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Predictors of hospitalisations for heart failure and mortality in patients with pulmonary hypertension associated with left heart disease: a systematic review

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ABSTRACT

Objectives: Left heart disease (LHD) is the main cause of pulmonary hypertension (PH), but little is known regarding the predictors of adverse outcome of PH associated with LHD (PH-LHD). We conducted a systematic review to investigate the predictors of hospitalisations for heart failure and mortality in patients with PH-LHD.

Design: Systematic review.

Data sources: PubMed MEDLINE and SCOPUS from inception to August 2013 were searched, and citations identified via the ISI Web of Science.

Study selection: Studies that reported on hospitalisation and/or mortality in patients with PH-LHD were included if the age of participants was greater than 18 years and PH was diagnosed using Doppler echocardiography and/or right heart catheterisation. Two reviewers independently selected studies, assessed their quality and extracted relevant data.

Results: In all, 45 studies (38 from Europe and USA) were included among which 71.1% were of high quality. 39 studies were published between 2003 and 2013. The number of participants across studies ranged from 46 to 2385; the proportion of men from 21% to 91%; mean/median age from 63 to 82 years; and prevalence of PH from 7% to 83.3%. PH was consistently associated with increased mortality risk in all forms of LHD, except for aortic valve disease where findings were inconsistent. Six of the nine studies with data available on hospitalisations reported a significant adverse effect of PH on hospitalisation risk. Other predictors of adverse outcome were very broad and heterogeneous including right ventricular dysfunction, functional class, left ventricular function and presence of kidney disease.

Conclusions: PH is almost invariably associated with increased mortality risk in patients with LHD. However, effects on hospitalisation risk are yet to be fully characterised; while available evidence on the adverse effects of PH have been derived essentially from Caucasians.

Strengths and limitations of this study

- Our search strategy was likely limited by its focus on a full-report article published in English and French, and traceable via PubMed MEDLINE and/or SCOPUS.
- Important heterogeneity in the included studies precluded the pooling of data to perform a meta-analysis.
- This is the first systematic review on determinants of hospitalisations and mortality in patients with pulmonary hypertension associated with left heart disease, which presents the available up-to-date and high-quality evidence on the subject matter.

INTRODUCTION

Pulmonary hypertension (PH) describes a group of disorders resulting from an increase in pulmonary vascular resistance, pulmonary blood flow, pulmonary venous pressure or a combination of these features.[1] Based on shared pathological and haemodynamic characteristics, and therapeutic approaches, five clinical groups of PH have been distinguished[2] with PH associated with left heart disease (PH-LHD) or PH group 2 credited to be the most frequent form of PH in contemporary clinical settings.[3] Indeed, PH is common in patients with LHD, where it often reflects the background LHD, but has also been reported to be a maker of disease severity and unfavourable prognosis. Patients with PH-LHD have more severe symptoms, worse tolerance to effort, experience higher hospitalisation rates and are more likely to receive an indication of the need for cardiac transplant[3] with major implications for the quality of life of patients and healthcare costs. Several studies have reported PH-LHD

to be associated with increased mortality, both in patients with systolic dysfunction and those with preserved left ventricular ejection fraction (LVEF).[3–6] Furthermore, the presence of preoperative PH has been associated with poor outcomes in patients with valve disease undergoing valve replacement.[7] However, there are still several gaps in the existing evidence, including the prevalence of PH-LHD and measurement of the true impact of PH on symptoms and outcome of various LHDs. Equally, little is known regarding the effect of the severity of PH on hospitalisations, rehospitalisations and death, and their co-factors in patients with LHD. Considering the number of recent advances in the management of PH, it is likely that a better understanding of the impact of PH-LHD on major outcomes might assist the clinical management of patients with PH.

We performed a systematic review of the existing literature to determine the predictors of hospitalisation and mortality in patients with PH secondary to LHDs including systolic dysfunction, diastolic dysfunction and/or valve disease. Additionally, we aimed to assess whether the severity of PH affects the risk of the two outcomes.

METHODS

We searched MEDLINE via PubMed and SCOPUS from inception to August 2013 for all published studies on PH-LHD, using a combination of key words described in the online supplementary box 1. All searches were restricted to studies in humans published in 'English' or 'French' languages. In addition, we manually searched the reference lists of eligible studies and relevant reviews, and traced studies that had cited them through the ISI Web of Science for any relevant published and unpublished data. Two independent reviewers (AD and APK) performed the study selection, data extraction and quality assessment; and disagreements were resolved by consensus or consulting a third reviewer (KS).

Studies that reported on hospitalisation and/or mortality in patients with PH-LHD were included if the following criteria were met: (1) age of participants greater than 18 years; (2) Right ventricular systolic pressure (RVSP) measured by transthoracic Doppler echocardiography (DE) and calculated from the maximum tricuspid regurgitation jet velocity using the modified Bernoulli equation ($4v^2$) and adding right atrial pressure (RAP). RAP could be a fixed value from 5 to 10 mm Hg, could have been estimated clinically using the jugular venous pressure (JVP), or estimated by measuring the inferior vena cava size and change with spontaneous respiration using echocardiography; and/or (3) mean pulmonary artery pressure (mPAP) measured by right heart catheterisation (RHC) or by DE. We excluded narrative reviews and case series. Studies on persistent PH following heart transplantation were not included because of the complexity of the classification of PH in this population.

The following variables were extracted from each study: publication year, country of origin of the study, study design, study population's demographics, the mean/median follow-up duration, the outcome predicted, the proportion of measurable RVSP, the mean/median baseline RVSP or mPAP, the prevalence of PH, the readmission rate, the mortality rate with odds ratio (OR) or hazard ratio (HR) for PH where reported and the predictors of outcome including the tricuspid annular plan systolic excursion (TAPSE). One study[8] reported the effect of PH in relation with survival. Effects on mortality were obtained by taking the inverse of the HR for survival.

Quality assessment

The methodological quality of the selected studies was assessed using the Quality In Prognosis Studies (QUIPS) tool, designed for systematic reviews of prognostic studies through an international expert consensus (table 1).[52] The QUIPS contains six domains assessing the following: (1) bias due to patient selection; (2) attrition; (3) measurement of prognostic factors; (4) outcome measurement; (5) confounding on statistical analysis and reporting results; and (6) confounding on presentation. In prognosis studies designed to predict a specific outcome based on a combination of several possible prognostic factors, confounding is not an issue. Therefore, the items on confounding were considered irrelevant for our quality assessment. The remaining 17 items of the five categories each were scored to assess the quality of the included studies. For each study, the five domains were scored separately as high (+), moderate (±) or low (−) quality (ie, presenting a low, moderate or high risk of bias, respectively). To strengthen the discriminative capacity of the QUIPS, we used the scoring algorithm developed by de Jonge *et al*,[53] as explained, described in detail in the online supplementary table.

Data synthesis

Hospitalisations or rehospitalisations for heart failure and mortality identified by multivariable analysis in individual studies are presented (table 2), including their estimated effect size (eg, OR or HR) and 95% CI. Quantitative analysis of results was not done due to important heterogeneity in study design, study population, PH definition and measurement, outcome definitions in the studies and confounding or other types of prognostic factors. We have therefore presented a narrative summary of the available evidence (table 2).

RESULTS

Studies selection

Figure 1 presents a flow diagram for the study selection process. Of the 7550 citations identified through searches, 6255 titles were examined and 6083 were excluded on the basis of the title scanning. The remaining 172 abstracts were examined and 55 articles were

Table 1 Results of quality assessment of studies on mortality and readmissions for heart failure in patients with pulmonary hypertension associated with left heart disease

N	Study	Country/ethnicity	Design	Statistical methods	Study participation	Study attrition	Measurement of prognostic factors	Assessment of outcomes	Statistical analysis and presentation	Quality score (points)	Quality: +=high ±=moderate −=low
1	Merlos *et al* [9]	Spain	Prospective hospital based cohort	KM, Cox regression	13.5	15	10	15	15	68.5	+
2	Agarwal *et al* [10]	USA—ethnicity data in 98 patients (63% whites)	Retrospective hospital based cohort	KM, Cox regression	13.5	7.5	12.5	15	15	63.5	+
3	Agarwal [11]	USA—96% blacks	Prospective hospital based cohort	KM, Cox regression	12	10	10	15	15	62	+
4	Aronson *et al* [12]	USA	Prospective hospital based cohort	Cox regression	15	15	15	15	12.5	72.5	+
5	Bursi *et al* [13]	USA Caucasians and blacks	Prospective population based cohort study	KM, Logistic regression	15	12.5	12.5	12.5	15	65	+
6	Strange *et al* [14]	Armadale-Australia	Retrospective population based cohort	KM, Logistic and Cox regression	15	7.5	10	12.5	12.5	58.5	±
7	Mutlak *et al* [15]	USA	Prospective hospital based cohort	KM, Logistic and Cox regression, KM	13.5	15	10	15	15	69	+
8	Tatebe *et al* [16]	Japan	Prospective hospital based cohort	KM, Logistic and Cox regression	15	10	15	15	15	72.5	+
9	Adhyapak *et al* [8]	India	Prospective hospital based cohort	Cox regression	13.5	10	10	12.5	5	53.5	±
10	Stern *et al* [17]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	15	12.5	12.5	12.5	66	+
11	Lee *et al* [18]	Korea	Prospective hospital based cohort	KM, Cox regression	15	15	15	12.5	15	72.5	+
12	Møller *et al* [19]	USA	Prospective hospital based cohort	KM, Logistic regression	13.5	15	12.5	15	15	71	+
13	Cappola *et al* [20]	USA, 35% blacks and 65% whites	Prospective hospital based cohort	KM, Cox regression	13.5	7.5	12.5	15	15	62.5	+
14	Szwejkowski *et al* [21]	UK	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	61	+
15	Abramson *et al* [22]	USA	Prospective hospital based cohort	KM, Cox regression	12	15	10	15	12.5	64.5	+
16	Kjaergaard *et al* [23]	Denmark	Prospective hospital based cohort	KM, Cox regression	13.5	15	12.5	15	15	71	+
17	Shalaby *et al* [24]	USA, 95% Caucasians	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	15	15	15	71	+
18	Damy *et al* [25]	UK	Prospective hospital based cohort	KM, Logistic and Cox regression	15	10	15	15	15	70	+
19	Ristow *et al* [26]	USA	Prospective hospital based cohort	Logistic regression	13.5	12.5	10	15	5	48.5	±
20	Grigioni *et al* [27]	Italy	Retrospective cohort	KM, Logistic regression	13.5	12.5	12.5	15	15	68.5	±
21	Levine *et al* [28]	USA, mainly Caucasians (78.3%)	Retrospective cohort	No Logistic regression, no KM analysis	12	10	10	7.5	2.5	42	−
22	Lam *et al* [29]	USA	Prospective observational community based cohort	KM, Logistic regression	12	15	10	15	12.5	68	+
23	Khush *et al* [30]	Multicentric USA and Canada	Prospective cohort in the ESCAPE trial	KM	15	10	15	15	12.5	68.5	+

Continued

Table 1 Continued

N	Study	Country/ethnicity	Design	Statistical methods	Study participation	Study attrition	Measurement of prognostic factors	Assessment of outcomes	Statistical analysis and presentation	Quality score (points)	Quality: +=high ±=moderate −=low
24	Ghio *et al*[31]	Italy	Prospective cohort	KM, Cox regression	13.5	12.5	12.5	12.5	12.5	63.5	+
25	Wang *et al*[32]	China	Retrospective cohort	KM	12	12.5	12.5	12.5	5	54.5	±
26	Ghio *et al*[33]	Italy	Prospective cohort	KM, Cox and Logistic regression	13.5	10	10	15	15	63.5	+
27	Naidoo *et al*[34]	South Africa, Blacks	Retrospective cohort	No Logistic regression, no Kaplan Meier analysis	12	7.5	10	5	7.5	42	−
28	Fawzy *et al*[35]	Saudi Arabia	Prospective cohort	No Logistic regression, no Kaplan Meier	12	10	12.5	15	7.5	57	±
29	Roseli *et al*[36]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	63.5	±
30	Melby *et al*[37]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	10	15	15	66	+
31	Le Tourneau*et al*[38]	France, mainly Caucasians	Prospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	63.5	+
32	Parker *et al*[7]	USA	Retrospective hospital based cohort	KM, Cox regression	12	15	12.5	15	15	71	+
33	Kainuma *et al*[39]	Japan, Asians	Retrospective hospital based cohort	KM, Cox regression	10.5	10	12.5	12.5	10	55.5	±
34	Barbieri *et al*[40]	Multicentric (Europe and USA)	Prospective hospital based cohort	KM, Cox regression	13.5	15	12.5	15	15	71	+
35	Manners *et al*[41]	United Kingdom	Retrospective hospital based cohort	No regression analysis, no KM estimation	10.5	7.5	5	5	2.5	30.5	−
36	Malouf *et al*[42]	USA	Prospective hospital based cohort	KM, Cox and Logistic regression	10.5	10	10	15	12.5	58	+
37	Khandhar *et al*[43]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	61	±
38	Zuern *et al*[44]	Germany	Prospective hospital based cohort	KM, Cox regression	15	7.5	10	15	15	62.5	+
39	Ben-Dor *et al*[45]	USA	Prospective hospital based cohort	KM, Logistic regression	15	10	10	15	15	68	+
40	Yang *et al*[46]	USA	Retrospective hospital based cohort	KM, Cox and logistic regression	15	7.5	15	12.5	15	65	+
41	Nozohoor *et al*[47]	Sweden	Retrospective cohort	KM, Cox and Logistic regression	13.5	10	10	15	12.5	61	+
42	Ward and Hancock[48]	UK	Retrospective cohort	No KM, no Logistic or Cox regression	12	5	2.5	7.5	2.5	29.5	−
43	Ghoreishi *et al*[49]	USA	Retrospective cohort	KM, Cox and Logistic regression	15	10	10	10	15	60	+
44	Cam *et al*[50]	USA	Retrospective cohort	KM, Cox and Logistic regression	13.5	15	10	10	12.5	61	+
45	Pai *et al*[51]	USA	Retrospective cohort	KM, Cox and Logistic regression	15	10	10	10	15	60	+

KM, Kaplan Meier.

Table 2 Study characteristics of studies on mortality and readmissions for heart failure in patients with pulmonary hypertension associated with left heart disease

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Studies in patients with heart failure and cardiomyopathies														
Merlos *et al*, 2013[9]	RVSP >35 mm Hg	1210 consecutive patients with HF, stratified into normal (RVSP <35), mild (RVSP 36–45), moderate (RVSP 46–60) and severe PH (RVSP >60 mm Hg)	12	72.6 54.1%	All-cause mortality Cardiovascular deaths	41.5	46	35.2	NR	NR	4.89/10 persons-year in severe PH	NA	NR	OR for mild PH 1.6 (0.7 to 3.74), moderate PH 1.34 (0.54 to 3.16) and severe PH 2.57 (1.07 to 6.27)
Agawal *et al*, 2012[10]	RHC with mPAP >25 mm Hg	339 patients with PH and LHD, 90% with HFpEF, NYHA class NR	54.2	63 / 21%	All-cause mortality	NA	43	NA	NR	NR	2.9%	4.4%	6.8%	UTSW cohort HR 1.4 (1.1 to 1.9) and NU cohort HR 1.4 (1.1 to 1.7)
Agawal, 2012[11]	RVSP >35	288 patients undergoing haemodialysis stratified into PH and NPH- based on RVSP	25.8	56.5 vs 53.1 / 65 vs 63%	All-cause mortality	NA	44.7 vs 27.2	38	NR	NR	26.4 vs 24.5	48.3 vs 46.3	62.9 vs 56.3	HR 2.17 (1.31 to 3.61)
Aronson *et al*, 2011[12]	RHC with mPAP ≥25 mm Hg and mPCWP >15 mm Hg	242 patients with acute HF, divided in 3 groups, NPH, passive PH and reactive PH, NYHA class IV	6	61; 42%	All-cause mortality	NA	34 vs 38 vs 44	76.0	NR	8.6 vs 21 vs 48.3	NR	NR	NR	HR for passive PH 1.7 (0.6 to 4.5) and reactive PH 4.8 (2.1 to 17.5)
Bursi *et al*, 2012[13]	RVSP >35 mm Hg	1049 patients with HF stratified into tertiles of RVSP (<41, 41–54 and >54 mm Hg)	81	76; 49.3%	All-cause mortality	NR	48	79	NA	NR	4, 10, and 17% for tertiles 1, 2, and 3, respectively	8 vs 19 vs 28	46	HR for tertile 2: 1.45 (1.13 to 1.85) and tertile 3: 2.07 (1.62 to 2.64)
Strange *et al*, 2012[14]	RVSP >40 mm Hg	15633 echo screening, 636 PH group 2 stratified into 3 groups (group 1 RVSP <40 mm Hg, group 2 between 41 and 60 and group 3 >60 mm Hg)	83	79; 48%	All-cause mortality	NR	52	NR	NA	NR	NR	NR	Mean survival 4.2 years	NR
Mutlak *et al*, 2012[15]	RVSP >35 mm Hg	1054 patients with acute myocardial infarction divided into NPH and PH groups	12	60 vs 69; 77 vs 64%	Readmission for HF All-cause mortality	NR	32 vs 43	44.6	2.1 vs 9.2; OR 3.1 (1.87 to 5.14)	NR	NR	NR	NR	HR for readmission 3.1 (1.87 to 5.14)
Tatebe *et al*, 2012[16]	RHC with mPAP ≥25 mm Hg mPCWP >15 mm Hg	676 consecutive patients with chronic HF, NYHA class ≥2, stratified into 3 groups, NPH (mPAP <25), passive PH (PH with PVR ≥2.5 WU) or reactive PH (PH with PVR >2.5 WU)	31.2	64vs 64vs 63; 63vs 48vs 66%	All-cause mortality and readmission for HF	NR	17 vs 30 vs 35 in NPH, passive PH and reactive PH, respectively	23	NR	NR	24.5 vs 18 vs 18.9% in NPH, passive and reactive PH, respectively	52.5 vs 50 vs 60.3% in NPH, passive and reactive PH, respectively	71.0 vs 77 vs 79.3 in NPH, passive PH and reactive PH, respectively	HR for reactive PH group 1.18 (1.03 to 1.35)
Adhyapak, 2010[8]	Echocardiography with mPAP >25 mm Hg	147 patients with HF stratified into: group 1, normal PASP/preserved RV function; group 2, normal PASP/RV dysfunction; group 3, high PASP/preserved RV function; and group 4, high PASP/RV dysfunction	11.2	54 91.8%	Cardiac death Readmissions	NR	Group 1 20±5 group 2 24.8 ±0.4 group 3 56.8±6 and group 4 58.9 ±8.8	53.7	19.7, OR and CI NR		Overall 5.1 at 11.2 months, 4.5 in group 3 vs 8.8 in group 4	NA	NA	HR in PH 2.27 (1.09 to 3.57)

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Stern *et al*, 2007[17]	Echocardiography but criteria for PH not reported	68 patients needing cardiac resynchronisation stratified into group 1 (RVSP ≥ 50 mm Hg, n=27) and group 2 (RVSP <50 mm Hg, n=41)	7.1	70 64.7%	Composite of hospitalisation for HF and all-cause mortality	NR	Group 1 39.7 ±6.7 and group 2 60.2±9.2	NR	NR	NR	Increased mortality in patients with RVSP ≥50 mm Hg	NR	NR	HR of 2.0 (1.2 to 5.5) for RVSP ≥50
Lee *et al*, 2010[18]	RVSP >39 mm Hg	813 patients with TR stratified into two groups based on the RVSP <39 mm Hg (group 1, n=530) and RVSP ≥39 mm Hg (group 2, n=283)	58.8	64 42.5%	All-cause mortality	NR	37.1 in patients who survived vs 43.8 in patients who died	NR	NR	NR	NR	10.5 vs 21.9	5-year survival rates 61.0 and 80.6% group 2 vs group 1 respectively	HR of 1.024 (1.017 to 1.032)
Møller *et al*, 2005[19]	RVSP >30 mm Hg	536 patients with acute myocardial infarction stratified into group 1 (RVSP <30 mm Hg), group 2 mild to moderate PH (RVSP of 31 to 55 mm Hg) and group 3 severe PH (RVSP >55 mm Hg)	40	65/ 68% 74/54% 78/44% in groups 1, 2 and 3, respectively	All-cause mortality	69	NR	75	NR	NR	NR	5% in group 1 52% in patients with a RVSP >65 mm Hg	NR	HR 1.22 (1.14 to 1.38) per 10 mm Hg increased
Cappola *et al*, 2012[20]	RHC with mPAP ≥25 mm Hg	1134 patients with cardiomyopathy stratified according to PVR: NPH (<2.5), group 1 PH (2.5–3), group 2 PH (3–3.5), group 3 PH(3.5–4) and group 4 PH (>4)	52.8	48 60%	All-cause mortality	NA	25	NR	NR	NR	NR	NR	33% of patients died during the mean FU	HR 1.86 (1.30 to 2.65) for group 2, 1.78 (1.13 to 2.81) for group 3 and 2.04 (1.51 to 2.74) for group 4
Szwejkowski *et al*, 2011[21]	RVSP >33 mm Hg	1612 patients with HF stratified into 5 groups according to RVSP (<33; 33–38; 39–44; 45–52 and >52 mm Hg)	33.6	75.2 57.4%	All-cause mortality	32	46	83.3	NR	NR	NR	NR	55.1% of patients died during the mean FU	HR 1.06 (1.03 to 1.08) for every 5 mm Hg increase in RVSP
Abramson *et al*, 1992[22]	Echocardiography with TRV >2.5 m/s	108 patients with dilated cardiomyopathy, stratified into 2 groups: group 1 (TRV <2.5 m/s) and group 2 (>2.5 m/s), 38.9% in NYHA class III and IV, 77.3% of ischaemic HF	28	67.5 81%	All-cause mortality, mortality due to HF and re-hospitalisations for HF	NR	5.6 m/s	26	75% during the study period 5.76 (1.97 to 16.90)	NR	NR	NR	17% in 28 months vs 57%	OR for increased TRV 3.77 (1.38 to 10.24)
Kjaergaard *et al*, 2007[23]	Echocardiography but cut-off for PH not reported	388 consecutive patients with known or presumed HF stratified into quartiles of RVSP (<31, 31–38, 39–50, >50)	33.6	75 60%	All-cause mortality	NR	38	75% and 50% with RVSP >31 and 40 mm Hg, respectively	NR		48% if COPD and 21% in HF without COPD	NR	57% at 33.6 months	HR 1.09 (1.04 to 1.14) for every increase of RVSP per 5 mm Hg
Shalaby *et al*, 2008[24]	RVSP ≥30 mm Hg	270 patients undergoing cardiac resynchronisation stratified into 3 groups on the basis of RVSP: group 1, (22–29, n=86); group 2 (30–44, n=90) and group 3 (45–88, n=94).	19.4	66.5 91%	All-cause mortality, cardiac transplantation (primary end point) or re-hospitalisation for HF	NR	40.4	NR	40% in group 3 vs 9% in group 1 (6.35 (2.55 to 15.79))	NR	NR	NR	12% in group 1% vs 34% in group 3 at mean follow-up	HR 2.62 (1.07 to 6.41)

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Damy *et al*, 2010[25]	Echocardiography with RVTG >25 mm Hg	1380 patients with congestive HF, 1026 with LVSD (EF <45%) and 324 without), further stratified into quartiles of RVSP	66	72 67%	All-cause mortality	30% of all, 26% in patients with LVSD and 40% in those without	25	46% of HFpEF,50% of HFrEF and 23% of patients without HF	NA (outpatient cohort)	NR	NR	NR	40.3% at median follow-up of 66 months	HR 1.72 (1.16 to 2.55) for RVSP >45 mm Hg)
Ristow *et al*, 2007[26]	Echocardiography with TR gradient >30 mm Hg	717 patients with coronary artery disease, 573 with measurable TR, stratified into group 1 (TR gradient ≤30 mm Hg, n=447) and group 2 (TR gradient >30 mm Hg, n=126)	36	65, 74% (group 1) 69, 75% (group 2)	Hospitalisation, CV death, all-cause death and the combined end point of all	80	NR	22	6% (group I) vs 21% (group II) OR per each 10 mm Hg increase of TR gradient 1.5 (1.03 to 2.2)	NR	NR	NR	11% (group 1) vs 17% (group 2)	OR for all-cause deaths 1.2 (0.85 to 1.6) per 10 mm Hg increase in TR OR for combined endpoint 1.6 (1.1 to 2.4)
Grigioni *et al*, 2006[27]	RHC with mPAP ≥25 mm Hg	196 patients with HF evaluated for PH and changes in mPAP	24	54 73%	Cardiovascular deaths, acute HF and combined end point of both	NA	25	NR	27% acute HF, 2.30 (1.42 to 3.73)	NR	NR	20% cardiovascular deaths	NR	HR for PH 2.3 (1.42 to 3.73) ; HR for worsening >30% in mPAP 2.6 (1.45 to 4.67)
Levine *et al*, 1996[28]	RHC assessed change in PH, no definition	60 patients with PH owing to HF awaiting heart transplantation, stratified into 2 groups: group A (persistent elevated sPAP, n=31), group B (decrease in sPAP, n=29)	10	50 85%	Transplant or all-cause death	NA	39 vs 57 in group A and group B, respectively	NA	NR	NR	NR	NR	90% vs 50% of death at 10months in group A and group B, respectively	NR
Lam al, 2010[29]	RVSP >35 mm Hg	244 patients with HFpEF compared with 719 subjects with HTN. 203 patients with HFpEF and PH later stratified into: group 1 (RVSP <48 mm Hg) and group 2 (RVSP >48 mm Hg)	33.6	74/47% vs 79*/ 41% in group 1 and group 2, respectively	All-cause mortality	65 vs 83% in HTN and HFpEF, respectively	28 vs 48 mm Hg in HTN and HFpEF, respectively	8 vs 83% in HTN and HFpEF, respectively	NR	NR	12.2 vs 25.7 in group 1 and group 2, respectively	18.4 vs 36.2 in group 1 and group 2, respectively	55.1 vs 63.8 in group 1 and group 2, respectively	HR 1.20 per each increase of 10 mm Hg in RVSP (p<0.001)
Kush *et al*, 2009[30]	RHC with mixed PH (MPH) defined as mPAP ≥25 mm Hg, PCWP >15 mm Hg, and PVR ≥3 WU	171 patients with severe HFrEF (NYHA class IV, LVEF ≤30%,systolic BP ≤125 mm Hg) further stratified into 2 groups: MPH group (mPAP >25 mm Hg and PVR >3 WU, n=80) and non-MPH (mPAP <25 mm Hg or PVR <3WU, n=91)	6	59/75% vs 54*/ 71% in MPH and non-MPH, respectively	Rehospitalisations and all-cause mortality	NA	mPAP: 42 vs 32 in MPH and non-MPH, respectively TPG:17 vs 7, respectively	47	HR for MPH 0.8 (0.59 to 1.08)	21 vs 22	NR	NR	NR	HR for MPH 0.89 (0.66 to 1.20)
Ghio *et al*, 2001[31]	RHC with mPAP ≥20 mm Hg, RV systolic dysfunction defined as RVEF <35%	377 patients with HF stratified into: group 1, normal mPAP/preserved RVEF (n=73); group 2 normal mPAP/low RVEF (n=68); group 3, high PAP/ preserved RVEF (n=21); and group 4, high PAP/low RVEF (n=215)	17.2	51 85.7%	Heart transplantation and all-cause mortality	NA	27.9	62.3	NR	NR	NR	NR	7.3 vs 12.3 vs 23.8 vs 40 in groups 1, 2, 3 and 4,* respectively	HR 1.1 (1.0 to 1.21) per each 5-mm Hg increment

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Wang *et al*, 2010[32]	RVSP >30 mm Hg	93 patients with HF undergoing cardiac resynchronisation stratified into group 1 (RVSP >50 mmH, n=29); group 2 (30 <RVSP ≤50 mm Hg, n=17) and group 3 (RVSP ≤30 mm Hg, n=47)	32 (6 to 60)	59.6 81.7%	All-cause mortality, HF mortality	NR	NR	49.5	NR	28 vs 6 vs 17% in groups 1,2 and 3, respectively	NR	NR	NR	Non-significant increased in all-cause mortality (p=0.33), increase in HF mortality but OR/ HR not reported
Ghio *et al*, 2013[33]	RVSP >40 mm Hg and RV dysfunction defined as TAPSE <14 mm	658 patients with chronic HF stratified into group 1 (no PH no RVD, n=256), group 2 (RVD, no PH, n=54), group 3 (PH, no RVD, n=167), and group 4 (RVD and PH, n=67)	38	63 86%	All-cause mortality, urgent cardiac transplantation or ventricular fibrillation	83	38	35.6	NR	17.5% in PH vs 4.5% in non-PH	21.4% in PH vs 8.7% in non-PH	42.3% in PH vs 20.3% in non-PH	59.4% in PH vs 45.2% in non-PH	HR 1.90 (2.18 to 3.06) for group 3 and 4.27 (3.45 to 7.43) for group 4
Studies in patients with heart valve disease														
Fawzy *et al*, 2004[35]	Severe PH defined as RVSP >50 mm Hg	559 patients with MS undergoing MBV stratified into three groups: group A (RVSP <50 mm Hg; n=345); group B (RVSP 50–79 mm Hg; n=183) and group C (RVSP ≥80 mm Hg; n=31)	63.6	31/28.1% vs 30/25.1% vs 27/16.1% in groups A, B and C, respectively	Reversibility of PH following MBV	NR	38.5 vs 59 vs 97.8 in groups A, B and C, respectively	62% vs 33% vs 5% for groups A, B, and C, respectively	NR	0	0	0	0	No mortality was encountered, PH normalised over a 6 to 12 months
Naidoo *et al*, 1991[34]	RHC with PASP ≥30 mm Hg	139 patients with AR (69 undergoing AVS) stratified into group 1 (normal or mild PH) and group 2 (moderate PH or marked PH)	6	32.9 vs 36.2 and 69.7 vs 77.8 in group 1 and 2, respectively	Immediate and 6 months postoperative mortality	NA	18 vs 43.7 in group 1 and 2, respectively	63.3	NR	3 in group 1 vs 2.8% in group 2	NR	NR	NR	No increased in mortality, HR not reported
Manners *et al*, 1977[41]	RHC with PASP >70 mm Hg	392 patients who had undergone prosthetic valve surgery stratified into 2 PASP <70 mm Hg, n=336 or PASP >70 mm Hg, n=56)	48	NR	Hospital mortality	NA	Mean PASP was 93 mm Hg	NR	NR	NR	NR	NR	5.4% at 4 years in both PH and non-PH	NR
Roseli *et al*, 2002[36]	RVSP >35 mm Hg	2385 patients undergoing AVR stratified into 3 groups: RVSP <35 mm Hg n=611; RVSP 35–50 mm Hg, n=1199; RVSP >50 mm Hg, n=575	51.6	74 55%	All-cause hospital and late mortality	NR	41	74	NR	15.8 vs 19.7 vs 25.9	NR	NR	NR	Higher RVSP was predictor of 5 and 10 years mortality, HR not reported
Melby *et al*, 2011[37]	RVSP >35 mm Hg	1080 patients with AS undergoing AVR, stratified into NPH, (RVSP <35 mm Hg, n=574) and PH group(mild PH, moderate and severe PH)	48	72.3 vs 70.2 59.1 vs 57.8% in PH and non PH, respectively	All-cause operative and long-term mortality	NR	51 in PH group	46.8	NR	NR	17.1 vs 17.6 vs 17.1 vs 23.5 for non-PH, mild, moderate and severe PH, respectively	25.7 vs 24 vs 23.2 vs 32.3	25.7 vs 38.4 vs 52.7 vs 46.1	OR 1.51 (1.16 to 1.96), persistent PH after AVR was associated with decreased survival
Le Tourneau *et al*, 2010[38]	RVSP ≥50 mm Hg	256 patients with MR undergoing MVO, stratified into group 1 (RVSP <50 mm Hg, n=174) and group 2 (RVSP ≥50 mm Hg, n=82)	49.2	63 66%	All-cause mortality Cardiovascular deaths	NR	45±14	32% had RVSP ≥50 mm Hg	NR	NR	NR	31.6 vs 31.7 in groups 1 and 2, respectively	NR	HR 1.43 (1.09 to 1.88) per 10 mm Hg increment of RVSP

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Parker *et al*, 2010[7]	RVSP >35 mm Hg	1156 patients with MR or AR stratified into normal (RVSP <30 mm Hg), borderline (31–34 mm Hg), mild (35–40 mm Hg) or moderate or greater (>40 mm Hg)	87.6	72 51%	All-cause mortality	52	29	NR	NR	NR	NR	NR	NR	HR for moderate or greater PH 1.95 (1.58 to 2.41) in AR and 1.48 (1.26 to 1.75) in MR
Barbieri *et al*, 2010[40]	RVSP >50 mm Hg	437 patients with MR, 35% NYHA class III or IV, normal LVEF, stratified into NPH (RVSP ≤50 mm Hg) and PH (RVSP >50 mm Hg)	57.6	67 66%	All-cause mortality, cardiovascular death, heart failure		45	23	1.70 (1.10 to 2.62) and 1.19 (1.06 to 1.35) for each 10 mm Hg increase of RVSP	NR		NR	23% at the mean follow-up	HR 2.03 (1.30 to 3.18) and 1.16 (1.03 to 1.31) for each 10 mm Hg increase of RVSP
Kainuma *et al*, 2011[39]	Echocardiography, PH definition not specified	46 patients undergoing MVR, NYHA III or IV, LVEF <40%, stratified into group 1 (RVSP <40 mm Hg, n=19), group 2 (moderate PH (40 <RVSP <60, n=17) and group 3 (RVSP >60, n=10)	36	64 35%	Cardiac death, myocardial infarction, endocarditis, thromboembolism, reoperation for recurrent MR, readmission for heart failure and fatal arrhythmia	NR	47	NR	30% in the severe PH but not significant, OR and CI NR	NR	15.8 vs 11.8 vs 20% for groups 1, 2, and 3, respectively	31.6 vs 29.4 vs 30%	47.4 vs 82.4 vs 50%	HR for all adverse cardiac events 6.9 (1.1 to 44) in group 3
Khandhar *et al*, 2009[43]	Severe PH defined as RVSP >60 mm Hg	506 patients with severe AR stratified into group 1, severe PH with RVSP >60 mm Hg, n=83 and group 2 (RVSP <60, n=423), NYHA NR	NR	63 47%	All-cause mortality	100	NR	16% of severe PH	NR	NR	NR	21.6 of patients with severe PH	NR	PH was associated with increased mortality in all groups, OR and CI NR
Malouf *et al*, 2002[42]	Severe PH defined as peak TRV ≥4 m/s	3171 patients with AS of whom 47 with severe PH, stratified into group 1 (no AVR, n=10) and group 2 (AVR, n=37), 79% in NYHA III and IV	15.3	78 47%	All-cause mortality	63% of the 3171 total population of patients with aortic stenosis	4.16 m/s	NA	NR	NR	NR	NR	80% vs 32% in groups 1 and 2, respectively, at median FU	OR for mortality risk in severe PH and AVS 1.76 (0.81 to 3.35)
Zuern *et al*, 2012[44]	RVSP >30 mm Hg	200 patients with AS undergoing AVR stratified into NPH (RVSP <30) vs mild-to-moderate PH (30 <RVSP <60) and severe PH (>60 mm Hg)	31.2	72.3 52.5%	All-cause mortality	NR	36.3	61	NR	NR	10.2 vs 14.1 vs 30.4	30.7 vs 40.4 vs 60.1	2.6, 15.2 and 26.1%	HR for mild-to-moderate PH 4.9 (1.1 to 21.8) and severe PH 3.3 (0.6 to 19.7)
Ben-Dor *et al*, 2011[45]	RVSP >40 mm Hg	509 patients with AS divided into group 1 (RVSP <40 mm Hg, n=161); group 2 (RVSP 40–59, n=175) and group 3 (RVSP >60 mm Hg, n=173)	6.73	82.3 vs 82.4 vs 80.5 in groups 1, 2 and 3, respectively, >75%	All-cause mortality	NR	33.7 vs 49.3 vs 70.7 in groups 1, 2, and 3, respectively	68.3	NR	NR	NR	NR	21.7 vs 39.3 vs 49.1 in groups 1, 2 and 3, respectively at median FU*	PH was significantly associated with increase in mortality, OR/HR not reported
Yang *et al*, 2012[46]	RVSP >40 mm Hg	845 patients who underwent valve surgery and/or CABG (444 without PH or NPH vs 401 PH), all with LVEF <40%	39	65.2 vs 67.8 78.8 vs 72.6% in NPH and PH group, respectively	Postoperative complications and mortality		NR	NR	NR	NR	4.6 vs 13.9 in NPH vs PH group, respectively	NR	16.7 vs 30.6* in NPH vs PH group, respectively	OR for mild/ moderate PH 1.475 (1.119 to 1.943)

Continued

Table 2 Continued

Author, year published	Diagnostic criteria (RVSP by echocardiography or mPAP by echocardiography or RHC)	Study population (sample size, heart disease, NYHA class, type of HF)	Mean/ median follow-up (months)	Age—years/ male sex—%	Definition of outcomes predicted	Proportion (%) of measurable RVSP	Median/mean (mm Hg) baseline RVSP (echo) or mPAP (RHC)	Prevalence of PH at baseline (%)	HF readmission rate or adjusted ORs/HRs and CI	Mortality (all-cause) rate at 6, 12, 24 and 36 months or at mean duration of follow-up				Adjusted ORs/ HRs and CI (or p value) for all-cause mortality, outcome
										6	12	24	36 or at mean/ median follow-up	
Nozohoor *et al*, 2012[47]	RVSP >50 mm Hg	270 patients with MR undergoing MVS, stratified into NPH group (RVSP <50 mm Hg) and PH group (RVSP ≥50 mm Hg)	61.2	61.5 vs 66.5 70 vs 54% in no PH and PH group, respectively	Perioperative complications and all-cause late mortality	NR	NR	27	NR	NR	7.6 vs 8.2 in no PH and PH, respectively	22.4 vs 17.6 in no PH and PH, respectively	31.1 in both groups	HR 4.3 (1.1 to 17.4) during the initial 3 years after MVS
Ward and Hancock 1975[48]	RHC with extreme PH defined as SPAP >80 mm Hg and PVR >10 WU: 8.2%	Mitral valve disease (n=586), 48 extreme PH stratified into group 1 (no operation), group 2 (all surgical) and group 3 (survive after surgery)	69.6	46.2 vs 42.4 43 vs 29% in group 1 and 2 respectively	All-cause mortality	NA	105 vs 96.6	8.2	NA	NR	NR	NR	NR	Extreme PH was associated with higher mortality, and surgery improved survival
Ghoreishi *et al*, 2012[49]	sPAP >40 mm Hg using RHC in 591 patients and RVSP >40 mm Hg using DE	873 patients with MR who underwent MVS, stratified into NPH and PH group (mild, moderate, severe) NHYA not reported	35	59 59%	Hospital mortality, Late all-cause mortality	NR	46 (echo), and sPAP was 43 by RHC	53	NR	NR	16.2 in non PH vs 32% in PH group*	33.9 in non PH vs 48.1% in PH group*	51.8 in non PH vs 60.9% in PH group*	HR 1.018 (1.007 to 1.028) per each 1 mm Hg increment in RVSP
Cam A *et al*, 2011[50]	RHC with severe PH defined as mPAP >35 mm Hg	317 patients with AS, 35 with severe PH underwent surgery and were compared to 114 mild moderate PH and to 46 severe PH treated conservatively, NHYA not reported	11.3	71/53.5 (mild-moderate PH) vs 75/51.4 (severe PH)	All-cause mortality	NA	22.5 (mild-moderate PH) vs 45.3 (severe PH)	47.0	NR	NR	NR	NR	74.5 vs 75.5	HR 1.008 (0.9 to 1.11) and early postoperative reduction in mPAP 0.93 (1.2 to 12.5)
Pai *et al*, 2007[51]	Severe PH defined as RVSP >60 mm Hg	116 patients (of 740 severe AS) with severe PH among which 36 underwent AVR and were compare to 83 remaining	18	75 39%	All-cause mortality	NR	69	15.7% (severe PH)	NR	NR	NR	30.5 (PH) vs 15.5 (NPH)	NR	AVR benefit HR 0.28 (0.16 to 0.51) independent of PH

*p<0.05.

AS(R), aortic stenosis (regurgitation); AVS(R), aortic valve surgery (replacement); CABG, coronary artery bypass graft; DE, Doppler echocardiography; eSPAP, estimated systolic pulmonary artery pressure; HFpEF, heart failure (HF) and preserved ejection fraction; LHD, left heart disease; LVEF, left ventricular (LV) ejection fraction; MBV, Mitral Balloon Valvotomy; mPAP, mean pulmonary arterial pressure; mPCWP, mean pulmonary capillary wedge pressure; MV(R/O), mitral valve (repair/operation); NA, not applicable; NPH, non-pulmonary hypertension; NR, not reported; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV(SP/TG), right ventricular systolic pressure/tricuspid gradient); TPG, transpulmonary gradient; TRV, tricuspid regurgitation (TR) velocity(TRV); TAPSE, tricuspid annular plan systolic excursion; UTSW, University of Texas—Southwestern; WU, wood units.

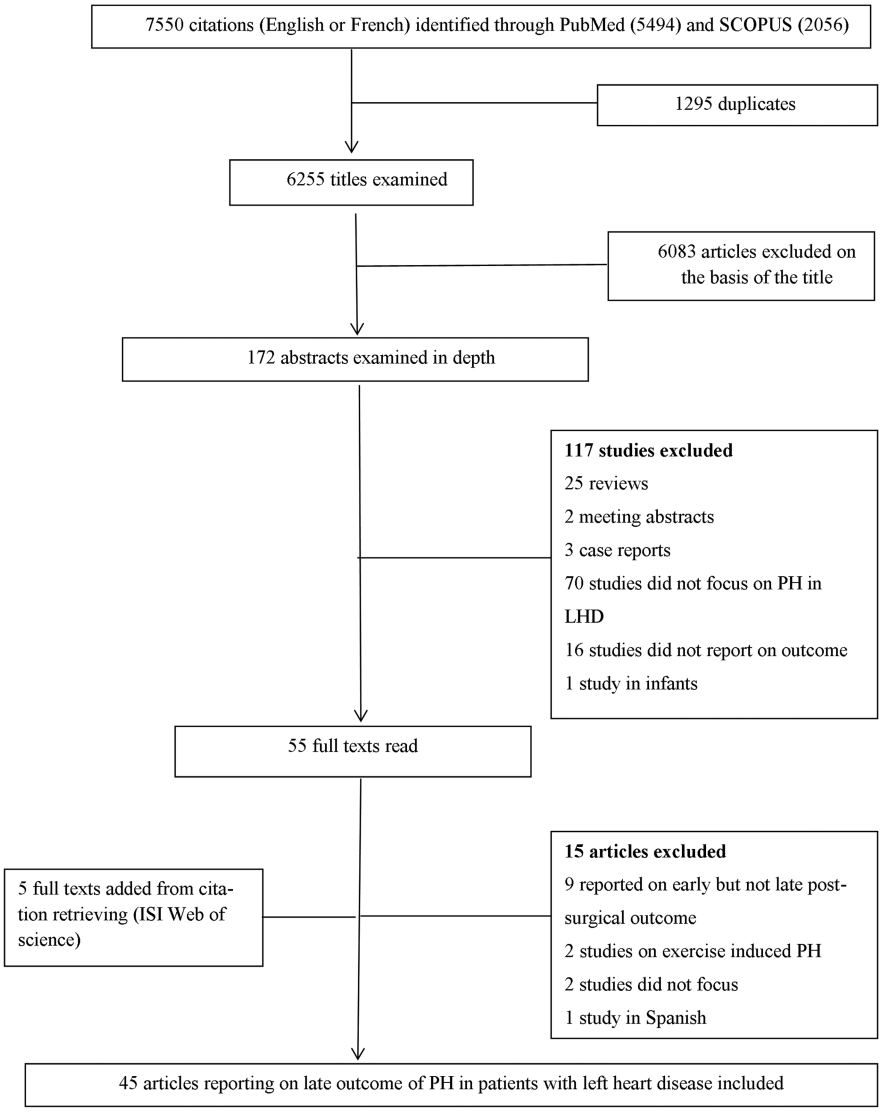

Figure 1 Flow diagram of literature search process. LHD, left heart disease; PH, pulmonary hypertension.

screened by full text of which 15 were excluded for various reasons (figure 1). Five studies were identified via citation search. Therefore, 45 articles were included in the final review among which 86.7% were published between 2003 and 2013 (see online supplementary figure S1).

Study characteristics and methodological quality

The characteristics and methodological quality of the 45 included studies are described in table 1. The overall quality score ranged from 29.5 to 72.5 points with a median of 63.5. Based on the cut-offs of ≥60 and ≥45 points, respectively, we classified 34 articles as being of high quality, 7 as moderate-to-high quality and four as low-quality studies (table 1). Studies of high quality were recent and scored well on patient selection, outcome measurement, statistical analysis and presentation. Studies classified as moderate/low quality scored relatively well on patient selection, but poorly on study attrition, statistical analysis and presentation. Twenty-four (53.3%) studies were from the USA, 12 (26.6%) from Europe (four from UK, three from Italy and one each from Spain, Germany, Denmark, France and Sweden), 6 (13.3%) from Asia (two from Japan, one each from India, China, Korea and Australia) and 1 from South Africa. One study was multicentric across Europe and the USA[40] and another one was multicentric across the USA and Canada.[30] Only three population-based cohorts were reported including two prospective[13 29] and one retrospective study.[14] For the remaining 42 hospital-based cohort studies, 20 had a retrospective design. The number of participants ranged from 46 to 2385 in hospital-based and from 244 to 1049 in population-based studies. The proportion of men ranged from 21% to 91%, and mean/median age from 63 to 82 years. Twenty-six studies were in patients with heart failure (HF) and cardiomyopathies (two in heart failure with preserved ejection fraction (HFpEF)) and 19 in patients with valve disease.

Twelve studies defined PH using RHC and 32 studies using DE. One study defined PH using both RHC and DE. Studies applied variable definitions of PH using both

RHC (based on mPAP >25 or 30 mm Hg, or on systolic pulmonary artery pressure (sPAP) >50 mm Hg, or sPAP >40 mm Hg, or on pulmonary vascular resistance (PVR) >2.5 wood units (WU)) and DE (based on RVSP with cut-offs varying from 35 to 50 mm Hg, or based on a mPAP >25 mm Hg[8] or on a right ventricular tricuspid gradient (RVTG) >25 mm Hg).[25] Prevalence of PH in HF ranged from 22% to 83.3% overall, 22–83.3% in studies of PH based on DE and 23–76% in studies of PH based on RHC (see online supplementary figure S2).

Outcome of PH

Admissions for heart failure

The duration of follow-up ranged from 6 to 87.6 months overall, 6–69.6 months in studies of PH based on RHC definition and 6–87.6 months in studies of PH based on DE definition. Readmission rates, when reported, ranged from 9.2% to 75% overall and 9.2–75% in studies of PH based on DE definition. Only one study with PH definition based on RHC reported a readmission rate of 27% (table 2). Admissions or readmissions for HF were reported in nine studies all based on DE definition among which seven reported HRs or ORs for admission/readmission in relation with PH. Effect estimates for six of the seven studies were statistically significant.

Mortality

Mortality was reported in all studies (table 2); however, not all studies provided multivariable-adjusted effect estimates of mortality risk associated with PH. PH was associated with increased all-cause mortality in 24 of 26 studies of HF, among which 6 studies were of PH based on RHC definition, while two studies failed to report an association between PH and all-cause mortality at 6 months. Of these two studies, one used PH definition based on RHC and was a multicentric trial of HF that reported effect estimates for mortality risk from PH (HR=0.89 (95% CI 0.66 to 1.20));[30] while the other one[32] did not. When reported, mortality rates at 12 months ranged from 0% to 32% overall, 0% to 32% in studies of PH based on DE and 2.9% to 18% in studies of PH based on RHC (see online supplementary figure S3). As summarised in table 3, over 35 potential predictors of mortality were tested across studies with variable and often inconsistent effects on the outcome of interest. Age was associated with mortality in 14 studies (among which 11 studies of PH were based on DE), male gender in 3/11 studies (all based on DE), LVEF in 6/10 studies, right ventricular (RV) function in 3/3 studies and renal disease (rising creatinine, decreasing glomerular filtration rate (GFR) or dialysis) in 6/17 studies (all based on DE), functional class (New York Heart Association (NYHA) or WHO) in 7/12 studies (five based on DE) while the 6 min walking distance was tested in only one study but was not integrated in the multivariable analysis for outcome risk.[32]

DISCUSSION

An increasing number of studies have assessed the risk of readmission and mortality in patients with LHD-related PH over the last decade, and mostly in North America and Europe. Available studies are mostly consistent on the adverse effect of PH (whether assessed using DE or RHC) on mortality risk in patients with heart failure as well as those with mitral valve disease, but less unanimous in those with aortic valve disease. The consistent adverse effect of PH in this population highlights the importance of early diagnosis of PH to reduce mortality. While available studies have been overall of acceptable quality, substantial heterogeneity in the study population, PH definition and measurement, outcome definitions as well as other prognostic factors limit direct comparisons across studies. Information on readmission for heart failure was limited and the assessment of other prognostic factors in an integrated multivariable model was very heterogeneous.

Mortality in patients with PH and heart failure with reduced ejection fraction

While PH was an independent prognostic factor for mortality in fatal-outcome studies, the prevalence of PH and effects on mortality varied according to LVEF. Differences in the prevalence of PH could be explained at least in part by population heterogeneity (age, level of HF, HF centres or community study) and differences in the criteria used to define PH across studies with a variety of cut-off values. Regardless of the prevalence of PH in HFrEF, there seems to be no uniformity in the association between the magnitude of reduction in LVEF, and the presence or absence of PH and the effects of PH on mortality risk. It is possible that the small size of studies and the short duration of follow-up precluded the accumulation of a substantial number of events to allow the detection of a relationship, if any. Furthermore, although the precise haemodynamic threshold beyond which RVSP is invariably associated with mortality is subject to debate; the risk of death associated with PH seems to increase with higher RVSP.[6 12 13 16] A possible pathophysiological explanation is that early and higher vascular remodelling occurs in patients with HF and severe PH, causing a reactive or 'postcapillary PH with a precapillary component', which in turn has a greater impact on the RV function. Equally, RV systolic function has been shown to be highly influenced by pressure overload and by vascular resistance in the pulmonary region[50]; and RV function assessed using RHC or echocardiography has been shown to be associated with mortality.[30 31 33] It is, however, remarkable that one study[30] reported no interaction between PH and RV function, with both variables being independently associated with mortality. This highlights the fact that RV function in HF does not only depend on pulmonary pressure but may also reflect intrinsic myocardial disease. As suggested by Vachiery *et al*[6] there might be a spectrum of clinical phenotypes of RV failing in PH-LHD that might evolve from one to the other, from isolated postcapillary PH with little effect on

Table 3 Other prognostic factors associated with mortality in patients with pulmonary hypertension associated with left heart disease

Factor	Number of studies reporting		Number of studies in which the factor was associated with poor outcome	
	overall	Studies based on DE	Studies of PH based on DE	Studies of PH based on RHC
Age	14	11	11	3
Sex (male vs female)	11	9	3	0
Racial/ethnic group	2	2	0	0
HF episodes	5	5	2	0
Prior hypertension	5	5	1	0
History of diabetes	8	8	3	0
Smoking	3	3	0	0
History of cardiovascular disease	1	1	1	0
Functional class (NYHA/WHO)	12	9	5	2
Killip class for MI	2	2	2	0
Heart rate	2	2	0	0
Systolic BP	4	4	2	0
Diastolic BP	1	1	1	0
Mean BP	1	1	1	0
SPO_2	3	3	1	0
Hypotension	1	1	1	0
Atrial fibrillation	5	5	5	0
Ischaemic aetiology of HF	4	4	0	0
Urea	2	2	1	0
Kidney disease (by creatinine, GFR or haemodialysis)	17	14	6	0
BNP	3	3	2	0
Haemoglobin	2	2	0	0
Presence of COPD	4	3	3	0
Use of medications (ACEI and or beta blockers or spironolactone)	6	6	3	0
LVEF	10	10	6	NA
LV end-diastolic diameter/index	6	6	3	NA
Atrial diameter	1	1	1	NA
Deceleration time	1	1	0	NA
RV function (by TAPSE or other means)	3	3	3	NA
Functional mitral regurgitation	5	5	4	NA
RVSP ≥50 or >60 mm Hg	9	9	5	NA
End diastolic pulmonary regurgitation	1	1	1	NA

ACEI, ACE inhibitors; BNP, brain natriuretic peptide; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; RHC, right heart catheterisation; RVSP, right ventricular systolic pressure; RV, right ventricle; TAPSE, tricuspid annular plan systolic excursion.

the RV to more advanced disease where the failing RV is the key determinant of outcome.

Mortality in patients with PH and heart failure with preserved ejection fraction

Over the past decades, the increasing prevalence of HFpEF[51] has been paralleled by an increasing presence of PH in patients with HFpEF.[5 6] When compared to heart failure with reduced ejection fraction (HFrEF), patients with HFpEF have their subset of risk factors; but finally, PH conveys similar morbidity and mortality risk in the two subgroups of patients.[13 17] The current incomplete understanding of HFpEF limits our ability to explain why these patients develop PH. However, it is estimated that over time left atrium and ventricular filling pressure from compromised left ventricle and, in some, left atrium relaxation and distensibility can lead to elevated pulmonary venous pressure, triggering vasoconstriction and arterial remodelling.[4 5] In total, the finding of PH as an independent prognostic factor for mortality in patients with HF tends to support the suggestion that PH should be considered as a potential therapeutic target at least in the group of patients with HF who exhibit persisting PH after optimisation of HF therapy. In this line, targeting both pulmonary vasculature and the heart would probably be more beneficial.

Mortality in patients with PH related to valvular heart disease

PH due to valvular heart disease (VHD) was not always related to mortality risk,[38 39 45] which is in contrast with PH in patients with heart failure. A simple explanation

of this difference could be that the prevalence and severity of PH correlates with the severity and type of VHD. Although mitral stenosis (MS) has been the classical disease associated with PH-LHD and reactive PH was initially described in these patients[4]; it is, however, noticeable that PH due to MS has received little attention over the last decade, probably because of the progressive decline in RHD in Western countries. Interestingly, the two studies included showed that surgery was safe and improved survival in patients with PH due to MS[35 48] with PH regressing to normal levels over 6–12 months after successful Mitral Balloon Valvotomy (MBV).[35] In mitral regurgitation (MR), nearly all cohort studies on outcomes of severe PH reported increased mortality.[38 39 40 46 49] The relevance of this finding is that PH can serve both as an indication for proceeding to surgical or catheter-based interventions, and also as an operative risk factor for mitral valve interventions.[54] By contrast, PH is not as common in the aortic valve surgical cohort. Mortality rates in different studies of patients with VHD depends on comorbidities, exclusion criteria and definition for PH. Studies that also evaluated changes in PH following valve surgery showed a decline in pulmonary pressures following surgery.[35 45 50 55] It is worth noting that the pathophysiology of the pulmonary vasculature in PH due to VHD is similar to that in patients with HF.[1]

Hospitalisations and other prognostic factors

The paucity of information on the effect of PH-LHD on hospitalisations or rehospitalisations as has been shown in this study highlights the need for more evidence on this outcome. Such information is important to fully characterise and quantify the contribution of PH-LHD to the global burden of disease, and assess future improvement from treating the underlying LHD and/or controlling PH in patients with LHD.

Of the 35 other potential prognostic factors of mortality in patients with PH that were tested in multivariable models across studies, investigations on echocardiographic parameters suggested that PH >60 mm Hg was associated with worse mortality in seven of the nine studies. Similarly, a greater degree of MR, deceleration time when reported[26] and RV function were almost constantly associated with adverse outcome while LVEF was associated with adverse outcome in 6 of the 10 studies. In the evolution of LHD, RV dysfunction usually occurs as a turning point. It shall be noted that PH incorporates information on diastolic function, MR and pulmonary vascular disease, and this might explain the pivotal role of PH in gauging the prognosis of patients with HF.

Strengths and limitations of the studies included in the review

The first limitation of the studies included in our review is the possibility of study population bias. The majority of studies originated from Western countries and included predominantly Caucasians and reported mostly on PH-LHD in a population with high prevalence of ischaemic heart disease. This precludes the generalisability of our findings to developing countries where aetiologies of LHDs are less of ischaemic origin and are more dominated by systemic hypertension, dilated cardiomyopathies and RHD in a younger population.[56] Therefore, PH-LHD may have a different prognosis in developing countries. Second, studies included in this review were defined PH based either on DE or RHC. RHC remains the gold standard to diagnose and confirm PH, but performing RHC on all patients with dyspnoea would bear excessive risks and be impractical in resource-limited settings. DE on the other hand is widely available, safe and relatively cheap for diagnosing PH, although the reproducibility of the approach in some circumstances has been questioned. However, a systematic review on the diagnostic accuracy of DE in PH by Janda *et al*[57] has shown that the correlation of pulmonary artery systolic pressure by DE compared to RHC was good with a pooled correlation coefficient of 0.70 (95% CI 0.67 to 0.73). However, studies to date examining the prognostic impact of PH in LHD have been performed in heterogeneous populations, using variable definitions of PH based both on RHC and echocardiography parameters, thus limiting any possibility of pooling. Finally, readmissions were not frequently reported and multivariable analysis when performed was characterised by a great heterogeneity in the number and range of candidate predictors included in the models, thus limiting interpretation and generalisability. Therefore, findings on these other prognostic factors must be interpreted with caution. For studies that performed only univariate analysis, we cannot rule out the possibility that the reported factors may not preserve a significant association with the outcome once adjusted for the effect of other extraneous factors. In spite of these limitations, the majority of studies included were recent and all reported on the relation of PH-LHD with all-cause mortality, making the conclusions on this relation appropriate for contemporary Western populations.

Strengths and limitations of the review

First, by restricting our search strategy to full-report articles published in English and French, and in journals available in the used electronic databases, we cannot rule out the possibility of language or publication bias. Second, we used the QUIPS instrument, designed for prognosis studies, to address common sources of bias. The QUIPS, however, lacks discriminative power; we addressed this by using the scoring algorithm suggested by de Jonge *et al*.[6] This scoring algorithm can still be subject to criticisms, especially because the cut-off points used to determine the quality of the studies are quite arbitrary. Third, because of important heterogeneity in the included studies, we were not able to pool data to perform a meta-analysis or to stratify data by clinically important subgroups (such as mild, moderate or severe PH). However, to the best of our knowledge, this is the

first systematic review on determinants of hospitalisations and mortality in patients with PH-LHD, and the search strategy used allowed us to present the results of several recent and high-quality publications on the topic.

CONCLUSION

The majority of studies included in this review showed that PH is an independent predictor of mortality in patients with LHD, with the more consistent evidence being in those with HF and MR. Information on readmission for heart failure was somehow very limited. The majority of this information derives from studies in Western and developed countries, and may not apply to populations in other settings. All together, these findings suggest that the hypothesis of targeting PH to improve the outcomes of patients with LHD s should be actively investigated.

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