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Original Research

Prevalence and significance of pulmonary hypertension among hospitalized patients with left heart disease

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ABSTRACT

Background: Pulmonary hypertension associated with left heart disease (PH-LHD) prevalence ranges significantly across studies with limited real-world evidence.
Objectives: To investigate the prevalence and prognostic influence of PH-LHD in a nationwide sample.
Methods: Using the 2018 US Nationwide Inpatient Sample we calculated the prevalence of PH across heart failure (HF), cardiomyopathies, aortic, and mitral valve disease. We used logistic regression to assess the impact of PH on LHD and to find significant contributors to in-hospital mortality in the PH-LHD population.
Results: Among 6,270,625 hospitalizations with LHD, 801,535 (12.8 %) had a secondary PH diagnosis. PH-LHD prevalence was 17.2 % in HF with preserved ejection fraction (HFpEF), 11.8 % in HF with reduced ejection fraction (HFrEF), 16.8 % in dilated cardiomyopathy, 12.6 % in hypertrophic cardiomyopathy, 18.7 % in mitral regurgitation, 28.5 % in mitral stenosis, 13.5 % in aortic stenosis, and 13.9 % in aortic regurgitation. PH was associated with increased in-hospital mortality in HFpEF (OR 1.23; 95%CI 1.17–1.28), hypertrophic cardiomyopathy (1.42; 1.06–1.89), mitral regurgitation (1.17; 1.07–1.28), and aortic stenosis (1.14; 1.04–1.26), but not in HFrEF (1.04; 0.99–1.10), or dilated cardiomyopathy (1.13; 0.99–1.29). Among PH-LHD, in-hospital mortality was associated with age, atrial fibrillation/flutter, cancer, and acute cardiac (acute right HF, myocardial infarction, ventricular arrhythmia), or extra-cardiac (stroke, sepsis, pneumonia, acute renal failure, venous thromboembolism) diagnoses.
Conclusion: In a nationwide inpatient analysis the prevalence of PH-LHD was lower than previously reported indicating reduced recognition of this disease in real world clinical practice. The diagnosis of PH-LHD was associated with worse fatality rates across all forms of LHD, except for HFrEF.

1. Introduction

Pulmonary hypertension associated with left heart disease (PH-LHD) is by far the most prevalent type of PH, accounting for 60–85 % of all PH cases [1]. PH can be manifested across a wide array of LHD, including heart failure (HF) with reduced ejection fraction (HFrEF) and preserved EF (HFpEF), primary cardiomyopathies, and/or left-sided valvular heart disease. The occurrence of PH, right ventricular dysfunction and hemodynamic deterioration are associated with disease progression, decrease exercise tolerance, low quality of life and worse morbidity and mortality among patients with various types of LHD [2–4]. However, the prevalence of PH as a sequela of LHD is difficult to assess and ranges significantly across observational studies, due to differences among definitions, measurement methods, and included populations. In particular, the prevalence of PH in HFrEF may vary between 40 % and 72 %, in HFpEF between 36 % and 83 %, in severe aortic stenosis up to 65 %, while it may potentially affect all patients with severe mitral stenosis [5]. Employing large administrative databases, such as the US Nationwide Inpatient Sample, could provide valuable insight on the

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Abbreviations

ICD	International Classification of Diseases
IQR	interquartile range
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
NIS	Nationwide Inpatient Sample
LHD	left heart disease
PH	pulmonary hypertension

epidemiology of PH-LHD, since it encompasses an unselected population of hospitalized patients with LHD and reflects 'real-world' practice.

Aim of this analysis is to assess the prevalence of PH-LHD across different types of LHD in a large sample of hospitalized patients. A further aim is to quantify the prognostic effect of secondary PH on the underlying LHD, as well as to identify factors for increased in-hospital mortality among patients with PH-LHD.

2. Methods

We used the Nationwide Inpatient Sample (NIS) database in 2018, as provided by the Agency for Healthcare Research and Quality. This database consists the largest publicly available all-payer inpatient healthcare database in the United States (US) and is developed for the Healthcare Cost and Utilization Project (HCUP). The NIS contains a 20 % stratified sample of discharges from US hospitals (excluding rehabilitation and long-term acute care hospitals) that participate in the HCUP representing up to 97 % of the US population. No institutional review board approval is required for the analysis of the database since it contains only de-identified data. The HCUP NIS Database Documentation website (www.hcup-us.ahrq.gov) provides additional information on the NIS.

2.1. Study population and data definition

The 2018 NIS database includes 40 diagnosis and 25 procedure variables for each discharge record, which are coded according to the 10th revision of the International Classification of Diseases (ICD-10-CM for diagnoses and ICD-10-PCS for procedures). We identified all hospitalizations of adult (≥18 years) patients with a discharge diagnosis of LHD, and in particular HF (ICD-10-CM I50.*, excluding right HF diagnosis), cardiomyopathies (ICD-10-CM I42.*, I43.*), mitral valve disease (ICD-10-CM I34.*, I05.*), and aortic valve disease (ICD-10-CM I35.*, I06.*). Further, HF diagnosis was characterized as systolic (HFrEF), diastolic (HFpEF), combined systolic/diastolic, and end-stage HF, cardiomyopathies were characterized as dilated (DCM), hypertrophic (HCM), or other (such as restrictive, alcoholic, due to drugs or external agents, metabolic, and secondary to malignancy among others), while mitral valve and aortic valve disease was characterized as regurgitation or stenosis. We defined the presence of PH-LHD in hospitalizations with an additional diagnosis of ICD-10-CM I27.20, I27.21, I27.22, and I27.29 codes. These ICD-10-CM codes for secondary PH were first introduced and have been effective as of October 2017.

In order to reduce misclassification bias, hospitalizations with an additional diagnosis of primary PH (ICD-10-CM I27.0), PH associated with chronic lung disease (PH-CLD, ICD-10-CM I27.23), and chronic thromboembolic pulmonary hypertension (ICD-10-CM I27.24) were not defined as having PH secondary to LHD (PH-LHD) even if they had a diagnosis code among ICD-10-CM I27.20, I27.21, I27.22, and I27.29. To that end, we additionally performed two sensitivity analyses: (i) excluding patients with a diagnosis of chronic obstructive pulmonary disease (COPD, ICD-10-CM J40.*, J41.*, J42.*, J43.*, J44.*) or interstitial lung disease (ILD, ICD-10-CM J84.*, J70.3), considering that they could be causes of secondary PH apart from LHD (coded with the "generic" I27.20, I27.21, I27.29 ICD-10-CM codes), and (ii) including only patients with the specific diagnosis of PH due to LHD (ICD-10-CM I27.22).

The ICD-10-CM codes used for the variable definitions, including comorbidities (hypertension, coronary artery disease, diabetes mellitus, obesity, atrial fibrillation, chronic pulmonary disease, renal disease, cancer, dementia) and acute diagnoses (acute HF, myocardial infarction, ventricular tachyarrhythmia, acute ischemic stroke, acute renal failure, sepsis, pneumonia, venous thromboembolism), are presented in Supplementary Table 1.

2.2. Statistical analysis

Proportions of missing data were below 3 % for all variables and we performed a complete case analysis assuming that the missing data were missing at random. Descriptive statistics of categorical variables are reported as counts and percentages, while continuous variables as medians and interquartile range (IQR). Logistic regression was used to calculate odds ratios of all-cause in-hospital mortality based on the presence of PH for each of the left heart diseases defined above. In addition, logistic regression was used to identify variables associated with increased in-hospital mortality in the subgroup of patients with PH-LHD. All models were adjusted for age, sex, comorbidities, and acute in-hospital diagnoses. The discharge-level weights provided in the HCUP database were applied to produce national estimates for the descriptive and inferential analyses. Clustered covariance estimation was used to compute clustered confidence intervals in order to take into account the stratification and hospitals defining the clusters. A two-sided p-value <0.05 indicated statistical significance. R (R Project for Statistical Computing, version 4.1.2.) and packages *tidyverse, survey, sandwich, forplo* were used for the statistical analysis and figure creation.

3. Results

We identified 6,270,625 hospitalizations of patients with different types of LHD in the US during 2018. Among them 801,535 were diagnosed with secondary PH; thus, the diagnosis of PH-LHD was present in 12.8 %. Patients with PH were older, more likely women, and showed a higher prevalence of atrial fibrillation/flutter, obesity, chronic pulmonary disease, and renal disease compared to their counterparts without PH (Table 1). Of cardiac diagnoses, acute left HF was the most frequent reason for hospitalization among patients with secondary PH, followed by myocardial infarction and ventricular tachycardia, while the prevalence of acute right HF was low (1.1 %) (Table 2). Of extra-cardiac causes acute renal failure, pneumonia, and sepsis were the most commonly reported reasons of hospitalization (Table 2). Of patients, 2,100,760 (33.5 %) and 123,290 (2.0 %) were also diagnosed with COPD and ILD, respectively. The baseline characteristics of patients without COPD/ILD according to the presence of secondary PH, as well as the reasons for hospitalization are presented in Supplementary Tables 2 and 3

Fig. 1 graphically depicts the prevalence of secondary PH among patients with different types of LHD. The prevalence of secondary PH in patients with HF was 15.0 %. Among the HF subtypes, secondary PH was more prevalent in diastolic HF (17.2 %) and combined systolic/diastolic HF (18.5 %) than in systolic HF (11.8 %). Among patients with cardiomyopathies the prevalence of secondary PH was 14.3 %. This percentage was higher in patients with DCM (16.8 %), as compared with patients with HCM (12.6 %), or other cardiomyopathy (13.7 %). In valvular heart disease, patients with mitral valve disease showed higher prevalence of secondary PH than patients with aortic valve disease (19.2 % vs 13.5 %). The prevalence of secondary PH was the highest among patients with mitral stenosis (28.5 %), whilst it was lower among patients with aortic valve stenosis (13.5 %).

Case fatality rates across patients with LHD are presented in

Table 1
Baseline characteristics of patients with left heart disease according to the presence of secondary pulmonary hypertension.

Characteristic	Secondary PH N = 801,535	No secondary PH N = 5,469,090
Age, years in median (IQR)	75 (64, 84)	72 (62, 82)
Women	451,460 (56.3 %)	2,604,165 (47.6 %)
Race		
White	535,145 (68.3 %)	3,785,355 (70.8 %)
Black	149,645 (19.1 %)	868,365 (16.2 %)
Hispanic	60,350 (7.7 %)	433,755 (8.1 %)
Asian/Pacific Islander	17,370 (2.2 %)	111,910 (2.1 %)
Native American	4200 (0.5 %)	29,555 (0.6 %)
Other	16,630 (2.1 %)	121,755 (2.3 %)
Comorbidities		
Hypertension	718,925 (89.7 %)	4,777,370 (87.4 %)
Atrial fibrillation/flutter	429,805 (53.6 %)	2,224,260 (40.7 %)
Coronary artery disease	419,015 (52.3 %)	2,895,615 (53.0 %)
Diabetes mellitus	356,855 (44.5 %)	2,486,745 (45.5 %)
Obesity	218,240 (27.2 %)	1,242,325 (22.7 %)
Chronic pulmonary disease	372,300 (46.5 %)	2,044,955 (37.4 %)
Renal disease	397,655 (49.6 %)	2,229,245 (40.8 %)
Cancer	136,425 (17.0 %)	996,480 (18.2 %)
Cerebrovascular disease	62,155 (7.8 %)	545,440 (10.0 %)
Dementia	71,430 (8.9 %)	569,455 (10.0 %)
Left heart disease		
Systolic heart failure	220,555 (27.5 %)	1,647,445 (30.1 %)
Diastolic heart failure	357,410 (44.6 %)	1,726,150 (31.6 %)
Combined systolic/diastolic heart failure	116,680 (14.6 %)	514,770 (9.4 %)
End-stage heart failure	8785 (1.1 %)	24,960 (0.5 %)
Dilated cardiomyopathy	37,295 (4.7 %)	184,490 (3.4 %)
Hypertrophic cardiomyopathy	7000 (0.9 %)	48,420 (0.9 %)
Mitral valve regurgitation	97,365 (12.2 %)	422,175 (7.7 %)
Mitral valve stenosis	9035 (1.1 %)	22,685 (0.4 %)
Aortic valve regurgitation	15,725 (2.0 %)	97,070 (1.8 %)
Aortic valve stenosis	64,470 (8.0 %)	412,590 (7.5 %)

IQR: interquartile range; PH: pulmonary hypertension.

Table 2
Reasons for hospitalization among patients with pulmonary hypertension associated with left heart disease.

Characteristic	N = 801,535 [1]
Cardiac causes	
Acute left heart failure	413,875 (52 %)
Myocardial infarction	69,440 (8.7 %)
Ventricular tachycardia	45,345 (5.7 %)
Acute right heart failure	9180 (1.1 %)
Infective endocarditis	6625 (0.8 %)
Acute myocarditis	250 (<0.1 %)
Acute pericarditis	645 (<0.1 %)
Extra-cardiac causes	
Acute renal failure	278,945 (35 %)
Pneumonia	140,910 (18 %)
Sepsis	86,395 (11 %)
Venous thromboembolism	24,300 (3.0 %)
Acute ischemic stroke	15,195 (1.9 %)

Supplementary Table 4. Secondary PH had an unfavorable effect on in-hospital mortality among most types of LHD (Fig. 2). Among different types of HF, patients with secondary PH and diastolic HF had particularly high odds of in-hospital mortality (OR 1.23 95 % CI 1.17–1.28), in contrast to patients with systolic HF (OR 1.04 95 % CI 0.99–1.10). Similarly, the effect of secondary PH on in-hospital mortality was stronger in patients with HCM (OR 1.42, 95 % CI 1.06–1.89) compared to patients with DCM (OR 1.13, 95 % CI 0.99–1.29). In valvular heart disease, secondary PH was associated with increased mortality among patients with mitral regurgitation and aortic stenosis, but not among patients with mitral stenosis and aortic regurgitation, possibly due to limited power.

Among patients with PH-LHD, significant predictors of all-cause in-hospital mortality included age, atrial fibrillation/flutter, cancer, and acute cardiac (acute right HF, myocardial infarction, ventricular arrhythmia), or extra-cardiac (stroke, sepsis, pneumonia, acute renal failure, venous thromboembolism) diagnoses (Fig. 3). An acute left heart failure diagnosis as opposing to all other diagnoses was associated with a favorable outcome regarding in-hospital mortality among patients with PH-LHD (OR 0.94, 95 % CI 0.89–0.98).

The results of all analyses remained unchanged in the sensitivity analyses, which are presented in Supplementary Figs. 1–6.

4. Discussion

In this epidemiological analysis of a large administrative database of inpatients with LHD, PH was prevalent in 15 % in heart failure, 14.3 % in cardiomyopathies, 19.2 % in mitral valve disease, and 13.5 % in aortic valve disease. These figures are substantially smaller than the ones previously reported in the literature [6]. In particular, previous studies which employed right heart catheterization (RHC) to define the presence of PH in patients with left heart disease have shown: a prevalence in the range of 62–77 % in HFrEF [7,8], 47–62 % in HFpEF [9,10], while regarding valvular disease prevalence has been shown to range from 36 % to 62 % in aortic stenosis [11,12] and 53 % up to 85 % in mitral regurgitation [13,14], according to the severity of the valvulopathy. There could be two main reasons for the discrepancies in PH prevalence between previous studies and our study. First, the observations in the literature are mostly obtained in a unique disease severity stage in each study and these stages differ widely across studies. To that end, employing a large administrative database such as the NIS offers an advantage in investigating the PH prevalence across the spectrum of LHD severity, since all stages of the underlying disease are captured reducing the selection bias. However, no conclusions on PH prevalence across the spectrum of more mild or more serious forms of LHD can be drawn. It should also be noted here that this prevalence refers to hospitalized patients who might have proportionally greater chance for comorbidities and more severe forms of disease compared to outpatients. Second, the standards for diagnosing PH by RHC or echocardiography are not uniform among observational studies, since there is not an established, widely acceptable, reproducible definition of the disease. In a sample of patients from the National Echocardiographic Database of Australia, 52.5 %, 59.6 %, and 44.4 % had an estimated right ventricular systolic pressure over 40 mmHg defining the presence of PH in aortic stenosis, mitral regurgitation, and aortic regurgitation (of moderate/severe grade in all diseases), respectively [15–17]. On the other hand, in more recent studies using RHC, the prevalence of PH in HFpEF patients after HF treatment was 27 % [18], while another found a PH prevalence of 44.8 % among HF patients [19]. The use of ICD-10 diagnosis codes to define the presence of PH in an unselected, nationwide population reflects a real-world prevalence of PH in hospitalized patients with LHD and although it ensures that the most serious PH cases are captured, milder forms of PH are likely to be underreported. Thus, the results of our epidemiological analysis could indicate both a reduced recognition and diagnosis of PH across several forms of LHD in a real-world population and a selection bias of previous observational studies.

Another novel observation in our study is that the presence of PH was significantly associated with increased in-hospital mortality in HFpEF patients, but not in HFrEF patients. This pattern was also observed in the primary cardiomyopathies: PH in DCM was not associated with increased in-hospital mortality, in contrast to PH in HCM. It has long been observed by community-based studies that the existence of secondary PH is associated with worse prognosis in HF [20,21]. In some patients the presence of PH could be dynamic, as such described in the initial echocardiographic examination before complete fluid decongestion during the hospitalization. Concerning HFrEF there are also some previous data indicating that right ventricular function has a particular importance in prognosis since patients with preserved right ventricular

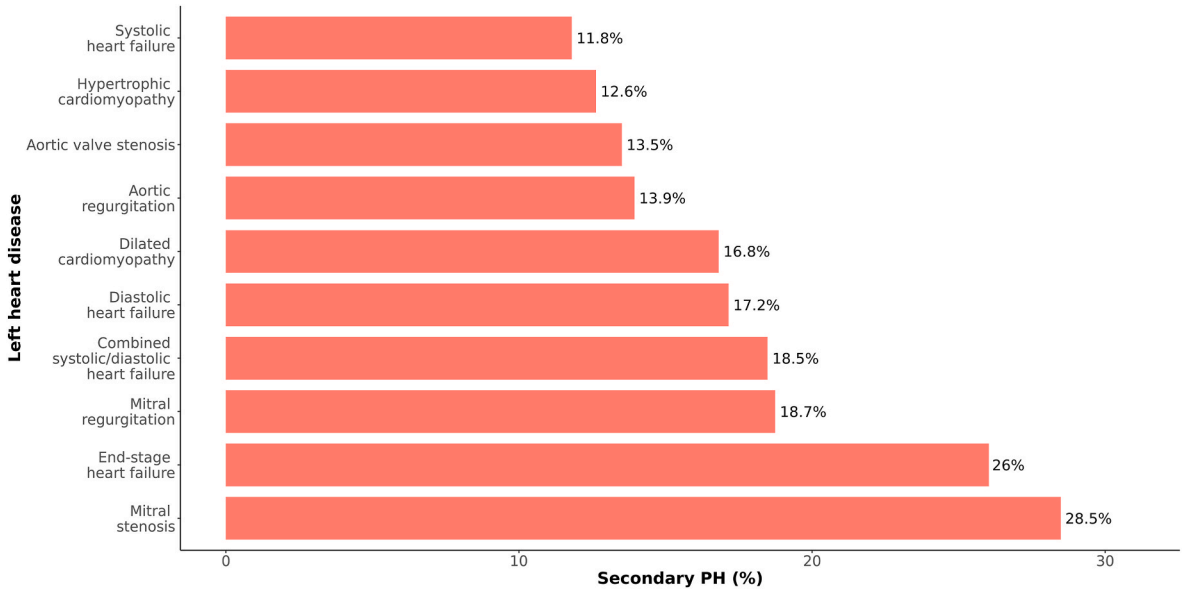

Fig. 1. Proportion of patients with secondary pulmonary hypertension (PH) among patients with different types of left heart disease.

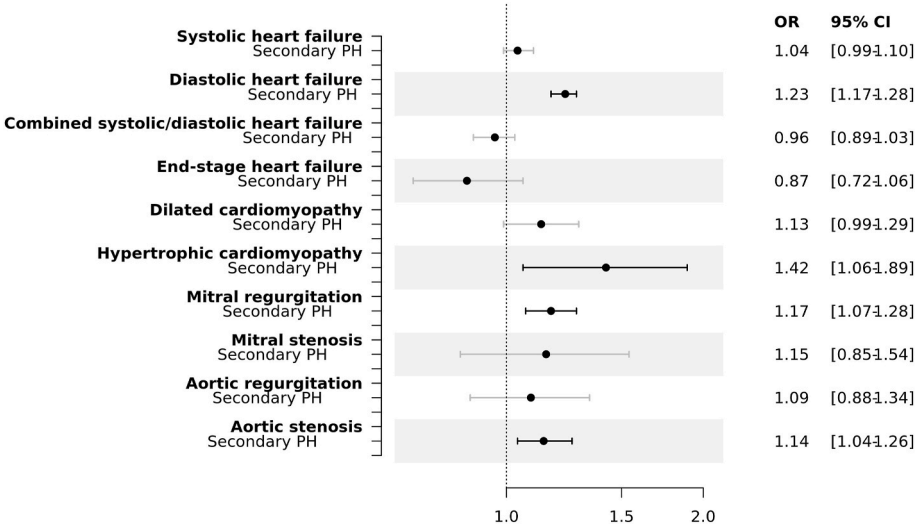

Fig. 2. Forest plot depicting the effect of secondary pulmonary hypertension (PH) on all-cause in-hospital mortality among patients with different types of left heart disease (LHD). Each type of LHD has been isolated and tested in a separate logistic regression model adjusting for age, sex, comorbidities (hypertension, coronary artery disease, diabetes mellitus, obesity, atrial fibrillation, chronic pulmonary disease, renal disease, cancer, dementia) and acute diagnoses (acute heart failure, myocardial infarction, ventricular tachyarrhythmia, acute ischemic stroke, acute renal failure, sepsis, pneumonia, venous thromboembolism).

EF in PH had similar prognosis with patients without PH [7]. In addition, combined pre- and post-capillary PH mostly in HFpEF, but also in HFrEF, has a detrimental effect on functional capacity and prognosis compared to isolated post-capillary PH [22–24], but specifically addressing the pulmonary vasculature in HFpEF or HFrEF stable out-patients has not been effective in multiple trials [25–28]. Furthermore, it has to be mentioned, that unlike HFrEF, there is a lack of evidence-based pharmacotherapies for HFpEF. Guideline-recommended pharmaco-therapies for HFrEF such as ACEIs/ARBs, ARNI, β-blockers, and/or MRAs may exert favorable effects on pulmonary hemodynamics [29,30] and are not without limitations for HFpEF [31]; which can lead to an unfavored congestion status and long-term prognosis in this special population with secondary PH.

PH was a significant predictor of in-hospital mortality in patients with aortic stenosis and mitral regurgitation. Our findings are confirmed by numerous studies, also performed in the era of the interventional treatment of valve diseases. For instance, PH is associated with worse long-term prognosis in patients undergoing transcatheter aortic valve replacement for symptomatic aortic stenosis [32,33] or transcatheter mitral valve repair for secondary mitral regurgitation [34].

All acute diagnoses were associated with worse in-hospital mortality among patients with PH-LHD as expected. Acute right heart failure was not as common as acute left heart failure among these patients (52 % vs 1.1 %); however, it was associated with a 2-fold increase in in-hospital mortality. Right ventriculoarterial coupling has previously been shown to have particular prognostic importance in PH-LHD [2]. On the other hand, acute left heart failure was not associated with worse outcomes: this attenuated effect could be possibly driven by hospitalizations caused by mild decompensations of LHD rapidly treated with intrave-nous diuretics.

5. Limitations

This study has several limitations. The main limitation is the PH

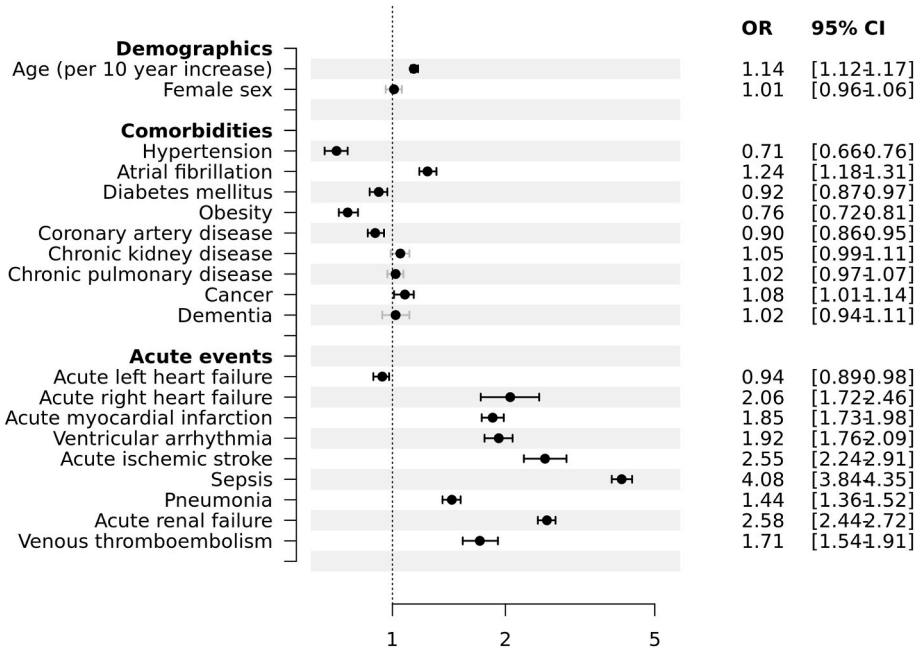

Fig. 3. Forest plot depicting the effect of demographics, comorbidities, and acute diagnoses on all-cause in-hospital mortality among patients with secondary pulmonary hypertension (PH) associated with left heart disease (LHD).

diagnosis, since it cannot be ascertained that this was made through RHC or echocardiography, which is the gold standard. Timing of measurement of the right heart pressures and the mode in which they were assessed was not possible to be ascertained. Nevertheless, we regard that the registration of PH diagnosis should be specific enough (the most severe PH cases would be registered as such), even if some diagnosed PH cases would not have been registered (reduced sensitivity). Furthermore, we could not discriminate between groups of the severity of PH, whether the PH diagnosis concerns isolated post-capillary PH or combined pre- and post-capillary PH, as well as of the severity of the underlying LHD. This analysis refers to hospitalized patients and findings may cannot be extrapolated for all outpatients. In addition, it would not be possible to discriminate whether the diagnosis of PH was an acute finding during the hospitalization (that it subsequently normalized after treatment of the underlying LHD) or a persistent characteristic of the underlying chronic LHD. Moreover, although we have undertaken a sensitivity analysis excluding patients with COPD or ILD and another one including only patients with the specific PH-LHD code, we cannot be certain of the cause of secondary PH in patients with concurrent LHD and lung disease. The patients' medication was not available through the NIS database. Also, the classification of comorbidities and acute diagnoses was defined according to ICD-10 codes, therefore misclassification is likely. The NIS contains data on hospitalizations and thus patient-level data are not available for analysis. Last but not least, this study is observational and thus no causation can be ascertained regarding the inferential analysis of in-hospital mortality; the results are hypothesis generating.

6. Conclusion

In a nationwide analysis of hospitalized patients due to LHD the prevalence of PH was lower than previously reported indicating reduced recognition of this disease in real world clinical practice. The diagnosis of PH-LHD was associated with worse fatality rates across all forms of LHD, except for HFrEF. This finding should be further explored in future prospective studies.

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None to declare.

CRediT authorship contribution statement

Ioannis T. Farmakis: Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Lukas Hobohm:** Writing – original draft, Methodology, Conceptualization. **Luca Valerio:** Writing – review & editing, Validation. **Karsten Keller:** Writing – review & editing, Supervision. **Kai-Helge Schmidt:** Writing – review & editing, Validation. **Ralph Stephan von Bardeleben:** Writing – review & editing, Validation, Supervision. **Philipp Lurz:** Writing – review & editing, Validation, Supervision. **Stephan Rosenkranz:** Writing – review & editing, Supervision. **Stavros V. Konstantinides:** Writing – original draft, Validation, Conceptualization. **George Giannakoulas:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization.

Declaration of competing interest

LH received lecture/consultant fees from MSD and Actelion, outside the submitted work. SVB has served in unpaid trial activities for Abbott, Edwards Lifesciences, and University of Göttingen (IIT); and has served on an advisory or Speakers Bureau for Abbott Cardiovascular, Bioventrix, Boston Scientific, Cardiac Dimensions, Edwards Lifesciences, and Neochord. PL has received institutional fees and research grants from Abbott Vascular, Edwards Lifesciences, and ReCor, honoraria from Edwards Lifesciences, Abbott Medical, Innoventric, ReCor, Boehringer Ingelheim, Daiichi Sankyo and has stock options with Innoventric. SR reports grants or contracts from Actelion, AstraZeneca, Bayer, Janssen, and Novartis; consulting fees from Abbott, Acceleron, Actelion, Bayer, Janssen, MSD, Novartis, Pfizer, United Therapeutics, and Vifor; payment or honoraria from Actelion, Bayer, BMS, Ferrer, GSK, Janssen, MSD, Novartis, Pfizer, United Therapeutics, and Vifor. SVK reports institutional grants and personal lecture/advisory fees from Bayer AG, Daiichi Sankyo, and Boston Scientific; institutional grants from Inari Medical; and personal lecture/advisory fees from MSD and Bristol Myers Squibb/Pfizer. GG has received speaker or consulting fees from ELPEN

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None to declare.

Appendix A. Supplementary data

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