without PH n = 2555	With PH n = 226	P value	SMD	Overall N = 904	Without PH n = 678	With PH n = 226	P value	SMD
Time, year (median [IQR])	4.54 [2.13—7.99]	4.78 [2.23—8.38]	2.57 [1.45—4.89]	<0.001	0.589	3.20 [1.66—5.89]	3.54 [1.80—6.14]	2.57 [1.45—4.89]	0.001	0.303
All-cause mortality, n (%)	519 (18.7)	457 (17.9)	62 (27.4)	0.001	0.23	243 (26.9)	181 (26.7)	62 (27.4)	0.897	0.017
Cardiovascular mortality, n (%)	292 (10.5)	251 (9.8)	41 (18.1)	<0.001	0.242	141 (15.6)	100 (14.7)	41 (18.1)	0.266	0.092
SCD, n (%)	128 (4.6)	112 (4.4)	16 (7.1)	0.091	0.116	50 (5.5)	34 (5.0)	16 (7.1)	0.313	0.087

3.3. Follow-up results in the matched cohort

After matching, significant differences were observed in cardiovascular mortality (log-rank $P = 0.011$) and SCD (log-rank $P = 0.042$), whereas the trend for all-cause mortality was merely similar (log-rank $P = 0.052$) (Figure2. d-f).

Cox regression analysis indicated that PH was an independent risk predictor of cardiovascular mortality [HR: 1.666; 95 % CI: 1.145–2.424; $P = 0.008$] and a univariate risk predictor of SCD [HR: 1.85; 95 % CI: 1.01–3.36; $P = 0.045$]. However, PH was not a significant predictor for all-cause mortality [HR: 1.33; 95 % CI: 1–1.78; $P = 0.053$] (Table2).

3.4. Competing risk regression analysis

Patients with PH had a greater cumulative risk of cardiovascular mortality ($P1 = 0.008$). In contrast, there was no significant difference in non-cardiovascular mortality or competing events between patients with and without PH ($P2 = 0.768$) (Figure 3. a). Additionally, the competing risk model for SCD showed no significant difference between the two groups ($P1 = 0.060$ vs. $P2 = 0.141$) (Fig. 3.b).

According to the results presented in Table 2, after multivariate adjustment, PH was identified as an independent cumulative risk factor for cardiovascular mortality [HR: 1.673; 95 % CI: 1.135–2.466; $P = 0.009$], but not in SCD [HR: 1.376; 95 % CI: 0.748–2.532; $P = 0.31$] (Table 2).

3.5. Subgroup analysis

To further investigate the impact of PH on the prognosis of HCM, we conducted subgroup analyses (Fig. 4). The results indicated that all-cause mortality and SCD of PH did not show significant differences in each subgroup (Fig. 4a,c). In cardiovascular mortality (Fig. 4b), PH emerged as a risk predictor in the following subgroups: age $\geq$ 60 years [HR: 1.792; 95 % CI: 1.124–2.856; $P = 0.014$], NYHA class III-IV[HR: 2.011; 95 % CI: 1.101–3.67; $P = 0.023$], absence of syncope[HR: 1.918; 95 % CI: 1.265–2.908; $P = 0.002$], AF[HR: 1.696; 95 % CI: 1.07–2.688; $P = 0.025$], ventricular arrhythmia [HR: 4.496; 95 % CI: 1.792–11.28; $P = 0.001$], CAD[HR: 3.152; 95 % CI: 1.45–6.849; $P = 0.004$], non-familial HCM[HR: 1.655; 95 % CI: 1.109–2.47; $P = 0.014$], RA diameter not enlarged [HR: 1.927; 95 % CI: 1.25–2.971; $P = 0.003$], LA diameter [HR: 1.704; 95 % CI: 1.01–2.874; $P = 0.046$ for $<$ 45 mm; HR: 1.836; 95 % CI: 1.024–3.292; $P = 0.041$ for $\geq$ 45 mm] and LV diameter $<$ 55 mm[HR: 1.625; 95 % CI: 1.09–2.422; $P = 0.017$], among others. These findings highlight the varying impacts of PH on cardiovascular mortality within specific subgroups of HCM patients.

4. Discussion

The findings of our study indicate that patients with HCM who also have PH have a higher risk of cardiovascular mortality and SCD, with a similar trend observed for all-cause mortality. Furthermore, PH was identified as an independent risk predictor of cardiovascular mortality and a univariate risk predictor of SCD.

PH is a significant global health concern that affects individuals across all age groups, with an increasingly critical impact on elderly individuals, especially in countries with aging populations[8]. Current estimates indicate that PH affects approximately 1 % of the global population, with the prevalence increasing to approximately 10 % in individuals over the age of 65[8,20]. Globally, left-sided heart and lung diseases are now the most common causes of PH[8,21]. Remarkably, approximately 80 % of those affected reside in developing countries, where the condition is often linked to congenital heart defects and infectious diseases such as schistosomiasis, HIV, and rheumatic heart disease[8]. These forms of PH are particularly prevalent in those under 65 years of age. Regardless of the underlying cause, the onset of PH is associated with clinical decline and a significant increase in the risk of mortality[21,22]. Therefore, global research initiatives are essential for developing preventive strategies and effective treatments for the various forms of PH.

The incidence of PH in HCM patients is significantly different from that in other populations [11–13,18,23–26]. In the present study, the incidence of PH among patients with HCM was 8 %, which is notably lower than the levels reported in some other studies[12,18]. For example, Chakraborty et al. reported an incidence of 30.4 %[12], whereas Ong et al. reported an incidence of 38 %[18]. However, our findings are comparable to those of Wu et al., who reported an incidence of 12.3 %[23], and Musumeci et al., who observed an incidence of 11.4 % in their initial assessment of an outpatient cohort, additionally, the annual incidence of PH in their study was 1.1 % after a follow-up period of 3.4 years[11]. Notably, in patients with hypertrophic obstructive cardiomyopathy (HOCM) receiving septal reduction therapy, the incidence of PH can reach 53 %[25]. And Covella et al. conducted a study in patients with late-stage HF, in whom the prevalence of PH was 51 % [26]. The significant differences in PH incidence rates reported in different studies may be due to the different PH thresholds or measurement methods used. Additionally, selection bias and ethnic differences may also be important factors contributing to these differences.

PH can predict mortality in the general population and HF patients [4,27]. Recent studies have shown that an elevated PH is associated with an increased mortality rate in HCM patients[18,28]. In the present study, patients with PH experiencing increased all-cause mortality, cardiovascular mortality and SCD. And PH is independently associated with increased cardiovascular mortality. Although there was no significant difference in all-cause mortality after matching, a corresponding trend was evident. Our findings are consistent with those of previous studies, indicating that patients with PH have a poor outcomes[11,18]. As reported by Anand et al.[28], PH is independently associated with all-cause mortality, and factors such as female sex, AF, and congestive HF are closely related to the development of PH. Ong et al. reported that PH is associated with an increased risk of mortality in HOCM patients who have not undergone SRT[18]. Moreover, several studies have shown that PH is associated with the incidence of other cardiovascular complications in patients with HCM and that PH is considered an independent risk factor for the occurrence of HCM-related morbidity [11–13,24,26,29].

In the present study, patients with PH had increased cardiovascular

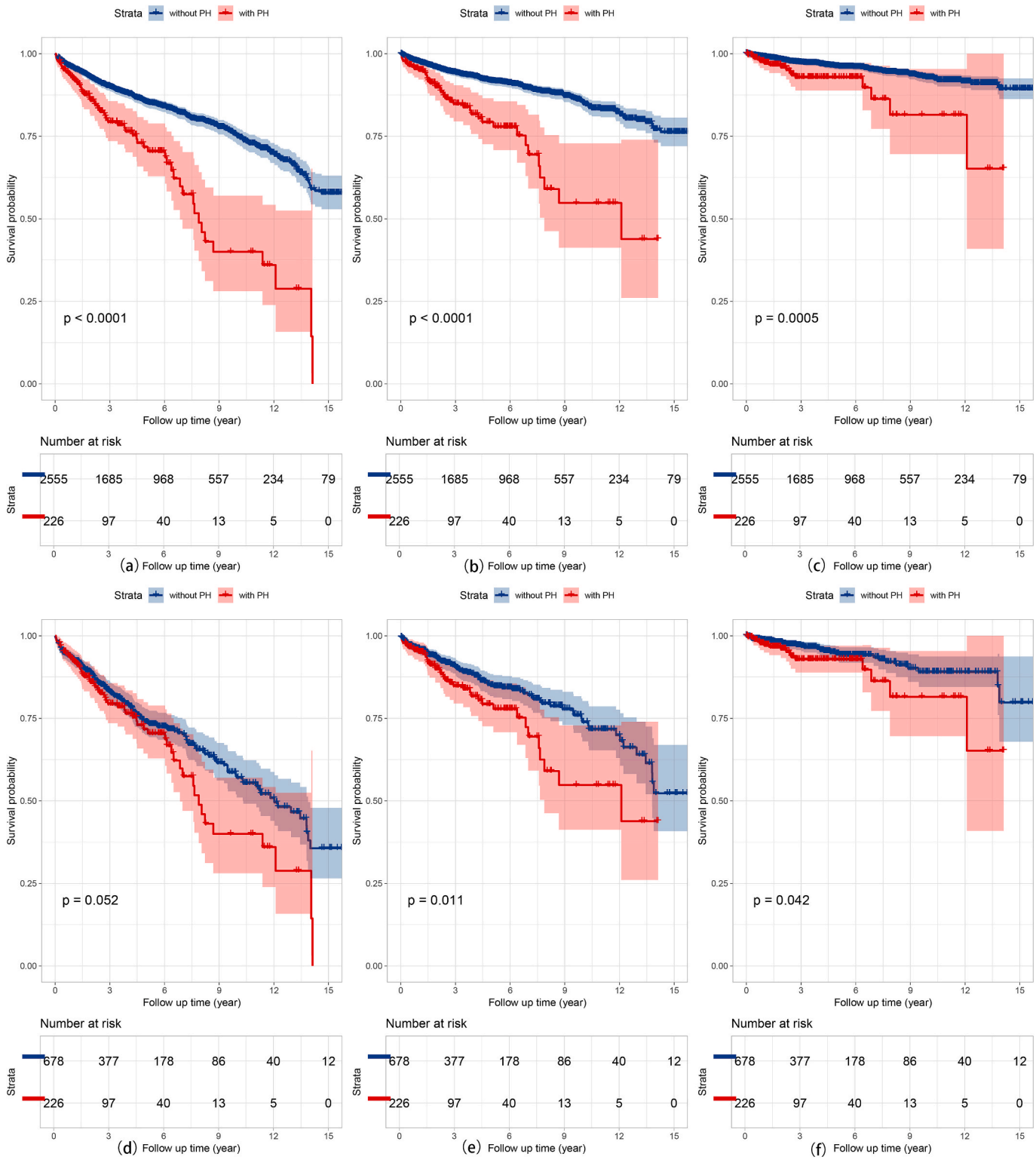

Fig. 2. Kaplan-Meier survival curves of patients without PH and with PH before and after matching. a)All-cause mortality in before matching, b)Cardiovascular mortality in before matching, c)SCD in before matching. d)All-cause mortality in after matching, e)Cardiovascular mortality in after matching, f)SCD in after matching.

mortality and SCD, possibly because patients with PH typically have more cardiovascular diseases, such as AF (34.5 %) and stroke (17.7 %), are more likely to be elderly patients (65 %), and are more likely to have familial HCM. Previous studies have shown that the prognosis of patients with familial HCM is poor[30]. And previous studies have also shown that AF and stroke are associated with poor prognosis[31], and older patients are more likely to have traditional cardiovascular risk factors[32]. Additionally, 53 % of the patients with PH were female, probably due to the influence of sex hormones[33]. In our study cohort, the number of cardiovascular deaths among female patients was greater than that among male patients. We believe that this is the reason for the poor prognosis observed in HCM patients with PH in our cohort.

Table 2
Univariate and multivariate Cox regression and competing risk regression analyses before and after matching.

	Before matching						After matching								
	Univariate Cox regression			Multivariate Cox regression			Univariate Cox regression			Multivariate Cox regression			Multivariate competing risk regression		
	HR	95 %CI	P	HR	95 %CI	P value	HR	95 %CI	P	HR	95 %CI	P value	HR	95 %CI	P value
All-cause mortality															
PH	2.39	1.83–3.13	<0.001	1.315	0.997–1.734	0.053	1.33	1–1.78	0.053	——	——	——			
Cardiovascular mortality															
PH	2.85	2.04–3.98	<0.001	1.712	1.203–2.437	0.003	1.6	1.11–2.31	0.012	1.666	1.145–2.424	0.008	1.673	1.135–2.466	0.009
SCD															
PH	2.48	1.46–4.2	0.001	1.676	0.962–2.921	0.068	1.85	1.01–3.36	0.045	——	——	——	1.376	0.748–2.532	0.31

Note: all-cause mortality before matching was adjusted for: age, sex, diabetes mellitus, stroke, VT, ventricular arrhythmia, AF, AVB, ASA or SM, RA, AHCM, HOCM, MSI, DBP, QT, PR, LAD, LVEF, maximal LV thickness, Log (NT-proBNP), TP, ALB, AST/ALT, ALP, TB, random blood glucose, creatinine, TG/HDL-C, CHOL, LDL-C, LDH, CRP.
cardiovascular mortality before matching was adjusted for: age, sex, stroke, VT, ventricular arrhythmia, AF, AVB, IVCD, ASA or SM, RA, AHCM, HOCM, MSI, DBP, PR, LVD, LAD, LVEF, maximal LV thickness, Log (NT-proBNP), TP, ALB, AST/ALT, ALP, TB, creatinine, TG/HDL-C, CHOL, TyG, LDL-C, LDH, CRP.
SCD before matching was adjusted for: age, AF, AVB, IVCD, AHCM, HOCM, MSI, LVD, LAD, LVEF, LVOTG, Log (NT-proBNP), ALP, creatinine, TyG.
all-cause mortality after matching was adjusted for: age, stroke, ASA or SM, HOCM, MSI, QT, LVEF, maximal LV thickness, Log (NT-proBNP), ALB, ALP, DB, random blood glucose, creatinine, CHOL, LDL-C, LDH, CRP, RA.
cardiovascular mortality after matching was adjusted for: stroke, MSI, SBP, LVEF, Log (NT-proBNP), ALP, DB, creatinine, CHOL, LDL-C, LDH, CRP, RA.
SCD after matching was adjusted for: age, AVB, RA, Log (NT-proBNP), LDL-C.

The occurrence mechanism of PH in patients with HCM involves a variety of complex physiological and pathological processes, differentiating between precapillary and postcapillary PH or their combination [29]. Postcapillary PH is more common and is due to elevated left atrial pressure, often resulting from mitral regurgitation, diastolic dysfunction, or LVOTO[29]. Meanwhile, hemodynamic changes caused by increased left atrial pressure led to vascular remodeling, which in turn triggers PH[34,35]. Additionally, HCM not only affects the left ventricle but may also impact the right ventricle, which undergoes hypertrophy and functional impairment in response to increased afterload, thereby further exacerbating the condition of PH[29,36]. However, the current research on the relationship between PH and HCM patients is still relatively limited. Therefore, it is necessary to conduct further, larger-scale studies to explore the pathophysiology of precapillary and postcapillary PH and its impact on HCM.

Although RHC is regarded as the gold standard for diagnosing PAH. In clinical practice, echocardiography is widely used due to its non-invasive nature, repeatability and wide accessibility, especially in resource-limited circumstances[37]. But studies have shown that the estimated values by echocardiography may be influenced by various factors, including the patient's position, the operator's level of echocardiography technique, and changes in cardiac structure, etc[37]. These factors may result in false positive or false negative results, thereby affecting the diagnostic accuracy of PAH.

Also, studies have shown that when tricuspid regurgitation jets are fully visible, there is no difference in the correlation between sPAP displayed by echocardiography and RHC, nor is there any difference in the diagnostic accuracy of PH by echocardiography[37–39]. But the accuracy of echocardiography in diagnosing PAH is limited, with an overall sensitivity of 83 % (95 % CI 73 – 90) and a specificity of 72 % (95 % CI 53–85)[37]. In the subgroup analysis with a cutoff value of 40 mmHg, the overall sensitivity was 76 % (95 % CI 64–85), and the overall specificity was 58 % (95 % CI 36 – 77)[40–45]. Therefore, when using sPAP $\geq$ 40 mmHg as the threshold, the diagnostic accuracy of echocardiography for PAH is limited.

In our study, PASP $\geq$ 40 mmHg was chosen as the definition of PH mainly based on the operability and clinical practicability of echocardiography. PH is estimated by TRV and is widely used in clinical practice. In contrast, mPAP is directly measured by RHC and is generally regarded as a more accurate standard[46]. According to current guidelines, mPAP $\geq$ 20 mmHg is defined as the diagnostic criterion for PH[6,46]. This standard reflects the average level of PAP, while PASP represents the instantaneous pressure during systole. Due to the different measurement methods and clinical significance of these two parameters, the threshold values differ. PASP $\geq$ 40 mmHg is generally regarded as a relatively high-pressure level and may correspond to mPAP $\geq$ 20 mmHg in some cases, but they are not always completely consistent[47]. Therefore, to enhance the overall diagnostic accuracy of echocardiography for PH, it is recommended to conduct a comprehensive assessment by integrating clinical background, the prevalence of PH in the patient population, and other right ventricular echocardiographic parameters. Despite its limitations, echocardiography remains a useful non-invasive tool for the initial screening of potential PAP and cardiac anatomical and functional abnormalities in patients suspected of having PH.

4.1. Study limitations

There are several limitations to this study. First, we did not conduct a quantitative analysis of PH, so we cannot explore the relationship between PH as a continuous variable and the prognosis of HCM. Second, due to the limited number of patients with PH, we were unable to assess the prognostic differences between PH and subgroups of HCM. Third, this is a multicenter cohort study of HCM, and the time span for the collected data varies significantly, so there may be a certain degree of heterogeneity in data from different hospitals. Finally, the present study

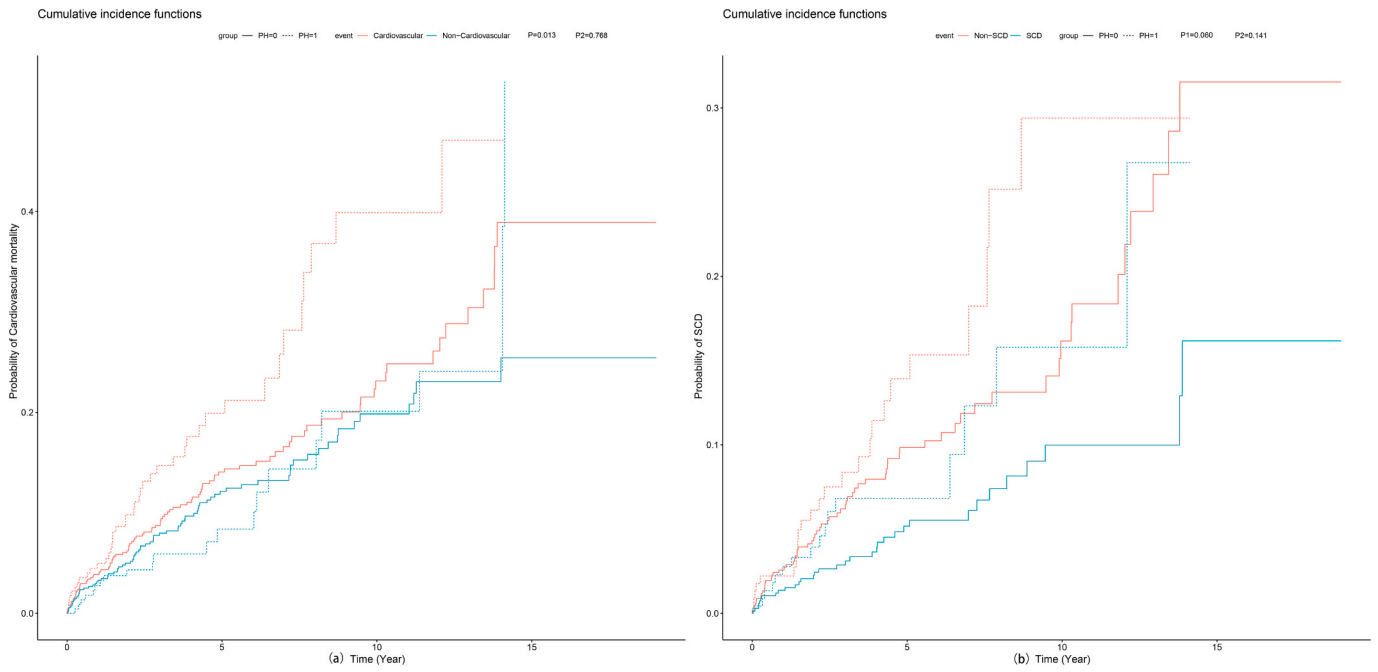

Fig. 3. Univariate Competing risk regression model of Cardiovascular and SCD. a)Competing risk regression analysis of cardiovascular mortality vs non-cardiovascular mortality, b)Competing risk regression analysis of SCD vs non-SCD.

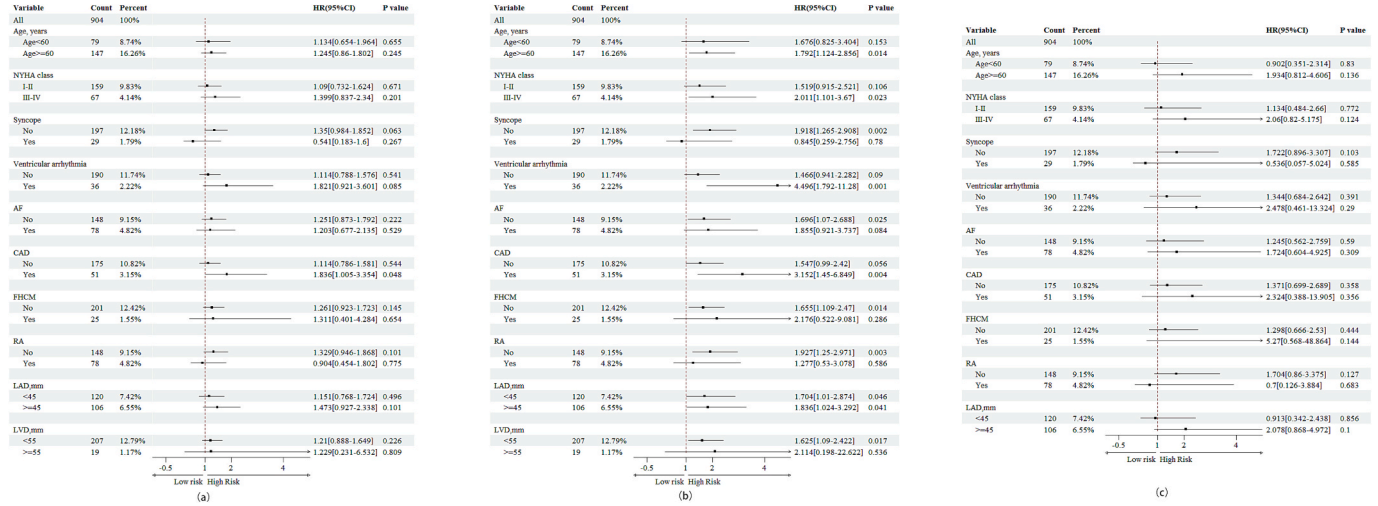

Fig. 4. Forest plot for subgroup analysis. a)All-cause mortality, b)Cardiovascular mortality, c)SCD.

was a retrospective cohort. Although PH was mainly estimated by the TRV, there might be human measurement differences in echocardiographic assessment among different centers, thereby introducing potential bias.

5. Conclusion

Patients with HCM who also have PH are at increased risk of cardiovascular mortality and SCD, and there is a similar trend for all-cause mortality. Furthermore, PH has been identified as an independent risk predictor of cardiovascular mortality.

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CRediT authorship contribution statement

Huihui Ma: Writing – original draft, Data curation. **Fengcheng Xu:** Data curation. **Lei Liu:** Methodology. **Hong Kong:** Formal analysis. **Rong Luo:** Data curation. **Mingjiang Liu:** Project administration. **Tianhu Liu:** Writing – review & editing, Project administration. **Xiaoping Li:** Writing – review & editing, Project administration, Data curation.

Author Contribution

Huihui Ma, Fengcheng Xu, Xiaoping Li and Tianhu Liu designed the study, interpreted the data. Huihui Ma, Fengcheng Xu responsible for patient follow-up and Huihui Ma compiled the data and wrote the

manuscript. Lei Liu carried out the descriptive statistical analysis. Mingjiang Liu, Hong Kong and Rong Luo critically reviewed the manuscript; Tianhu Liu and Xiaoping Li took full responsibility for its content. All authors read and approved the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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