Predictors of hospitalizations 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 hospitalizations 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 hospitalization 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 catheterization. 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. Thirty-nine 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 hospitalizations reported a significant adverse effect of PH on hospitalization 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 hospitalization risk are yet to be fully characterized; while available evidence on the adverse effects of PH have been derived essentially from Caucasians.

Word count - 289

Key words:

Pulmonary hypertension, left heart disease, outcome, mortality, predictors, hospitalization

ARTICLE SUMMARY

Article focus

A systematic review to identify and synthesize the evidence on predictors of hospitalizations for heart failure (HF) and mortality in patients with pulmonary hypertension due to left heart disease (PH-LHD)

Key messages

- PH is an independent predictor of mortality in patients with LHD, but the evidence is more consistent in patients with HF and mitral regurgitation.
- Existing evidence on the outcomes of patients with LHD-PH have been derived essentially from studies in Western and developed countries, and may not apply to populations in other settings
- The hypothesis of targeting PH to improve the outcomes of patients with left heart diseases should be actively investigated.

Strengths and limitations

- Our search strategy was likely limited by its focus on full report 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 metaanalysis.

- This is the first systematic review on determinants of hospitalizations and mortality in patients with PH-LHD, 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, hemodynamic 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, pulmonary hypertension is common in patients with left heart disease (LHD), where it often reflects the background LHD, but has also been reported to be a maker of disease severity and unfavorable prognosis. Patients with PH-LHD have more severe symptoms, worse tolerance to effort, experience higher hospitalization 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 (5, 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 left heart diseases. Equally, little is known regarding the effect of the severity of PH on hospitalizations, re-hospitalization and death, and their co-factors in patients with LHD. Considering the number of recent advances in the management of pulmonary hypertension, it is likely that a better understanding of the impact of PH-LHD on major outcomes might assist the clinical management of patients with pulmonary hypertension.

We performed a systematic review of the existing literature to determine the predictors of hospitalization and mortality in patients with pulmonary hypertension secondary to left heart

diseases 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 search 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 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 hospitalization 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) RVSP (Right ventricular systolic pressure) measured by transthoracic Doppler echocardiography 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 mmHg to 10 mmHg, 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 catheterization or by Doppler echocardiography. We excluded narrative reviews and case series.

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 hazards 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) (9). 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 (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 (i.e. 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 (10), as explained described in details in the Online Table1.

Data synthesis

Hospitalizations or re-hospitalizations for heart failure and mortality identified by multivariable analysis in individual studies are presented, including their estimated effect size (e.g. odds or hazard ratio) and 95% confidence interval (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 type of prognostic factors. We have therefore presented a narrative summary of the available evidence.

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 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 (Online Figure 2).

Study characteristics and methodological quality

The characteristics of the 45 included studies are described in Table 2. The overall quality score ranged from 29.5 to 72.5 points with a median of 63.5. Based on the cutoffs 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. 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 USA, twelve (26.6%) from Europe (four from UK, three from Italy, and one from Spain, Germany, Denmark, France, Sweden), six (13.3%) from Asia (two from Japan, one from India, China, Korea and Australia) and one from South Africa. One study was multicentric across Europe and USA (11) and another one was multicentric across USA and Canada (12). Only three population based cohorts were reported including two prospective (13, 14) and one retrospective studies (15). 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 nineteen in patients with valve disease.

Thirteen studies defined PH using right heart catheterization (RHC) and 32 studies using Doppler echocardiography. 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 on pulmonary vascular resistance (PVR)>2.5 wood units (WU) and Doppler echocardiography (based on RVSP with cutoffs 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 (16).

Outcome of pulmonary hypertension

Admissions for heart failure

The duration of follow-up ranged from six months up to 15 years, and the incidence of the outcome of interest when reported ranged from 19.7 to 75% for readmission. Admissions or readmissions for HF was reported in 9 studies among which 7 reported hazard ratios or odd ratios for admission/readmission in relation with PH. Effect estimates for 6 out of the 7 studies were statistically significant.

Mortality

Mortality was reported in all studies; however, not all of them provided multivariable adjusted effect estimates of mortality risk associated with PH. PH was associated with increased all-cause mortality in 24 out of 26 studies of HF, while two studies failed to report an association between

PH and all-cause mortality at 6 months. One of these two studies, which was a multicentric trial of HF reported an effect estimates for mortality risk from PH [HR 0.89 (95% CI: 0.66-1.20)] (12), while the other one (17) didn't. As summarized 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, male gender in 3/11 studies, left ventricular ejection fraction (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, functional class [New York Heart Association (NYHA) or World Heart Organization (WHO)] in 7/12 studies while the six minutes walking distance was tested in only one study but was not integrated in the multivariable analysis for outcome risk (17).

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 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 limits 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 pulmonary hypertension and heart failure

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 centers or community study) and differences in the criteria used to define PH across studies with a variety of cutoff values. Regardless of the prevalence of PH, there seems to be no significant association between the magnitude of reduction in LVEF, 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 substantial number of events to allow the detection of a relationship if any. Furthermore, although the precise hemodynamic threshold beyond which RVSP is invariably associated with mortality is subject to debate; the risk of death associated with PH seems to be higher with increase RVSP (9, 14). A possible pathophysiologic explanation is that early and higher vascular remodeling occurs in patients with HF and severe PH, causing a reactive or "post capillary PH with a pre-capillary component", which in turn has a greater impact on the RV function. This of course is consistent with late diagnosis in heart valve disease, especially rheumatic heart disease (RHD) presenting with HF. Equally, RV systolic function has been shown to be highly influenced by pressure overload and by vascular resistance in the pulmonary region (52); and RV function assessed using right heart catheterization or echocardiography has been shown to be associated with mortality (20, 32, 33). It is however remarkable that one study (32) 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 post-capillary PH

with little effect on the RV to more advanced disease where the failing RV is the key determinant of outcome.

Over the last decades, the increasing prevalence of HFpEF (53) has been paralleled by an increasing presence of PH in patients with HFpEF (10). When compare to heart failure with reduced ejection fraction (HFrEF), patients with HFpEF have their subset of risks factors but finally, PH convey similar morbidity and mortality risk in the two subgroups of patients (10, 15, 19). 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 remodeling (2). 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 patients with HF who exhibit persisting PH after optimization 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 (34, 35, 40, 41, 47), 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. Though 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(18, 19), with PH regressing to normal

levels over 6-12 months after successful Mitral Balloon Valvotomy (MBV)(19). In mitral regurgitation (MR), nearly all cohort studies on outcomes of severe PH reported increase mortality (3, 7, 38, 39, 42, 48). 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 (20). 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 (19, 21-23). 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).

The paucity of information on the effect of PH-LHD on hospitalizations or re- hospitalizations as showed in this study highlights the need for more evidence on this outcome. Such information is important to fully characterize 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 7 out of 9 studies. Similarly, a greater degree of MR, deceleration time when reported (28) and RV function were almost constantly associated with adverse outcome while LVEF was associated with adverse outcome in 6 of 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 ischemic heart disease. This precludes the generalizability of our findings to developing countries where etiologies of left heart diseases are less of ischemic origin and are more dominated by systemic hypertension, dilated cardiomyopathies and RHD in a younger population (24). Therefore PH-LHD may have a different prognosis in developing countries. Secondly, there was a multiplicity of PH definitions based both on RHC and echocardiography parameters, limiting any possibility of pooling. Finally, readmissions were not frequently reported and multivariable analysis when performed was characterized by a great heterogeneity in the number and range of candidate predictors included in the models, thus limiting interpretation and generalizability. 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. Secondly, we used the QUIPS instrument, designed for prognosis studies to address common sources of bias. The QUIPS, however, lacks discriminative power, henceforth we addressed this by using of the scoring algorithm suggested by de Jonge et al (6).

This scoring algorithm can still be subject to criticisms, especially because the cutoff points used to determine the quality of the studies are quite arbitrary. Thirdly, because of important heterogeneity in studies included, we were not able to pool data to perform a metaanalysis or to stratify data by clinically important subgroups (such as mild, moderate, or severe PH). However, to our knowledge, this is the first systematic review on determinants of hospitalizations and mortality in patients with PH-LHD and the search strategy used allowed us to present in large the results of more 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 left heart diseases should be actively investigated.

Declaration of competing interest

None for all co-authors

Authors 'contribution statement

Conceived and designed the protocol: AD and APK. Performed the literature search, selection and quality assessment of the articles and extraction of data: AD, APK and KS. Interpreted the data: AD, APK, FT and KS. Wrote the first draft of the manuscript: AD. Contributed to the

writing of the manuscript: AD, APK, KS and FT. Agree with manuscript results and conclusions: AD, APK, FT and KS. All authors read and approved the final manuscript.

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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, 2013(25)	Spain	Prospective hospital based cohort	KM, Cox regression	13.5	15	10	15	15	68.5	+
2.	Agawal et al, 2012(26)	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.	Agawal R, 2012(27)	USA – 96% blacks	Prospective hospital based cohort	KM, Cox regression	12	10	10	15	15	62	+
4.	Aronson et al, 2011(28)	USA	Prospective hospital based cohort	Cox regression	15	15	15	15	12.5	72.5	+
5.	Bursi et al, 2012(13)	USA - Caucasian and blacks	Prospective population based cohort study	KM, Logistic regression	15	12.5	12.5	12.5	15	65	+
6.	Strange et al, 2012(15)	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, 2012(29)	USA	Prospective hospital based cohort	KM, Logistic and cox regression, KM	13.5	15	10	15	15	69	+
8.	Tatebe et al, 2012(30)	Japan	Prospective hospital based cohort	KM, Logistic and cox regression	15	10	15	15	15	72.5	+
9.	Adhyapak et al, 2010(8)	India	Prospective hospital based cohort	Cox regression	13.5	10	10	12.5	5	53.5	+/-
10.	Stern et al, 2007(31)	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	15	12.5	12.5	12.5	66	+
11.	Lee et al, 2010(32)	Korea	Prospective hospital based cohort	KM, Cox regression	15	15	15	12.5	15	72.5	+
12.	Møller et al, 2005(33)	USA	Prospective hospital based cohort	KM, Logistic regression	13.5	15	12.5	15	15	71	+
13.	Cappola et al, 2012(34)	USA, 35% black ands 65% whites	Prospective hospital based cohort	KM, Cox regression	13.5	7.5	12.5	15	15	62.5	+
14.	Szwejkowski et al, 2011(35)	UK	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	61	+
15.	Abramson et al, 1992(36)	USA	Prospective hospital based cohort	KM, Cox regression	12	15	10	15	12.5	64.5	+
16.	Kjaergaard et	Denmark	Prospective hospital	KM, Cox	13.5	15	12.5	15	15	71	+

	al, 2007(37)		based cohort	regression							
17.	Shalaby et al, 2008(38)	USA, 95% Caucasians	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	15	15	15	71	+
18.	Damy et al, 2010(16)	United Kingdom	Prospective hospital based cohort	KM, logistic and Cox regression	15	10	15	15	15	70	+
19.	Ristow et al, 2007(39)	USA	Prospective hospital based cohort	Logistic regression	13.5	12.5	10	15	5	48.5	+/-
20.	Grigioni et al, 2006(40)	Italy	Retrospective cohort	KM, logistic regression	13.5	12.5	12.5	15	15	68.5	+/-
21.	Levine et al, 1996(41)	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, 2010(14)	USA	Prospective observational community based cohort	KM, Logistic regression	12	15	10	15	12.5	68	+
23.	Kush et al, 2009(12)	Multicentric USA and Canada	Prospective cohort in the ESCAPE trial	KM	15	10	15	15	12.5	68.5	+
24.	Ghio et al, 2001(42)	Italy	Prospective cohort	KM, Cox regression	13.5	12.5	12.5	12.5	12.5	63.5	+
25.	Wang et al, 2010(17)	China	Retrospective cohort	KM	12	12.5	12.5	12.5	5	54.5	+/-
26.	Ghio et al, 2013(43)	Italy	Prospective cohort	KM, Cox and logistic regression	13.5	10	10	15	15	63.5	+
27.	Naidoo et al, 1991(44)	South Africa, Blacks	Retrospective cohort	No logistic regression, no Kaplan Meier analysis	12	7.5	10	5	7.5	42	-
28.	Fawzy et al, 2004(19)	Saudi Arabia	Prospective cohort	No logistic regression, no Kaplan Meier	12	10	12.5	15	7.5	57	+/-
29.	Roseli et al, 2002(45)	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	63.5	+/-
30.	Melby et al, 2011(46)	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	10	15	15	66	+
31.	Le Tourneau et al, 2010(47)	France, mainly Caucasians	Prospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	63.5	+
32.	Parker et al, 2010(7)	USA	Retrospective hospital based cohort	KM, Cox regression	12	15	12.5	15	15	71	+
33.	Kainuma et al, 2011(48)	Japan, Asians	Retrospective hospital based cohort	KM, Cox regression	10.5	10	12.5	12.5	10	55.5	+/-
34.	Barbieri et al, 2010(11)	Multicentric (Europe and USA)	Prospective hospital based cohort	KM, Cox regression	13.5	15	12.5	15	15	71	+

35.	Manners et al, 1977(49)	United Kindom	Retrospective hospital based cohort	No regression analysis, no KM estimation	10.5	7.5	5	5	2.5	30.5	-
36.	Malouf et al, 2002(50)	USA	Prospective hospital based cohort	KM, Cox and logistic regression	10.5	10	10	15	12.5	58	+
37.	Khandhar et al, 2009(51)	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	61	+/-
38.	Zuern et al, 2012(52)	Germany	Prospective hospital based cohort	KM, Cox regression	15	7.5	10	15	15	62.5	+
39.	Ben-Dor et al, 2011(21)	USA	Prospective hospital based cohort	KM, Logistic regression	15	10	10	15	15	68	+
40.	Yang et al, 2012(53)	USA	Retrospective hospital based cohort	KM, Cox and logistic regression	15	7.5	15	12.5	15	65	+
41.	Nozohoor et al, 2012(54)	Sweden	Retrospective cohort	KM, Cox and logistic regression	13.5	10	10	15	12.5	61	+
42.	Ward et al 1975(18)	UK	Retrospective cohort	No KM, no logistic or Cox regression	12	5	2.5	7.5	2.5	29.5	-
43.	Ghoreishi et al, 2012(55)	USA	Retrospective cohort	KM, Cox and logistic regression	15	10	10	10	15	60	+
44.	Cam A et al, 2011(22)	USA	Retrospective cohort	KM, Cox and logistic regression	13.5	15	10	10	12.5	61	+
45.	Pai et al, 2007(56)	USA	Retrospective cohort	KM, Cox and logistic regression	15	10	10	10	15	60	+

KM: Kaplan Meier; UK: United Kindom; USA:United states of America

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 Odd/Hazard ratios and CI	Mortality (all cause) rate at 6, 12, 24, 36 months or at mean duration of follow up				Adjusted odd/Hazard ratios 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(25)	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 per 10 persons-year in severe PH	NA	NA	OR for mild PH 1.6 (0.7-3.74), moderate PH 1.34 (0.54-3.16) and severe PH 2.57 (1.07-6.27)
Agawal et al, 2012(26)	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 (1.1-1.9) and NU cohort HR 1.4 (1.1–1.7)
Agawal, 2012(27)	RVSP>35	288 patients undergoing hemodialysis 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 (1.31-3.61)

Aronson et al, 2011(28)	RHC with mPAP≥25 mmHg mPCWP >15 mmHg	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 (0.6-4.5) and reactive PH 4.8 (2.1-17.5)
Bursi et al, 2012(13)	RVSP > 35 mm Hg	1049 patients with HF stratified into tertiles of RVSP	81	76; 49.3%	All cause mortality	NR	48	79	NA	NR	4, 10, and 17% for tertiles 1, 2, and 3 respect ively	8 vs 19 vs 28	46*	HR for tertile 2: 1.45 (1.13-1.85) and tertile 3: 2.07 (1.62-2.64)
Strange et al, 2012(15)	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(29)	RVSP > 35 mm Hg	1054 patients with acute myocardial infarction divided into NPH and PH groups	12	60 vs 69; 77 vs 64%	Readmissio n for HF All cause mortality	NR	32 vs 43	44.6	2.1 vs 9.2; OR 3.1 (1.87-5.14)	NR	NR	NR	NR	HR for readmissio n 3.1 (1.87-5.14)

Tatebe et al, 2012(30)	RHC with mPAP≥25 mmHg mPCWP >15 mmHg	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 mortalityand 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 (1.03-1.35)
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 (1.09–3.57)
Stern et al, 2007(31)	Echocardiography but criteria for PH not reported	68 patients needing cardiac resynchronization stratified into group 1 (RVSP ≥ 50 mmHg, n = 27) and group 2(RVSP< 50 mmHg, n =	7.1	70 64.7%	composite of hospitalization on for HF and all cause mortality	NR	Group 1 39.7 ± 6.7 and group 1 60.2 ± 9.2	NR	NR	NR	Increased mortality in patients with RVSP≥50 mm Hg	NR	NR	HR of 2.0 (1.2-5.5) for RVSP≥50

		41)												
Lee et al, 2010(32)	RVSP>39 mm Hg	813 patients with TR stratified into two groups based on the RVSP < 39 mmHg (group 1, n = 530) and RVSP ≥ 39 mmHg (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 (1.017–1.032)
Møller et al, 2005(33)	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 group 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 (1.14-1.38) per 10 mm Hg increased
Cappola et al, 2012(34)	RHC with mPAP ≥ 25 mm Hg	1134 patients with cardiomyopathy stratified according to PVR: NPH (<2.5), group1 PH (2.5-3), group2 PH (3-	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 (1.30–2.65) for group2, 1.78 (1.13–2.81) for group3 and 2.04

		3.5), group3 PH(3.5-4) and group4 PH (>4)												(1.51–2.74) for group4
Szwejkowski et al, 2011(35)	RVSP>33 mm Hg	1612 patients with HF stratified into 5 groups according to RVSP (< 33; 33-38; 39-44; 45-52 and >52 mmHg)	33.6	75.2 57.4%	All cause mortality	32	46	8(35)3.3	NR	NR	NR	NR	55.1% of patients died during the mean FU	HR 1.06 (1.03-1.08) for every 5 mm Hg increase in RVSP
Abramson et al, 1992(36)	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 ischemic HF	28	67.5 81%	All cause mortality, mortality due to HF and re-hospitalizations for HF	NR	5.6 m/s	26	75% during the study period 5.76 (1.97-16.90)	NR	NR	NR	57% in 28 months vs 17%	OR for increased TRV 3.77 (1.38-10.24)
Kjaergaard et al, 2007(37)	Echocardiographybut cutoff 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 mm Hg and 40 mm Hg respectively	NR		48% if COPD and 21% in HF without COPD	NR	57% at 33.6 months	HR 1.09(1.04-1.14) for every increase of RVSP per 5 mm Hg
Shalaby et al, 2008(38)	RVSP≥30 mm Hg	270 patients undergoing cardiac resynchronization stratified	19.4	66.5 91%	All cause mortality, cardiac transplantation (primary	NR	40.4	NR	40% in group 3 vs 9% in group 1 [6.35	NR	NR	NR	12% in group 1 vs 34% in group 3 at mean	HR 2.62 (1.07–6.41)

		into 3 groups on the basis of RVSP: group 1, (22 to 29, n= 86); group 2 (30 to 44, n=90) and group 3 (45 to 88, n=94).			end point) or re-hospitalization for HF				(2.55–15.79)]				follow up	
Damy et al, 2010(16)	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(1.16–2.55) for RVSP>45 mm Hg)
Ristow et al, 2007(39)	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)	hospitalization, 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(1.03-2.2)	NR	NR	NR	11% (group I) vs 17% (group II)	OR for all cause deaths 1.2(0.85-1.6) per 10 mm Hg increase in TR OR for combined endpoint 1.6(1.1-2.4)
Grigioni et al, 2006(40)	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(1.42-3.73)	NR	NR	20% cardiovascular deaths	NR	HR for PH 2.3 (1.42-3.73) ; HR for worsening >30% in mPAP 2.6(1.45-4.67)

Levine et al, 1996(41)	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 10 months in group A and group B respectively	NR
Lam al, 2010(14)	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 group1 and group2 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 mmHg in RVSP (p<0.001)
Kush et al, 2009(12)	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,	6	59/75 % vs 54*/71 % in MPH and non-MPH respectively	Rehospitalizations 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(0.59-1.08)	21 vs 22	NR	NR	NR	HR for MPH 0.89(0.66-1.20)

		n= 80) and non-MPH (mPAP<25 mm Hg or PVR<3WU, n=91)												
Ghio et al, 2001(42)	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); group3, 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 group 1, 2, 3 and 4* respectively	HR 1.1(1.0-1.21) per each 5-mmHg increment
Wang et al, 2010(17)	RVSP > 30 mm Hg	93 patients with HF undergoing cardiac resynchronization stratified into Group 1: (RVSP>50mmH, n=29); Group 2: (30<RVSP≤50 mmHg, n=17) and Group 3: (RVSP≤30mm Hg, n=47)	32 (6-60)	59.6 81.7%	All cause mortality, HF mortality	NR	NR	49.5	NR	28 vs 6 vs 17% in group1,2, 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(43)	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	4.5% in PH vs 17.4% in non PH	8.7% in PH vs 21.4% in non PH	20.3% in PH vs 42.3% in non PH	45.2% in PH vs 59.4% in non PH	HR 1.90 (2.18–3.06) for group3 and 4.27 (3.45–7.43) for group 4
Studies in patients with heart valve disease														
Fawzy et al, 2004(19)	Severe PH defined as RVSP> 50 mm Hg	559 patients undergoing MBV stratified into three groups: group A (RVSP <50 mmHg; n = 345); group B (RVSP 50-79 mmHg; n = 183) and group C (RVSP ≥80 mmHg; n = 31)	63 .6	31/28.1% vs 30/25.1% vs 27/16.1% in group A, B and C respectively	Reversibility of PH following MBV	NR	38.5 vs 59 vs 97.8 in group A, B and C respectively	62% vs 33% vs 5% for group A, B, and C respectively	NR	0	0	0	0	No mortality was encountered, PH normalized over a 6-12 months
Naidoo et al, 1991(44)	RHC with PASP≥<30 mm Hg	139 patients with AR (69 undergoing AVS) stratified into group I (normal or mild PH) and group II (moderate PH or marked PH)	6	32.9 vs 36.2 and 69.7 vs 77.8 in group I and II respectively	Immediate and 6 months post-operative mortality	NA	18 vs 43.7 in group I and II respectively	63.3	NR	3 in group I vs 2.8% in group II	NR	NR	NR	No increased in mortality, HR not reported
Manners et al, 1977(49)	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	NR	5.4% at 4 years in both PH and non PH	NR

Roseli et al, 2002(45)	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(46)	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 (1.16-1.96), persistent PH after AVR was associated with Decreased survival.
Le Tourneau et al, 2010(47)	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 group1 and 2 respectively	NR	HR 1.43 (1.09-1.88) per 10 mmHg increment of RVSP
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(1.58–2.41) in AR and 1.48(1.26–1.75) in MR
Barbieri et al, 2010(11)	RVSP > 50 mm Hg	437 patients with MR, 35% NYHA class III or IV, normal LVEF, stratified into NPH (RVSP≤50mm Hg) and PH (RVSP>50 mm Hg)	57.6	67 66%	All cause mortality, cardiovascular death, heart failure		45	23	1.70 (1.10–2.62) and 1.19 (1.06–1.35) for each 10 mm Hg	NR		NR	23% at the mean follow up	HR 2.03 (1.30–3.18) and 1.16 (1.03–1.31) for each 10 mm Hg increase of RVSP

									increase of RVSP					
Kainuma et al, 2011(48)	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 group 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 (1.1-44) in group3
Khandhar et al, 2009(51)	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(50)	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 group1 and 2 respectively at median FU	OR for mortality risk in severe PH and AVS 1.76 (0.81-3.35)

Zuern et al, 2012(52)	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 (1.1-21.8) and severe PH 3.3(0.6-19.7)
Ben-Dor et al, 2011(21)	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 group1, 2, and 3 respectively, > 75%	All cause mortality	NR	33.7 vs 49.3 vs 70.7 in group1, 2, and3 respectively	68.3	NR	NR	NR	NR	21.7 vs 39.3 vs 49.1 in group1 , 2, and3 respectively at median FU*	PH was significantly associated with increase in mortality, OR/HR not reported
Yang et al, 2012(53)	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	Post operative 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 (1.119-1.943)
Nozohoor et al, 2012(54)	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(1.1–17.4) during the initial 3 years after MVS
Ward and Ward, 1975(18)	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 43vs29% 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(55)	RVSP>40 mm Hg	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(1.007-1.028) per each 1 mm Hg increment in RVSP
Cam A et al, 2011(22)	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 (0.9-1.11) and early post-operative reduction in mPAP 0.93 (1.2-12.5)
Pai et al, 2007(56)	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 (0.16-0.51) independent of PH.

AS(R): Aortic stenosis(regurgitation); AVS(R): Aortic valve surgery(replacement); CABG: Coronary artery bypass graft; eSPAP: Estimated systolic pulmonary artery pressure; HFpEF: Heart failure (HF) and preserved ejection fraction; 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); NPH: Non pulmonary hypertension; 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); UTSW: University of Texas—Southwestern; WU: Wood units; P<0.05 **

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
Age	14	14
Sex (male vs female)	11	3
Racial / ethnic group	2	0
HF episodes	5	2
Prior hypertension	5	1
History of diabetes	8	3
Smoking	3	0
History of cardiovascular disease	1	1
Functional class (NYHA/WHO)	12	7
Killip class for MI	2	2
Heart rate	2	0
Systolic BP	4	2
Diastolic BP	1	1
Mean BP	1	1
SPO2	3	1
Hypotension	1	1
Atrial fibrillation	5	2
Ischemic etiology of HF	4	0
Urea	2	1
Kidney disease (by creatinine, GFR, or hemodialysis)	17	6
BNP	3	1
Hemoglobin	2	0
LVEF	10	6
LV end diastolic diameter /index	6	3
Atrial diameter	1	1
Deceleration time	1	1
RV function (by TAPSE or other means)	3	3
Use of medications (ACEI and or beta blockers or spironolactone)	6	3
Functional mitral regurgitation	5	4
RVSP≥50 or > 60 mm Hg	9	7
Presence of COPD	4	3
End diastolic pulmonary regurgitation	1	1

ACEI: Angiotensin converting enzyme inhibitors; BNP: Brain natriuretic peptide; BP: Blood pressure; COPD: Chronic obstructive pulmonary disease; GFR: Glomerular filtration rate; HF: Heart failure; MI: Myocardial infarction; NYHA: New York Heart Association; RVSP: Right ventricular systolic pressure; RV: Right ventricle; TAPSE: Tricuspid annular plan systolic excursion; WHO: World Heart Organization.

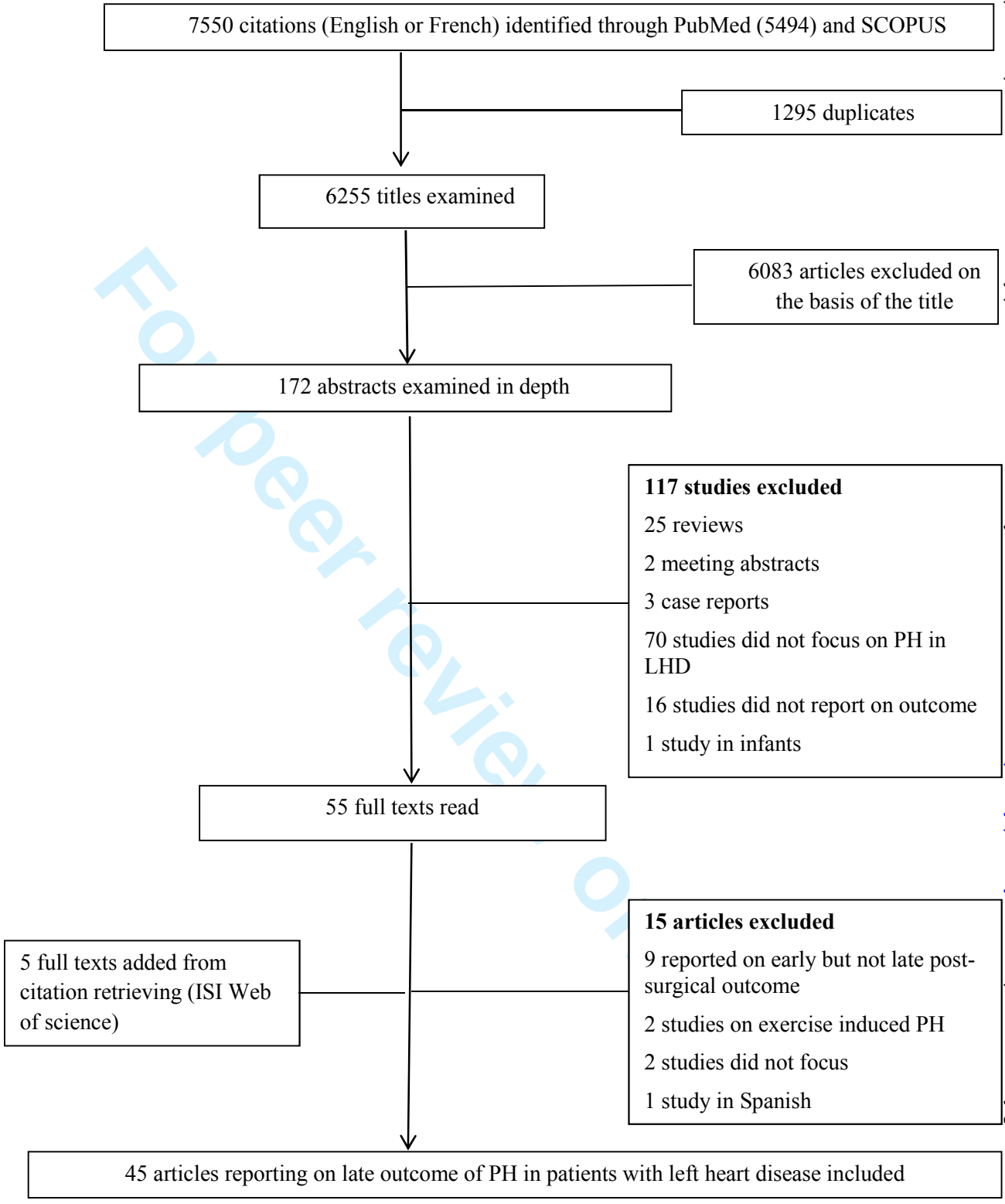


Figure 1: Flow diagram of literature search process

- Online section -

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

Online box 1: Search terms used in the builder

For pubmed:

((((pulmonary hypertension) OR pulmonary pressure)) AND (((heart failure) OR left heart disease) OR valvular heart disease)) AND ((((((predict) OR outcome) OR risk) OR prognosis) OR discrimination) OR c statistic)

For Scopus:

((((pulmonary hypertension) OR pulmonary pressure)) AND (((heart failure) OR left heart disease) OR valvular heart disease)) AND ((((((predict) OR outcome) OR risk) OR prognosis) OR discrimination) OR c statistic) AND (LIMIT-TO(SUBJAREA, "MEDI")) AND (LIMIT-TO(EXACTKEYWORD, "Heart failure") OR LIMIT-TO(EXACTKEYWORD, "Mortality") OR LIMIT-TO(EXACTKEYWORD, "Prognosis") OR LIMIT-TO(EXACTKEYWORD, "Echocardiography") OR LIMIT-TO(EXACTKEYWORD, "Risk Factors") OR LIMIT-TO(EXACTKEYWORD, "Heart Failure") OR LIMIT-TO(EXACTKEYWORD, "Pulmonary hypertension") OR LIMIT-TO(EXACTKEYWORD, "Treatment Outcome") OR LIMIT-TO(EXACTKEYWORD, "Follow up")) AND (LIMIT-TO(SUBJAREA, "MEDI")) AND (LIMIT-TO(LANGUAGE, "English") OR LIMIT-TO(LANGUAGE, "French"))

Online table 1: Scoring algorithm developed by de Jonge et al[6] to strengthen the discriminative capacity of the QUIPS*

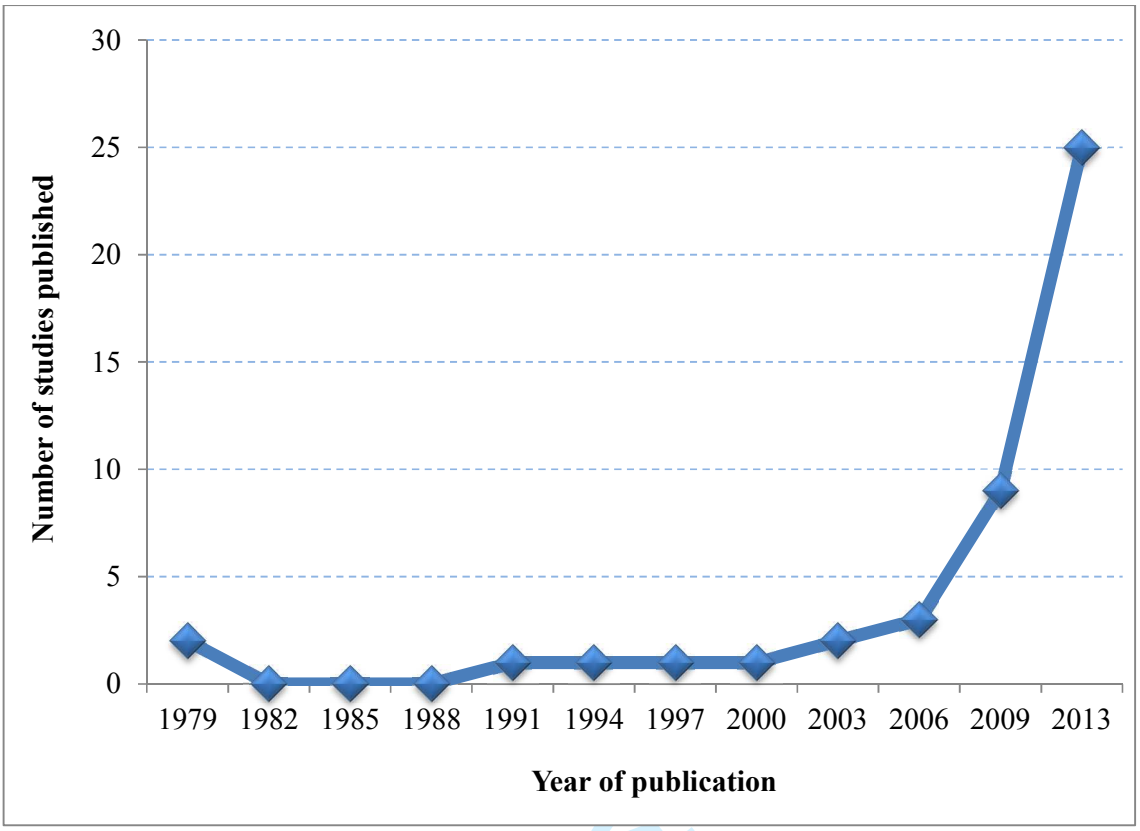
Criteria**	Score		
	+	+/-	-
1. Study participation			
• Target population	3	1.5	0
• Sampling frame	3	1.5	0
• Inclusion criteria	3	1.5	0
• Baseline study population	3	1.5	0
• Adequate study participation	3	1.5	0
2. Study attrition			
• Proportion of population available for analysis	5	2.5	0
• Outcome and prognostic factor information on	5	2.5	0
• Reasons and potential impact of subjects lost to	5	2.5	0
3. Measurement of prognostic factors			
• Definition of prognostic factor	5	2.5	0
• Valid and reliable measurement of prognostic	5	2.5	0
• Method and setting of prognostic factor	5	2.5	0
4. Measurement of outcomes			
• Definition of outcome	5	2.5	0
• Valid and reliable measurement of outcome	5	2.5	0
• Method and setting of outcome measurement	5	2.5	0
5. Statistical analysis and presentation			
• Presentation of analytical strategy	5	2.5	0
• Model development strategy	5	2.5	0
• Reporting of results	5	2.5	0

* QUIPS: Quality In Prognosis Studies

** Used (adapted) QUIPS list for scoring methodological quality of prognosis studies

All five domains were given a maximum of 15 points each, equally distributed across all items per category. For four items we assigned 5 points in case of low risk of bias and 2.5 and 0 in case of moderate and high risk of bias, respectively, except for category 1 (patient selection bias) containing five instead of three items, for which we assigned 3 points in case of low risk of bias and 1.5 and 0 in case of moderate and high risk of bias, respectively. A total score, with a maximum of 75 points, was calculated by summing up the scores per item. A priori, we chose to consider ≥60 points (≥80% of the maximum attainable score) as high quality, between 45 and 60 points (≥60% of the maximum attainable score) as moderate/high quality and <45 points as low quality studies.

Online figure 2: Number of studies on outcome of pulmonary hypertension associated with left heart disease identified over time



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6,7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, 40
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7,8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8,9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	24-38
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	25,25
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	26-38
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	24,25
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15,16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

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

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Pulmonary hypertension, left heart disease, outcome, mortality, predictors, hospitalization

Predictors of hospitalizations 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 hospitalizations 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 hospitalization 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 catheterization. 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. Thirty-nine 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 hospitalizations reported a significant adverse effect of PH on hospitalization 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 hospitalization risk are yet to be fully characterized; while available evidence on the adverse effects of PH have been derived essentially from Caucasians.

Word count - 289

Key words:

Pulmonary hypertension, left heart disease, outcome, mortality, predictors, hospitalization

ARTICLE SUMMARY

Article focus

A systematic review to identify and synthesize the evidence on predictors of hospitalizations for heart failure (HF) and mortality in patients with pulmonary hypertension due to left heart disease (PH-LHD)

Key messages

- PH is an independent predictor of mortality in patients with LHD, but the evidence is more consistent in patients with HF and mitral regurgitation.
- Existing evidence on the outcomes of patients with LHD-PH have been derived essentially from studies in Western and developed countries, and may not apply to populations in other settings
- The hypothesis of targeting PH to improve the outcomes of patients with left heart diseases should be actively investigated.

Strengths and limitations

- Our search strategy was likely limited by its focus on full report 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 metaanalysis.

- This is the first systematic review on determinants of hospitalizations and mortality in patients with PH-LHD, 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, hemodynamic 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, pulmonary hypertension is common in patients with left heart disease (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 hospitalization 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 [5 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 left heart diseases. Equally, little is known regarding the effect of the severity of PH on hospitalizations, re-hospitalization and death, and their co-factors in patients with LHD. Considering the number of recent advances in the management of pulmonary hypertension, it is likely that a better understanding of the impact of PH-LHD on major outcomes might assist the clinical management of patients with pulmonary hypertension.

We performed a systematic review of the existing literature to determine the predictors of hospitalization and mortality in patients with pulmonary hypertension secondary to left heart

diseases 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 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 hospitalization 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 mmHg to 10 mmHg, 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 catheterization (RHC) or by Doppler echocardiography. 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 hazards 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) [9]. 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 (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 17items 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 (i.e. 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 [10], as explained described in details in the Online Table.

Data synthesis

Hospitalizations or re-hospitalizations for heart failure and mortality identified by multivariable analysis in individual studies are presented (Table 2), including their estimated effect size (e.g.

odds or hazard ratio) and 95% confidence interval (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 type 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 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 (Online Figure1).

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 cutoffs 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 USA, twelve (26.6%) from Europe (four from UK, three from Italy, and one from Spain, Germany, Denmark, France, Sweden), six (13.3%) from Asia (two from Japan, one from India, China, Korea and Australia) and one from South Africa. One study was multicentric

across Europe and USA [11] and another one was multicentric across USA and Canada [12]. Only three population based cohorts were reported including two prospective[13 14] and one retrospective studies [15]. 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 nineteen in patients with valve disease.

Twelve studies defined PH using right heart catheterization (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 Doppler echocardiography [based on RVSP with cutoffs 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] [16]. Prevalence of PH in HF ranged from 22 to 83.3% overall, 22 to 83.3% in studies of PH based on DE and 23 to 76% in studies of PH based on RHC.

Outcome of pulmonary hypertension

Admissions for heart failure

The duration of follow-up ranged from six to 87.6 months overall, 6 to 69.6 months in studies of PH based of RHC definition, and 6 to 87.6 months in studies of PH based on DE definition. Readmission rates, when reported ranged from 9.2 to 75% overall, 9.2 to 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 was reported in 9 studies all based on

DE definition among which 7 reported hazard ratios or odd ratios for admission/readmission in relation with PH. Effect estimates for 6 out of the 7 studies were statistically significant.

Mortality

Mortality was reported in all studies (Table 2); however, not all of them provided multivariable adjusted effect estimates of mortality risk associated with PH. PH was associated with increased all-cause mortality in 24 out of 26 studies of HF among which 6 studies 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, it was a multicentric trial of HF that reported an effect estimates for mortality risk from PH [HR 0.89(95% CI: 0.66-1.20)] [12], while the other one [17] didn't. 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 (Online Figure 3). As summarized 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 based on DE), male gender in 3/11 studies (all based on DE), left ventricular ejection fraction (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 World Heart Organization (WHO)] in 7/12 studies (five based on DE) while the six minutes walking distance was tested in only one study but was not integrated in the multivariable analysis for outcome risk [17].

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 limits 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 pulmonary hypertension 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 centers or community study) and differences in the criteria used to define PH across studies with a variety of cutoff values. Regardless of the prevalence of PH in HFrEF, there seems to be no significant association between the magnitude of reduction in LVEF, 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 substantial number of events to allow the detection of a relationship if any. Furthermore, although the precise hemodynamic 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 (9, 14). A possible pathophysiologic explanation is that early and higher vascular remodeling occurs in patients with HF and severe PH, causing a reactive or "post capillary PH with a pre-capillary 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 (52); and RV function assessed using right heart catheterization or echocardiography has been shown to be associated with mortality (20, 32, 33). It is however remarkable that one study (32) 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 post-capillary PH with little effect on the RV to more advanced disease where the failing RV is the key determinant of outcome.

Mortality in patients with pulmonary hypertension and heart failure with preserved ejection fraction

Over the last decades, the increasing prevalence of HFpEF (53) has been paralleled by an increasing presence of PH in patients with HFpEF (10). When compare to heart failure with reduced ejection fraction (HFrEF), patients with HFpEF have their subset of risks factors but finally, PH convey similar morbidity and mortality risk in the two subgroups of patients (10, 15, 19). 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 remodeling (2). 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 patients with HF who exhibit persisting PH after

optimization 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 (34, 35, 40, 41, 47), 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. Though 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 [18 19], with PH regressing to normal levels over 6-12 months after successful Mitral Balloon Valvotomy (MBV) [19]. In mitral regurgitation (MR), nearly all cohort studies on outcomes of severe PH reported increase mortality (3, 7, 38, 39, 42, 48). 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 [20]. 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 [19 21-23]. 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).

Hospitalizations and other prognostic factors

The paucity of information on the effect of PH-LHD on hospitalizations or re- hospitalizations as showed in this study highlights the need for more evidence on this outcome. Such information is

important to fully characterize 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 7 out of 9 studies. Similarly, a greater degree of MR, deceleration time when reported (28) and RV function were almost constantly associated with adverse outcome while LVEF was associated with adverse outcome in 6 of 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 ischemic heart disease. This precludes the generalizability of our findings to developing countries where etiologies of left heart diseases are less of ischemic origin and are more dominated by systemic hypertension, dilated cardiomyopathies and RHD in a younger population [24]. Therefore PH-LHD may have a different prognosis in developing countries. Secondly, studies included in this review 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 a 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 [25] 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 basedboth on RHC and echocardiography parameters, thus limiting any possibility of pooling. Finally, readmissions were not frequently reported and multivariable analysis when performed was characterized by a great heterogeneity in the number and range of candidate predictors included in the models, thus limiting interpretation and generalizability. 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. Secondly, we used the QUIPS instrument, designed for prognosis studies to address common sources of bias. The QUIPS, however, lacks discriminative power, henceforth we addressed this by using of the scoring algorithm suggested by de Jonge et al (6). This scoring algorithm can still be subject to criticisms, especially because the cutoff points used to determine the quality of the studies are quite arbitrary. Thirdly, because of important heterogeneity in studies included, we were not able to pool data to perform a metaanalysis or to

stratify data by clinically important subgroups (such as mild, moderate, or severe PH). However, to our knowledge, this is the first systematic review on determinants of hospitalizations and mortality in patients with PH-LHD and the search strategy used allowed us to present in large the results of more 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 left heart diseases should be actively investigated.

Authors 'contribution statement

Conceived and designed the protocol: AD and APK. Performed the literature search, selection and quality assessment of the articles and extraction of data: AD, APK and KS. Interpreted the data: AD, APK, FT and KS. Wrote the first draft of the manuscript: AD. Contributed to the writing of the manuscript: AD, APK, KS and FT. Agree with manuscript results and conclusions: AD, APK, FT and KS. All authors read and approved the final manuscript.

Declaration of competing interest

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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, 2013[26]	Spain	Prospective hospital based cohort	KM, Cox regression	13.5	15	10	15	15	68.5	+
2.	Agawal et al, 2012[27]	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.	Agawal R, 2012[28]	USA – 96% blacks	Prospective hospital based cohort	KM, Cox regression	12	10	10	15	15	62	+
4.	Aronson et al, 2011[29]	USA	Prospective hospital based cohort	Cox regression	15	15	15	15	12.5	72.5	+
5.	Bursi et al, 2012[13]	USA - Caucasian and blacks	Prospective population based cohort study	KM, Logistic regression	15	12.5	12.5	12.5	15	65	+
6.	Strange et al, 2012[15]	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, 2012[30]	USA	Prospective hospital based cohort	KM, Logistic and cox regression, KM	13.5	15	10	15	15	69	+
8.	Tatebe et al, 2012[31]	Japan	Prospective hospital based cohort	KM, Logistic and cox regression	15	10	15	15	15	72.5	+
9.	Adhyapak et al, 2010[8]	India	Prospective hospital based cohort	Cox regression	13.5	10	10	12.5	5	53.5	+/-
10.	Stern et al, 2007[32]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	15	12.5	12.5	12.5	66	+
11.	Lee et al, 2010[33]	Korea	Prospective hospital based cohort	KM, Cox regression	15	15	15	12.5	15	72.5	+
12.	Møller et al, 2005[34]	USA	Prospective hospital based cohort	KM, Logistic regression	13.5	15	12.5	15	15	71	+
13.	Cappola et al, 2012[35]	USA, 35% black ands 65% whites	Prospective hospital based cohort	KM, Cox regression	13.5	7.5	12.5	15	15	62.5	+
14.	Szwejkowski et al, 2011[36]	UK	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	61	+
15.	Abramson et al, 1992[37]	USA	Prospective hospital based cohort	KM, Cox regression	12	15	10	15	12.5	64.5	+
16.	Kjaergaard et	Denmark	Prospective hospital	KM, Cox	13.5	15	12.5	15	15	71	+

	al, 2007[38]		based cohort	regression							
17.	Shalaby et al, 2008[39]	USA, 95% Caucasians	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	15	15	15	71	+
18.	Damy et al, 2010[16]	United Kingdom	Prospective hospital based cohort	KM, logistic and Cox regression	15	10	15	15	15	70	+
19.	Ristow et al, 2007[40]	USA	Prospective hospital based cohort	Logistic regression	13.5	12.5	10	15	5	48.5	+/-
20.	Grigioni et al, 2006[41]	Italy	Retrospective cohort	KM, logistic regression	13.5	12.5	12.5	15	15	68.5	+/-
21.	Levine et al, 1996[42]	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, 2010[14]	USA	Prospective observational community based cohort	KM, Logistic regression	12	15	10	15	12.5	68	+
23.	Kush et al, 2009[12]	Multicentric USA and Canada	Prospective cohort in the ESCAPE trial	KM	15	10	15	15	12.5	68.5	+
24.	Ghio et al, 2001[43]	Italy	Prospective cohort	KM, Cox regression	13.5	12.5	12.5	12.5	12.5	63.5	+
25.	Wang et al, 2010[17]	China	Retrospective cohort	KM	12	12.5	12.5	12.5	5	54.5	+/-
26.	Ghio et al, 2013[44]	Italy	Prospective cohort	KM, Cox and logistic regression	13.5	10	10	15	15	63.5	+
27.	Naidoo et al, 1991[45]	South Africa, Blacks	Retrospective cohort	No logistic regression, no Kaplan Meier analysis	12	7.5	10	5	7.5	42	-
28.	Fawzy et al, 2004[19]	Saudi Arabia	Prospective cohort	No logistic regression, no Kaplan Meier	12	10	12.5	15	7.5	57	+/-
29.	Roseli et al, 2002[46]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	63.5	+/-
30.	Melby et al, 2011[47]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	10	15	15	66	+
31.	Le Tourneau et al, 2010[48]	France, mainly Caucasians	Prospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	63.5	+
32.	Parker et al, 2010[7]	USA	Retrospective hospital based cohort	KM, Cox regression	12	15	12.5	15	15	71	+
33.	Kainuma et al, 2011[49]	Japan, Asians	Retrospective hospital based cohort	KM, Cox regression	10.5	10	12.5	12.5	10	55.5	+/-
34.	Barbieri et al, 2010[11]	Multicentric (Europe and USA)	Prospective hospital based cohort	KM, Cox regression	13.5	15	12.5	15	15	71	+

35.	Manners et al, 1977[50]	United Kindom	Retrospective hospital based cohort	No regression analysis, no KM estimation	10.5	7.5	5	5	2.5	30.5	-
36.	Malouf et al, 2002[51]	USA	Prospective hospital based cohort	KM, Cox and logistic regression	10.5	10	10	15	12.5	58	+
37.	Khandhar et al, 2009[52]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	61	+/-
38.	Zuern et al, 2012[53]	Germany	Prospective hospital based cohort	KM, Cox regression	15	7.5	10	15	15	62.5	+
39.	Ben-Dor et al, 2011[21]	USA	Prospective hospital based cohort	KM, Logistic regression	15	10	10	15	15	68	+
40.	Yang et al, 2012[54]	USA	Retrospective hospital based cohort	KM, Cox and logistic regression	15	7.5	15	12.5	15	65	+
41.	Nozohoor et al, 2012[55]	Sweden	Retrospective cohort	KM, Cox and logistic regression	13.5	10	10	15	12.5	61	+
42.	Ward and Hancock 1975[18]	UK	Retrospective cohort	No KM, no logistic or Cox regression	12	5	2.5	7.5	2.5	29.5	-
43.	Ghoreishi et al, 2012[56]	USA	Retrospective cohort	KM, Cox and logistic regression	15	10	10	10	15	60	+
44.	Cam A et al, 2011[22]	USA	Retrospective cohort	KM, Cox and logistic regression	13.5	15	10	10	12.5	61	+
45.	Pai et al, 2007[57]	USA	Retrospective cohort	KM, Cox and logistic regression	15	10	10	10	15	60	+

KM: Kaplan Meier; UK: United Kindom; USA:United states of America

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 Odd/Hazard ratios and CI	Mortality (all cause) rate at 6, 12, 24, 36 months or at mean duration of follow up				Adjusted odd/Hazard ratios 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[26]	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 per 10 persons-year in severe PH	NA	NA	OR for mild PH 1.6 (0.7-3.74), moderate PH 1.34 (0.54-3.16) and severe PH 2.57 (1.07-6.27)
Agawal et al, 2012[27]	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 (1.1-1.9) and NU cohort HR 1.4 (1.1–1.7)
Agawal, 2012[28]	RVSP>35	288 patients undergoing hemodialysis 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 (1.31-3.61)

Aronson et al, 2011[29]	RHC with mPAP≥25 mmHg and mPCWP >15 mmHg	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 (0.6-4.5) and reactive PH 4.8 (2.1-17.5)
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 (1.13-1.85) and tertile 3: 2.07 (1.62-2.64)
Strange et al, 2012[15]	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[30]	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 (1.87-5.14)	NR	NR	NR	NR	HR for readmission 3.1 (1.87-5.14)

Tatebe et al, 2012[31]	RHC with mPAP≥25 mmHg mPCWP >15 mmHg	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 mortalityand 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 (1.03-1.35)
Adhyapak, 2010[8]	Echocardiography with mPAP > 25 mm Hg	147 patients with HF stratifiedinto: 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 (1.09–3.57)
Stern et al, 2007[32]	Echocardiography but criteria for PH not reported	68 patients needing cardiac resynchronization stratifiedinto group1 (RVSP ≥ 50 mmHg, n = 27) and group2(RVSP < 50 mmHg, n	7.1	70 64.7%	composite of hospitalization on for HF and all cause mortality	NR	Group 1 39.7 ± 6.7 and group 1 60.2 ± 9.2	NR	NR	NR	Increased mortality in patients with RVSP≥50 mm Hg	NR	NR	HR of 2.0 (1.2-5.5) for RVSP≥50

		= 41)												
Lee et al, 2010[33]	RVSP>39 mm Hg	813 patients with TR stratifiedinto two groups based on the RVSP < 39 mmHg (group 1, n = 530) and RVSP ≥ 39 mmHg (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 (1.017–1.032)
Møller et al, 2005[34]	RVSP>30 mm Hg	536 patients with acute myocardial infarction stratifiedinto 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 group 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 (1.14-1.38) per 10 mm Hg increased
Cappola et al, 2012[35]	RHC with mPAP ≥ 25 mm Hg	1134 patients with cardiomyopathy stratifiedaccording to PVR: NPH (<2.5), group1 PH (2.5-3),	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 (1.30–2.65) for group2, 1.78 (1.13–2.81) for group3 and 2.04

		group2 PH (3-3.5), group3 PH(3.5-4) and group4 PH (>4)												(1.51–2.74) for group4
Szwejkowski et al, 2011[36]	RVSP>33 mm Hg	1612 patients with HF stratifiedinto 5 groups according to RVSP (< 33; 33-38; 39-44; 45-52 and >52 mmHg)	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 (1.03-1.08) for every 5 mm Hg increase in RVSP
Abramson et al, 1992[37]	Echocardiography with TRV>2.5 m/s	108 patients with dilated cardiomyopathy, stratifiedinto 2 groups: group1 (TRV< 2.5 m/s) and group 2 (>2.5 m/s), 38.9% in NYHA class III and IV, 77.3% of ischemic HF	28	67.5 81%	All cause mortality, mortality due to HF and re-hospitalizations for HF	NR	5.6 m/s	26	75% during the study period 5.76 (1.97-16.90)	NR	NR	NR	17% in 28 months vs 57%	OR for increased TRV 3.77 (1.38-10.24)
Kjaergaard et al, 2007[38]	Echocardiographybut cutoff for PH not reported	388 consecutive patients with known or presumed HF stratifiedinto quartiles of RVSP (<31, 31-38, 39-50, >50)	33.6	75 60%	All cause mortality	NR	38	75% and 50% with RVSP> 31 mm Hg and 40 mm Hg respectively	NR		48% if COPD and 21% in HF without COPD	NR	57% at 33.6 months	HR 1.09(1.04-1.14) for every increase of RVSP per 5 mm Hg
Shalaby et al, 2008[39]	RVSP≥30 mm Hg	270 patients undergoing cardiac resynchronization	19.4	66.5 91%	All cause mortality, cardiac transplantation (primary	NR	40.4	NR	40% in group 3 vs 9% in group 1 [6.35	NR	NR	NR	12% in group 1 vs 34% in group 3 at mean	HR 2.62 (1.07–6.41)

		stratifiedinto 3 groups on the basis of RVSP: group 1, (22 to 29, n= 86); group2(30 to 44, n=90) and group 3 (45 to 88, n=94).			end point) or re-hospitalization for HF				(2.55–15.79)]				follow up	
Damy et al, 2010[16]	Echocardiography with RVTG>25 mm Hg	1380 patients with congestive HF, 1026 with LVSD (EF<45%) and 324 without), further stratifiedinto 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(1.16–2.55) for RVSP>45 mm Hg)
Ristow et al, 2007[40]	Echocardiography with TR gradient > 30 mm Hg	717 patients with coronary artery disease, 573 with measurable TR, stratifiedinto group1 (TR gradient≤30 mm Hg, n=447) and group2 (TR gradient>30 mm Hg, n=126)	36	65, 74% (group 1) 69, 75% (group 2)	hospitalization, 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(1.03-2.2)	NR	NR	NR	11% (group I) vs 17% (group II)	OR for all cause deaths 1.2(0.85-1.6) per 10 mm Hg increase in TR OR for combined endpoint 1.6(1.1-2.4)
Grigioni et al, 2006[41]	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(1.42-3.73)	NR	NR	20% cardiovascular deaths	NR	HR for PH 2.3 (1.42-3.73) ; HR for worsening >30% in mPAP 2.6(1.45-

														4.67)
Levine et al, 1996[42]	RHC assessed change in PH, no definition	60 patients with PH owing to HF awaiting heart transplantation, stratifiedinto 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 10 months in group A and group B respectively	NR
Lam al, 2010[14]	RVSP> 35 mm Hg	244 patients with HFpEF compared with 719 subjects with HTN. 203 patients with HFpEF and PH later stratifiedinto: group 1 (RVSP<48 mm Hg) and group 2 (RVSP>48 mm Hg)	33.6	74/47 % vs 79*/41 % in group1 and group2 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 mmHg in RVSP (p<0.001)
Kush et al, 2009[12]	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 stratifiedinto 2	6	59/75 % vs 54*/71 % in MPH and non-MPH respectively	Rehospitalizations and all cause mortality	NA	mPAP: 42 vs 32 in MPH and non-MPH respectively TPG:17 vs 7 respective	47	HR for MPH 0.8(0.59-1.08)	21 vs 22	NR	NR	NR	HR for MPH 0.89(0.66-1.20)

		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)					ly							
Ghio et al, 2001[43]	RHC with mPAP≥20 mm Hg, RV systolic dysfunction defined as RVEF<35%	377 patients with HF stratifiedinto: group 1, normal mPAP/preserved RVEF (n=73); group 2 normal mPAP/low RVEF (n=68); group3, 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 group 1, 2, 3 and 4* respectively	HR 1.1(1.0-1.21) per each 5-mmHg increment
Wang et al, 2010[17]	RVSP> 30 mm Hg	93 patients with HF undergoing cardiac resynchronization stratifiedinto Group1: (RVSP>50mmH, n=29); Group2: (30<RVSP≤50 mmHg, n=17) and Group3:	32 (6-60)	59.6 81.7%	All cause mortality, HF mortality	NR	NR	49.5	NR	28 vs 6 vs 17% in group1,2, 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

		(RVSP≤30mm Hg, n=47)												
Ghio et al, 2013[44]	RVSP>40 mm Hg and RV dysfunction defined as TAPSE<14 mm	658 patients with chronic HF stratifiedinto 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 (2.18–3.06) for group3 and 4.27 (3.45–7.43) for group 4
Studies in patients with heart valve disease														
Fawzy et al, 2004[19]	Severe PH defined as RVSP> 50 mm Hg	559 patients with MS undergoing MBV stratifiedinto three groups: group A (RVSP<50 mmHg; n = 345); group B (RVSP 50-79 mmHg; n = 183) and group C (RVSP ≥80 mmHg; n = 31)	63 .6	31/28.1% vs 30/25.1% vs 27/16.1% in group A, B and C respectively	Reversibility of PH following MBV	NR	38.5 vs 59 vs 97.8 in group A, B and C respectively	62% vs 33% vs 5% for group A, B, and C respectively	NR	0	0	0	0	No mortality was encountered, PH normalized over a 6-12 months
Naidoo et al, 1991[45]	RHC with PASP≥30 mm Hg	139 patients with AR (69 undergoing AVS) stratifiedinto groupI (normal or mild PH) and group II (moderate PH or marked PH)	6	32.9 vs 36.2 and 69.7 vs 77.8 in group I and II respectively	Immediate and 6 months post-operative mortality	NA	18 vs 43.7 in group I and II respectively	63.3	NR	3 in group I vs 2.8% in group II	NR	NR	NR	No increased in mortality, HR not reported
Manners et al, 1977[50]	RHC with PASP > 70 mm Hg	392 patients who had undergone prosthetic valve surgery stratifiedinto 2 PASP<70 mm Hg,	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

		n=336 or PASP>70 mm Hg, n=56)												
Roseli et al, 2002[46]	RVSP>35 mm Hg	2385 patients undergoing AVR stratifiedinto 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[47]	RVSP>35 mm Hg	1080 patients with AS undergoing AVR, stratifiedintoNPH, (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 respective ly	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 respective ly	25.7 vs 24 vs 23.2 vs 32.3	25.7 vs 38.4 vs 52.7 vs 46.1	OR 1.51 (1.16-1.96), persistent PH after AVR was associated with Decreased survival.
Le Tourneau et al, 2010[48]	RVSP≥50 mm Hg	256 patients with MR undergoing MVO, stratifiedinto group1(RVSP<50 mm Hg, n=174) and group2(RVSP≥50 mm Hg, n=82)	49 .2	63 66%	All cause mortality Cardiovascu lar deaths	NR	45±14	32% had RVSP≥ 50 mm Hg	NR	NR	NR	31.6 vs 31.7 in group1 and 2 respectiv ely	NR	HR 1.43 (1.09-1.88) per 10 mmHg increment of RVSP
Parker et al, 2010[7]	RVSP> 35 mm Hg	1156 patients with MR or AR stratifiedinto 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(1.58–2.41) in AR and 1.48(1.26–1.75) in MR

Barbieri et al, 2010[11]	RVSP> 50 mm Hg	437 patients with MR, 35% NYHA class III or IV, normal LVEF, stratifiedintoNPH (RVSP≤50mm Hg) and PH (RVSP>50 mm Hg)	57 .6	67 66%	All cause mortality, cardiovascular death, heart failure		45	23	1.70 (1.10–2.62) and 1.19 (1.06–1.35) for each 10 mm Hg increase of RVSP	NR		NR	23% at the mean follow up	HR 2.03 (1.30–3.18) and 1.16 (1.03–1.31) for each 10 mm Hg increase of RVSP
Kainuma et al, 2011[49]	Echocardiography, PH definition not specified	46 patients undergoing MVR, NYHA III or IV, LVEF<40%, stratifiedinto group1(RVSP< 40 mm Hg, n=19), group2(moderate PH (40<RVSP<60, n=17) and group3(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 group 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 (1.1-44) in group3
Khandhar et al, 2009[52]	Severe PH defined as RVSP>60 mm Hg	506 patients with severe AR stratifiedinto 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[51]	Severe PH defined as peak TRV≥4 m/s	3171 patients with AS of whom 47 with severe PH , stratifiedinto 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 group1 and 2 respectively at median FU	OR for mortality risk in severe PH and AVS 1.76 (0.81-3.35)

Zuern et al, 2012[53]	RVSP > 30 mm Hg	200 patients with AS undergoing AVR stratifiedinto 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 (1.1-21.8) and severe PH 3.3(0.6-19.7)
Ben-Dor et al, 2011[21]	RVSP > 40 mm Hg	509 patients with AS divided into group1(RVSP< 40 mm Hg, n= 161); group2 (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 group1, 2, and 3 respectively, > 75%	All cause mortality	NR	33.7 vs 49.3 vs 70.7 in group1, 2, and3 respectively	68.3	NR	NR	NR	NR	21.7 vs 39.3 vs 49.1 in group1 , 2, and3 respectively at median FU*	PH was significantly associated with increase in mortality, OR/HR not reported
Yang et al, 2012[54]	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	Post operative 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 (1.119-1.943)
Nozohoor et al, 2012[55]	RVSP> 50 mm Hg	270 patients with MR undergoing MVS, stratifiedinto 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(1.1–17.4) during the initial 3 years after MVS
Ward and Hancock 1975[18]	RHC with extreme PH defined as SPAP>80 mmHg and PVR >10 Wu: 8.2%	Mitral valve disease (n = 586), 48 extreme PH stratifiedinto group 1 (no operation), group 2 (all surgical) and group 3 (survive after surgery)	69 .6	46.2 vs 42.4 43vs29% 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[56]	sPAP>40 mm Hg using RHC in 591 patients and RVSP>40 mm Hg using DE	873 patients with MR who underwent MVS, stratifiedintoNPH 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(1.007-1.028) per each 1 mm Hg increment in RVSP
Cam A et al, 2011[22]	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 (0.9-1.11) and early post-operative reduction in mPAP 0.93 (1.2-12.5)
Pai et al, 2007[57]	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 (0.16-0.51) independent of PH.

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; 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); NPH: Non pulmonary hypertension; 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); UTSW: University of Texas—Southwestern; WU: Wood units; P<0.05 **

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
SPO2	3	3	1	0
Hypotension	1	1	1	0
Atrial fibrillation	5	5	5	0
Ischemic etiology of HF	4	4	0	0
Urea	2	2	1	0
Kidney disease (by creatinine, GFR, or hemodialysis)	17	14	6	0
BNP	3	3	2	0
Hemoglobin	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: Angiotensin converting enzyme inhibitors; BNP: Brain natriuretic peptide; BP: Blood pressure; COPD: Chronic obstructive pulmonary disease; GFR: Glomerular filtration rate; HF: Heart failure; MI: Myocardial infarction; NYHA: New York Heart Association; RVSP: Right ventricular systolic pressure; RV: Right ventricle; TAPSE: Tricuspid annular plan systolic excursion; WHO: World Heart Organization.

Predictors of hospitalizations 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 hospitalizations 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 hospitalization 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 catheterization. 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. Thirty-nine 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 hospitalizations reported a significant adverse effect of PH on hospitalization 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 hospitalization risk are yet to be fully characterized; while available evidence on the adverse effects of PH have been derived essentially from Caucasians.

Word count - 289

Key words:

Pulmonary hypertension, left heart disease, outcome, mortality, predictors, hospitalization

ARTICLE SUMMARY

Article focus

A systematic review to identify and synthesize the evidence on predictors of hospitalizations for heart failure (HF) and mortality in patients with pulmonary hypertension due to left heart disease (PH-LHD)

Key messages

- PH is an independent predictor of mortality in patients with LHD, but the evidence is more consistent in patients with HF and mitral regurgitation.
- Existing evidence on the outcomes of patients with LHD-PH have been derived essentially from studies in Western and developed countries, and may not apply to populations in other settings
- The hypothesis of targeting PH to improve the outcomes of patients with left heart diseases should be actively investigated.

Strengths and limitations

- Our search strategy was likely limited by its focus on full report 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 metaanalysis.

- This is the first systematic review on determinants of hospitalizations and mortality in patients with PH-LHD, 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, hemodynamic 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, pulmonary hypertension is common in patients with left heart disease (LHD), where it often reflects the background LHD, but has also been reported to be a maker of disease severity and ~~unfavorable~~unfavourable prognosis. Patients with PH-LHD have more severe symptoms, worse tolerance to effort, experience higher hospitalization 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[5 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 left heart diseases. Equally, little is known regarding the effect of the severity of PH on hospitalizations, re-hospitalization and death, and their co-factors in patients with LHD. Considering the number of recent advances in the management of pulmonary hypertension, it is likely that a better understanding of the impact of PH-LHD on major outcomes might assist the clinical management of patients with pulmonary hypertension.

We performed a systematic review of the existing literature to determine the predictors of hospitalization and mortality in patients with pulmonary hypertension secondary to left heart

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diseases 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 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 hospitalization 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) ~~RVSP (~~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 mmHg to 10 mmHg, 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 catheterization (RHC) or by Doppler echocardiography. 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 hazards 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~~Table 1~~)[9]. 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 (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 17items 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 (i.e. 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 [10], as explained described in details in the Online Table~~1~~.

Data synthesis

Hospitalizations or re-hospitalizations for heart failure and mortality identified by multivariable analysis in individual studies are presented (~~t~~Table 2), including their estimated effect size (e.g.

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odds or hazard ratio) and 95% confidence interval (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 type of prognostic factors. We have therefore presented a narrative summary of the available evidence (tTable 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 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 (Online Figure12).

Study characteristics and methodological quality

The characteristics and methodological quality of the 45 included studies are described in Table 12. The overall quality score ranged from 29.5 to 72.5 points with a median of 63.5. Based on the cutoffs 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 (tTable 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 USA, twelve (26.6%) from Europe (four from UK, three from Italy, and one from Spain, Germany, Denmark, France, Sweden), six (13.3%) from Asia (two from Japan, one from India, China, Korea and Australia) and one from South Africa. One study was multicentric

across Europe and USA,[11] and another one was multicentric across USA and Canada[12]. Only three population based cohorts were reported including two prospective[13 14] and one retrospective studies[15]. 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 nineteen in patients with valve disease.

Twelve studies defined PH using right heart catheterization (RHC) and 32 studies using ~~Doppler echocardiography(~~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 Doppler echocardiography ~~(~~[based on RVSP with cutoffs 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]][16]. Prevalence of PH in HF ranged from 22 to 83.3% overall, 22 to 83.3% in studies of PH based on DE and 23 to 76% in studies of PH based on RHC.

Outcome of pulmonary hypertension

Admissions for heart failure

The duration of follow-up ranged from six to 87.6 months overall, 6 -to 69.6 months in studies of PH based of RHC definition, and 6 –to 87.6 months in studies of PH based on DE definition.~~,~~ Readmission rates, when reported ranged from 9.2 to 75% overall, 9.2 to 75% in studies of PH based on DE definition. Only one study with PH definition based on RHC reported a readmission

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rate of 27%. (Table 2). Admissions or readmissions for HF was reported in 9 studies all based on DE definition among which 7 reported hazard ratios or odd ratios for admission/readmission in relation with PH. Effect estimates for 6 out of the 7 studies were statistically significant.

Mortality

Mortality was reported in all studies (Table 2); however, not all of them provided multivariable adjusted effect estimates of mortality risk associated with PH. PH was associated with increased all-cause mortality in 24 out of 26 studies of HF among which 6 studies of PH based on RHC definition, while two studies failed to report an association between PH and all-cause mortality at 6 months. One of these two studies, one used PH definition based on RHC, it which was a multicentric trial of HF that reported an effect estimates for mortality risk from PH [HR 0.89(95% CI: 0.66-1.20)],[12], while the other one[17] didn't. 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 (Online Figure 3). As summarized 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 based on DE), male gender in 3/11 studies (all based on DE), left ventricular ejection fraction (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 World Heart Organization (WHO)] in 7/12 studies (five based on DE) while the six minutes walking distance was tested in only one study but was not integrated in the multivariable analysis for outcome risk [17].

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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 limits 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 pulmonary hypertension 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 centers or community study) and differences in the criteria used to define PH across studies with a variety of cutoff values. Regardless of the prevalence of PH in HFrEF, there seems to be no significant association between the magnitude of reduction in LVEF, 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 substantial number of events to allow the detection of a relationship if any. Furthermore, although the precise hemodynamic threshold beyond which RVSP is invariably associated with mortality is subject to debate; the risk of death associated with PH seems to increase~~be higher~~ with higher~~increase~~ RVSP (9, 14). A

possible pathophysiologic explanation is that early and higher vascular remodeling occurs in patients with HF and severe PH, causing a reactive or "post capillary PH with a pre-capillary component", which in turn has a greater impact on the RV function. ~~This of course is consistent with late diagnosis in heart valve disease, especially rheumatic heart disease (RHD) presenting with HF.~~ Equally, RV systolic function has been shown to be highly influenced by pressure overload and by vascular resistance in the pulmonary region (52); and RV function assessed using right heart catheterization or echocardiography has been shown to be associated with mortality (20, 32, 33). It is however remarkable that one study (32) 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 post-capillary PH with little effect on the RV to more advanced disease where the failing RV is the key determinant of outcome.

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Mortality in patients with pulmonary hypertension and heart failure with preserved ejection fraction

Over the last decades, the increasing prevalence of HFpEF (53) has been paralleled by an increasing presence of PH in patients with HFpEF (10). When compare to heart failure with reduced ejection fraction (HFrEF), patients with HFpEF have their subset of risks factors but finally, PH convey similar morbidity and mortality risk in the two subgroups of patients (10, 15, 19). 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

remodeling (2). 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 patients with HF who exhibit persisting PH after optimization 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 (34, 35, 40, 41, 47), 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. Though 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[18 19], with PH regressing to normal levels over 6-12 months after successful Mitral Balloon Valvotomy (MBV)[19]. In mitral regurgitation (MR), nearly all cohort studies on outcomes of severe PH reported increase mortality (3, 7, 38, 39, 42, 48). 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[20]. 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[19 21-23]. 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).

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Hospitalizations and other prognostic factors

The paucity of information on the effect of PH-LHD on hospitalizations or re- hospitalizations as showed in this study highlights the need for more evidence on this outcome. Such information is important to fully characterize 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 7 out of 9 studies. Similarly, a greater degree of MR, deceleration time when reported (28) and RV function were almost constantly associated with adverse outcome while LVEF was associated with adverse outcome in 6 of 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 ischemic heart disease. This precludes the generalizability of our findings to developing countries where etiologies of left heart diseases are less of ischemic origin and are more dominated by systemic hypertension, dilated cardiomyopathies and RHD in a younger population[24]. Therefore PH-LHD may have a different prognosis in developing countries. Secondly, studies included in this review defined PH based either on DE or RHC. RHC remains the gold standard to diagnose and confirm

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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 a 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 [25], 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 ~~multiplicity of PH definitions 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 characterized by a great heterogeneity in the number and range of candidate predictors included in the models, thus limiting interpretation and generalizability. 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. Secondly, we used the QUIPS instrument, designed for prognosis studies to address common sources of bias. The QUIPS, however, lacks discriminative power, henceforth we addressed this by using of the scoring algorithm suggested by de Jonge et al (6).

This scoring algorithm can still be subject to criticisms, especially because the cutoff points used to determine the quality of the studies are quite arbitrary. Thirdly, because of important heterogeneity in studies included, we were not able to pool data to perform a metaanalysis or to stratify data by clinically important subgroups (such as mild, moderate, or severe PH). However, to our knowledge, this is the first systematic review on determinants of hospitalizations and mortality in patients with PH-LHD and the search strategy used allowed us to present in large the results of more 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 left heart diseases should be actively investigated.

Authors 'contribution statement

Conceived and designed the protocol: AD and APK. Performed the literature search, selection and quality assessment of the articles and extraction of data: AD, APK and KS. Interpreted the data: AD, APK, FT and KS. Wrote the first draft of the manuscript: AD. Contributed to the writing of the manuscript: AD, APK, KS and FT. Agree with manuscript results and conclusions: AD, APK, FT and KS. All authors read and approved the final manuscript.

Declaration of competing interest

None for all co-authors

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Data sharing

No additional data available

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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, 2013[26]	Spain	Prospective hospital based cohort	KM, Cox regression	13.5	15	10	15	15	68.5	+
2.	Agawal et al, 2012[27]	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.	Agawal R, 2012[28]	USA – 96% blacks	Prospective hospital based cohort	KM, Cox regression	12	10	10	15	15	62	+
4.	Aronson et al, 2011[29]	USA	Prospective hospital based cohort	Cox regression	15	15	15	15	12.5	72.5	+
5.	Bursi et al, 2012[13]	USA - Caucasian and blacks	Prospective population based cohort study	KM, Logistic regression	15	12.5	12.5	12.5	15	65	+
6.	Strange et al, 2012[15]	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, 2012[30]	USA	Prospective hospital based cohort	KM, Logistic and cox regression, KM	13.5	15	10	15	15	69	+
8.	Tatebe et al, 2012[31]	Japan	Prospective hospital based cohort	KM, Logistic and cox regression	15	10	15	15	15	72.5	+
9.	Adhyapak et al, 2010[8]	India	Prospective hospital based cohort	Cox regression	13.5	10	10	12.5	5	53.5	+/-
10.	Stern et al, 2007[32]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	15	12.5	12.5	12.5	66	+
11.	Lee et al, 2010[33]	Korea	Prospective hospital based cohort	KM, Cox regression	15	15	15	12.5	15	72.5	+
12.	Møller et al, 2005[34]	USA	Prospective hospital based cohort	KM, Logistic regression	13.5	15	12.5	15	15	71	+
13.	Cappola et al, 2012[35]	USA, 35% black ands 65% whites	Prospective hospital based cohort	KM, Cox regression	13.5	7.5	12.5	15	15	62.5	+
14.	Szwejkowski et al, 2011[36]	UK	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	61	+
15.	Abramson et al, 1992[37]	USA	Prospective hospital based cohort	KM, Cox regression	12	15	10	15	12.5	64.5	+
16.	Kjaergaard et	Denmark	Prospective hospital	KM, Cox	13.5	15	12.5	15	15	71	+

	al, 2007[38]		based cohort	regression							
17.	Shalaby et al, 2008[39]	USA, 95% Caucasians	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	15	15	15	71	+
18.	Damy et al, 2010[16]	United Kingdom	Prospective hospital based cohort	KM, logistic and Cox regression	15	10	15	15	15	70	+
19.	Ristow et al, 2007[40]	USA	Prospective hospital based cohort	Logistic regression	13.5	12.5	10	15	5	48.5	+/-
20.	Grigioni et al, 2006[41]	Italy	Retrospective cohort	KM, logistic regression	13.5	12.5	12.5	15	15	68.5	+/-
21.	Levine et al, 1996[42]	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, 2010[14]	USA	Prospective observational community based cohort	KM, Logistic regression	12	15	10	15	12.5	68	+
23.	Kush et al, 2009[12]	Multicentric USA and Canada	Prospective cohort in the ESCAPE trial	KM	15	10	15	15	12.5	68.5	+
24.	Ghio et al, 2001[43]	Italy	Prospective cohort	KM, Cox regression	13.5	12.5	12.5	12.5	12.5	63.5	+
25.	Wang et al, 2010[17]	China	Retrospective cohort	KM	12	12.5	12.5	12.5	5	54.5	+/-
26.	Ghio et al, 2013[44]	Italy	Prospective cohort	KM, Cox and logistic regression	13.5	10	10	15	15	63.5	+
27.	Naidoo et al, 1991[45]	South Africa, Blacks	Retrospective cohort	No logistic regression, no Kaplan Meier analysis	12	7.5	10	5	7.5	42	-
28.	Fawzy et al, 2004[19]	Saudi Arabia	Prospective cohort	No logistic regression, no Kaplan Meier	12	10	12.5	15	7.5	57	+/-
29.	Roseli et al, 2002[46]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	63.5	+/-
30.	Melby et al, 2011[47]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	12.5	10	15	15	66	+
31.	Le Tourneau et al, 2010[48]	France, mainly Caucasians	Prospective hospital based cohort	KM, Cox regression	13.5	10	10	15	15	63.5	+
32.	Parker et al, 2010[7]	USA	Retrospective hospital based cohort	KM, Cox regression	12	15	12.5	15	15	71	+
33.	Kainuma et al, 2011[49]	Japan, Asians	Retrospective hospital based cohort	KM, Cox regression	10.5	10	12.5	12.5	10	55.5	+/-
34.	Barbieri et al, 2010[11]	Multicentric (Europe and USA)	Prospective hospital based cohort	KM, Cox regression	13.5	15	12.5	15	15	71	+

35.	Manners et al, 1977[50]	United Kindom	Retrospective hospital based cohort	No regression analysis, no KM estimation	10.5	7.5	5	5	2.5	30.5	-
36.	Malouf et al, 2002[51]	USA	Prospective hospital based cohort	KM, Cox and logistic regression	10.5	10	10	15	12.5	58	+
37.	Khandhar et al, 2009[52]	USA	Retrospective hospital based cohort	KM, Cox regression	13.5	10	10	15	12.5	61	+/-
38.	Zuern et al, 2012[53]	Germany	Prospective hospital based cohort	KM, Cox regression	15	7.5	10	15	15	62.5	+
39.	Ben-Dor et al, 2011[21]	USA	Prospective hospital based cohort	KM, Logistic regression	15	10	10	15	15	68	+
40.	Yang et al, 2012[54]	USA	Retrospective hospital based cohort	KM, Cox and logistic regression	15	7.5	15	12.5	15	65	+
41.	Nozohoor et al, 2012[55]	Sweden	Retrospective cohort	KM, Cox and logistic regression	13.5	10	10	15	12.5	61	+
42.	Ward and Hancock 1975[18]	UK	Retrospective cohort	No KM, no logistic or Cox regression	12	5	2.5	7.5	2.5	29.5	-
43.	Ghoreishi et al, 2012[56]	USA	Retrospective cohort	KM, Cox and logistic regression	15	10	10	10	15	60	+
44.	Cam A et al, 2011[22]	USA	Retrospective cohort	KM, Cox and logistic regression	13.5	15	10	10	12.5	61	+
45.	Pai et al, 2007[57]	USA	Retrospective cohort	KM, Cox and logistic regression	15	10	10	10	15	60	+

KM: Kaplan Meier; UK: United Kindom; USA:United states of America

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 Odd/Hazard ratios and CI	Mortality (all cause) rate at 6, 12, 24, 36 months or at mean duration of follow up				Adjusted odd/Hazard ratios 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[26]	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 per 10 person-s-year in severe PH	NA	NA	OR for mild PH 1.6 (0.7-3.74), moderate PH 1.34 (0.54-3.16) and severe PH 2.57 (1.07-6.27)
Agawal et al, 2012[27]	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 (1.1-1.9) and NU cohort HR 1.4 (1.1–1.7)
Agawal, 2012[28]	RVSP>35	288 patients undergoing hemodialysis 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 (1.31-3.61)

Aronson et al, 2011[29]	RHC with mPAP≥25 mmHg and mPCWP >15 mmHg	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 (0.6-4.5) and reactive PH 4.8 (2.1-17.5)
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 (1.13-1.85) and tertile 3: 2.07 (1.62-2.64)
Strange et al, 2012[15]	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[30]	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 (1.87-5.14)	NR	NR	NR	NR	HR for readmission 3.1 (1.87-5.14)

Tatebe et al, 2012[31]	RHC with mPAP≥25 mmHg mPCWP >15 mmHg	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 mortalityand 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 (1.03-1.35)
Adhyapak, 2010[8]	Echocardiography with mPAP > 25 mm Hg	147 patients with HF stratifiedinto: 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 (1.09–3.57)
Stern et al, 2007[32]	Echocardiography but criteria for PH not reported	68 patients needing cardiac resynchronization stratifiedinto group1 (RVSP ≥ 50 mmHg, n = 27) and group2(RVSP < 50 mmHg, n	7.1	70 64.7%	composite of hospitalization for HF and all cause mortality	NR	Group 1 39.7 ± 6.7 and group 1 60.2 ± 9.2	NR	NR	NR	Increased mortality in patients with RVSP≥50 mm Hg	NR	NR	HR of 2.0 (1.2-5.5) for RVSP≥50

		= 41)												
Lee et al, 2010[33]	RVSP>39 mm Hg	813 patients with TR stratifiedinto two groups based on the RVSP < 39 mmHg (group 1, n = 530) and RVSP ≥ 39 mmHg (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 (1.017–1.032)
Møller et al, 2005[34]	RVSP>30 mm Hg	536 patients with acute myocardial infarction stratifiedinto 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 group 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 (1.14-1.38) per 10 mm Hg increased
Cappola et al, 2012[35]	RHC with mPAP ≥ 25 mm Hg	1134 patients with cardiomyopathy stratifiedaccording to PVR: NPH (<2.5), group1 PH (2.5-3),	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 (1.30–2.65) for group2, 1.78 (1.13–2.81) for group3 and 2.04

		group2 PH (3-3.5), group3 PH(3.5-4) and group4 PH (>4)												(1.51–2.74) for group4
Szwejkowski et al, 2011[36]	RVSP>33 mm Hg	1612 patients with HF stratifiedinto 5 groups according to RVSP (< 33; 33-38; 39-44; 45-52 and >52 mmHg)	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 (1.03-1.08) for every 5 mm Hg increase in RVSP
Abramson et al, 1992[37]	Echocardiography with TRV>2.5 m/s	108 patients with dilated cardiomyopathy, stratifiedinto 2 groups: group1 (TRV< 2.5 m/s) and group 2 (>2.5 m/s), 38.9% in NYHA class III and IV, 77.3% of ischemic HF	28	67.5 81%	All cause mortality, mortality due to HF and re-hospitalizations for HF	NR	5.6 m/s	26	75% during the study period 5.76 (1.97-16.90)	NR	NR	NR	157% in 28 months vs 517%	OR for increased TRV 3.77 (1.38-10.24)
Kjaergaard et al, 2007[38]	Echocardiographybut cutoff for PH not reported	388 consecutive patients with known or presumed HF stratifiedinto quartiles of RVSP (<31, 31-38, 39-50, >50)	33.6	75 60%	All cause mortality	NR	38	75% and 50% with RVSP> 31 mm Hg and 40 mm Hg respectively	NR		48% if COPD and 21% in HF without COPD	NR	57% at 33.6 months	HR 1.09(1.04-1.14) for every increase of RVSP per 5 mm Hg
Shalaby et al, 2008[39]	RVSP≥30 mm Hg	270 patients undergoing cardiac resynchronization	19.4	66.5 91%	All cause mortality, cardiac transplantation (primary	NR	40.4	NR	40% in group 3 vs 9% in group 1 [6.35	NR	NR	NR	12% in group 1 vs 34% in group 3 at mean	HR 2.62 (1.07–6.41)

		stratifiedinto 3 groups on the basis of RVSP: group 1, (22 to 29, n= 86); group2(30 to 44, n=90) and group 3 (45 to 88, n=94).			end point) or re-hospitalization for HF				(2.55–15.79)]				follow up	
Damy et al, 2010[16]	Echocardiography with RVTG>25 mm Hg	1380 patients with congestive HF, 1026 with LVSD (EF<45%) and 324 without), further stratifiedinto 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(1.16–2.55) for RVSP>45 mm Hg)
Ristow et al, 2007[40]	Echocardiography with TR gradient > 30 mm Hg	717 patients with coronary artery disease, 573 with measurable TR, stratifiedinto group1 (TR gradient≤30 mm Hg, n=447) and group2 (TR gradient>30 mm Hg, n=126)	36	65, 74% (group 1) 69, 75% (group 2)	hospitalization, 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(1.03-2.2)	NR	NR	NR	11% (group I) vs 17% (group II)	OR for all cause deaths 1.2(0.85-1.6) per 10 mm Hg increase in TR OR for combined endpoint 1.6(1.1-2.4)
Grigioni et al, 2006[41]	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(1.42-3.73)	NR	NR	20% cardiovascular deaths	NR	HR for PH 2.3 (1.42-3.73) ; HR for worsening >30% in mPAP 2.6(1.45-

														4.67)
Levine et al, 1996[42]	RHC assessed change in PH, no definition	60 patients with PH owing to HF awaiting heart transplantation, stratifiedinto 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 10 months in group A and group B respectively	NR
Lam al, 2010[14]	RVSP> 35 mm Hg	244 patients with HFpEF compared with 719 subjects with HTN. 203 patients with HFpEF and PH later stratifiedinto: group 1 (RVSP<48 mm Hg) and group 2 (RVSP>48 mm Hg)	33.6	74/47 % vs 79*/41 % in group1 and group2 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 mmHg in RVSP (p<0.001)
Kush et al, 2009[12]	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 stratifiedinto 2	6	59/75 % vs 54*/71 % in MPH and non-MPH respectively	Rehospitalizations and all cause mortality	NA	mPAP: 42 vs 32 in MPH and non-MPH respectively TPG:17 vs 7 respective	47	HR for MPH 0.8(0.59-1.08)	21 vs 22	NR	NR	NR	HR for MPH 0.89(0.66-1.20)

		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)					ly							
Ghio et al, 2001[43]	RHC with mPAP≥20 mm Hg, RV systolic dysfunction defined as RVEF<35%	377 patients with HF stratifiedinto: group 1, normal mPAP/preserved RVEF (n=73); group 2 normal mPAP/low RVEF (n=68); group3, 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 group 1, 2, 3 and 4* respectively	HR 1.1(1.0-1.21) per each 5-mmHg increment
Wang et al, 2010[17]	RVSP> 30 mm Hg	93 patients with HF undergoing cardiac resynchronization stratifiedinto Group1: (RVSP>50mmH, n=29); Group2: (30<RVSP≤50 mmHg, n=17) and Group3:	32 (6-60)	59.6 81.7%	All cause mortality, HF mortality	NR	NR	49.5	NR	28 vs 6 vs 17% in group1,2, 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

		(RVSP≤30mm Hg, n=47)												
Ghio et al, 2013[44]	RVSP>40 mm Hg and RV dysfunction defined as TAPSE<14 mm	658 patients with chronic HF stratifiedinto 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 (2.18–3.06) for group3 and 4.27 (3.45–7.43) for group 4
Studies in patients with heart valve disease														
Fawzy et al, 2004[19]	Severe PH defined as RVSP> 50 mm Hg	559 patients with MS undergoing MBV stratifiedinto three groups: group A (RVSP<50 mmHg; n = 345); group B (RVSP 50-79 mmHg; n = 183) and group C (RVSP ≥80 mmHg; n = 31)	63 .6	31/28.1% vs 30/25.1% vs 27/16.1% in group A, B and C respectively	Reversibility of PH following MBV	NR	38.5 vs 59 vs 97.8 in group A, B and C respectively	62% vs 33% vs 5% for group A, B, and C respectively	NR	0	0	0	0	No mortality was encountered, PH normalized over a 6-12 months
Naidoo et al, 1991[45]	RHC with PASP≥<30 mm Hg	139 patients with AR (69 undergoing AVS) stratifiedinto groupI (normal or mild PH) and group II (moderate PH or marked PH)	6	32.9 vs 36.2 and 69.7 vs 77.8 in group I and II respectively	Immediate and 6 months post-operative mortality	NA	18 vs 43.7 in group I and II respectively	63.3	NR	3 in group I vs 2.8% in group II	NR	NR	NR	No increased in mortality, HR not reported
Manners et al, 1977[50]	RHC with PASP > 70 mm Hg	392 patients who had undergone prosthetic valve surgery stratifiedinto 2 PASP<70 mm Hg,	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

		n=336 or PASP>70 mm Hg, n=56)												
Roseli et al, 2002[46]	RVSP>35 mm Hg	2385 patients undergoing AVR stratifiedinto 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[47]	RVSP>35 mm Hg	1080 patients with AS undergoing AVR, stratifiedintoNPH, (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 (1.16-1.96), persistent PH after AVR was associated with Decreased survival.
Le Tourneau et al, 2010[48]	RVSP≥50 mm Hg	256 patients with MR undergoing MVO, stratifiedinto group1(RVSP<50 mm Hg, n=174) and group2(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 group1 and 2 respectively	NR	HR 1.43 (1.09-1.88) per 10 mmHg increment of RVSP
Parker et al, 2010[7]	RVSP> 35 mm Hg	1156 patients with MR or AR stratifiedinto 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(1.58–2.41) in AR and 1.48(1.26–1.75) in MR

Barbieri et al, 2010[11]	RVSP> 50 mm Hg	437 patients with MR, 35% NYHA class III or IV, normal LVEF, stratifiedintoNPH (RVSP≤50mm Hg) and PH (RVSP>50 mm Hg)	57.6	67 66%	All cause mortality, cardiovascular death, heart failure		45	23	1.70 (1.10–2.62) and 1.19 (1.06–1.35) for each 10 mm Hg increase of RVSP	NR		NR	23% at the mean follow up	HR 2.03 (1.30–3.18) and 1.16 (1.03–1.31) for each 10 mm Hg increase of RVSP
Kainuma et al, 2011[49]	Echocardiography, PH definition not specified	46 patients undergoing MVR, NYHA III or IV, LVEF<40%, stratifiedinto group1(RVSP< 40 mm Hg, n=19), group2(moderate PH (40<RVSP<60, n=17) and group3(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 group 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 (1.1-44) in group3
Khandhar et al, 2009[52]	Severe PH defined as RVSP>60 mm Hg	506 patients with severe AR stratifiedinto 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[51]	Severe PH defined as peak TRV≥4 m/s	3171 patients with AS of whom 47 with severe PH , stratifiedinto 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 group1 and 2 respectively at median FU	OR for mortality risk in severe PH and AVS 1.76 (0.81-3.35)

Zuern et al, 2012[53]	RVSP > 30 mm Hg	200 patients with AS undergoing AVR stratifiedinto 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 (1.1-21.8) and severe PH 3.3(0.6-19.7)
Ben-Dor et al, 2011[21]	RVSP > 40 mm Hg	509 patients with AS divided into group1(RVSP< 40 mm Hg, n= 161); group2 (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 group1, 2, and 3 respectively, > 75%	All cause mortality	NR	33.7 vs 49.3 vs 70.7 in group1, 2, and3 respectively	68.3	NR	NR	NR	NR	21.7 vs 39.3 vs 49.1 in group1, 2, and3 respectively at median FU*	PH was significantly associated with increase in mortality, OR/HR not reported
Yang et al, 2012[54]	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	Post operative 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 (1.119-1.943)
Nozohoor et al, 2012[55]	RVSP> 50 mm Hg	270 patients with MR undergoing MVS, stratifiedinto 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(1.1–17.4) during the initial 3 years after MVS
Ward and Hancock 1975[18]	RHC with extreme PH defined as SPAP>80 mmHg and PVR >10 Wu: 8.2%	Mitral valve disease (n = 586), 48 extreme PH stratifiedinto group 1 (no operation), group 2 (all surgical) and group 3 (survive after surgery)	69.6	46.2 vs 42.4 43vs29% 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

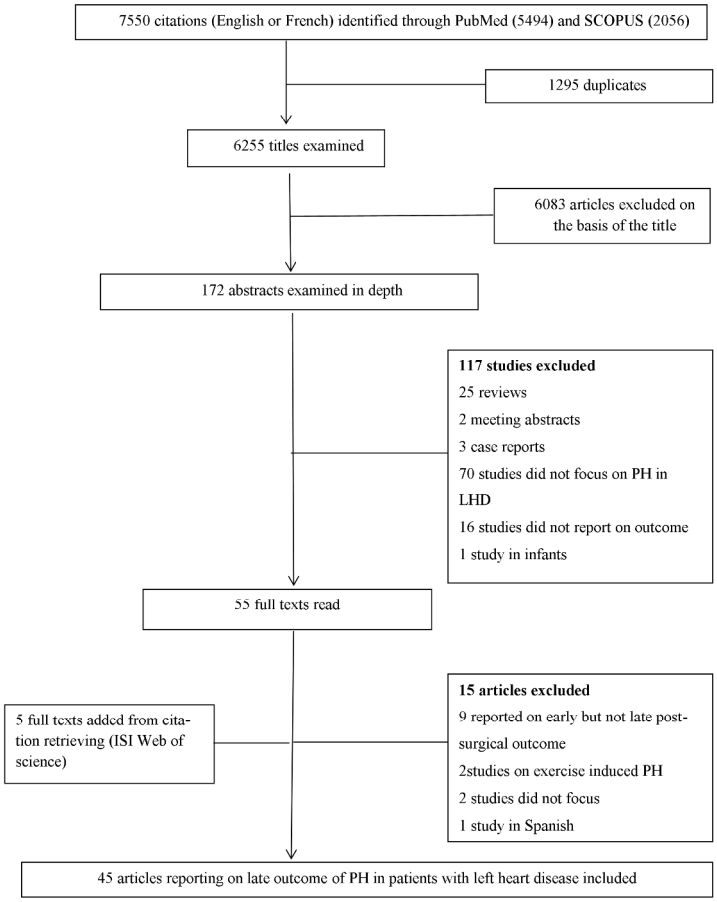
Ghoreishi et al, 2012[56]	sPAP>40 mm Hg using RHC in 591 patients and RVSP>40 mm Hg using DE	873 patients with MR who underwent MVS, stratifiedintoNPH and PH group (mild, moderate, severe) NHYA not reported	35	59 59%	Hospital mortality, Late all cause mortality	NR	46 (echo), and sPAP was 43 by RHC	53	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(1.007-1.028) per each 1 mm Hg increment in RVSP
Cam A et al, 2011[22]	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 (0.9-1.11) and early post-operative reduction in mPAP 0.93 (1.2-12.5)
Pai et al, 2007[57]	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 (0.16-0.51) independent of PH.

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; 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); NPH: Non pulmonary hypertension; 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); UTSW: University of Texas—Southwestern; WU: Wood units; P<0.05 **

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
SPO2	3	3	1	0
Hypotension	1	1	1	0
Atrial fibrillation	5	5	5	0
Ischemic etiology of HF	4	4	0	0
Urea	2	2	1	0
Kidney disease (by creatinine, GFR, or hemodialysis)	17	14	6	0
BNP	3	3	2	0
Hemoglobin	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: Angiotensin converting enzyme inhibitors; BNP: Brain natriuretic peptide; BP: Blood pressure; COPD: Chronic obstructive pulmonary disease; GFR: Glomerular filtration rate; HF: Heart failure; MI: Myocardial infarction; NYHA: New York Heart Association; RVSP: Right ventricular systolic pressure; RV: Right ventricle; TAPSE: Tricuspid annular plan systolic excursion; WHO: World Heart Organization.



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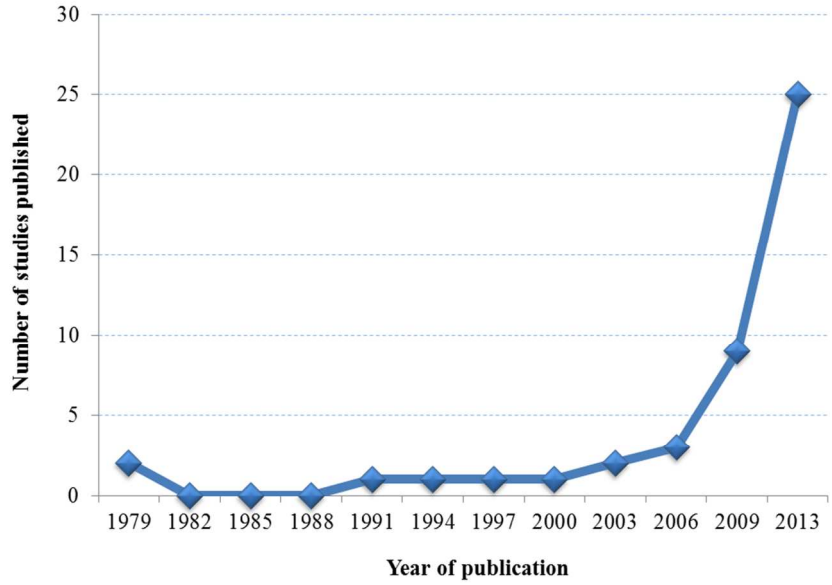

Number of studies on outcome of pulmonary hypertension associated with left heart disease identified over time
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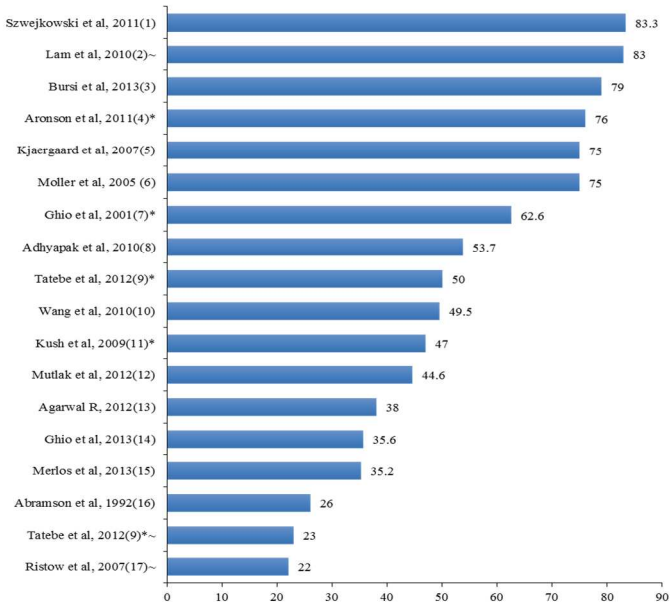

¤ Studies that used right heart catheterization for diagnosis of PH
~ Studies in patients with preserved ejection fraction

Prevalence of pulmonary hypertension in some selected studies in patients with heart failure
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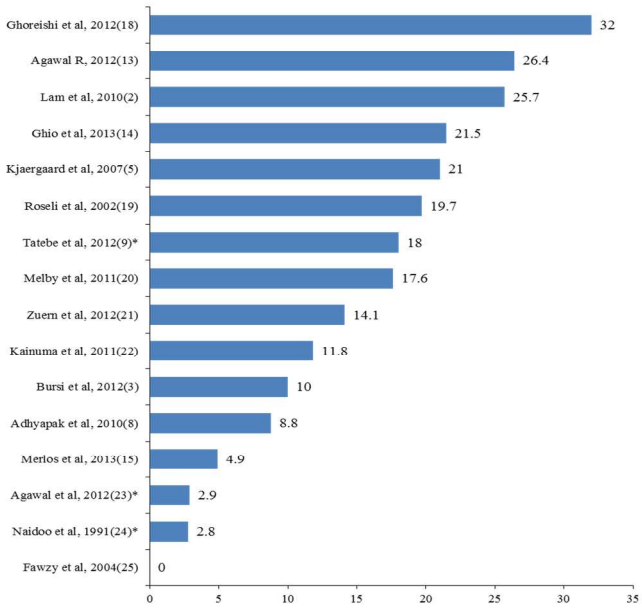

¤ Studies that used right heart catheterization for diagnosis of PH

Mortality rates at 12 months in some selected studies in patients with pulmonary hypertension associated with left heart disease¤¤
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- **Online box, table and references section for figures -**

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

(manuscript ID bmjopen-2014-004843.R1)

Online box: Search terms used in the builder

For pubmed:

((((pulmonary hypertension) OR pulmonary pressure)) AND (((heart failure) OR left heart disease) OR valvular heart disease)) AND ((((((predict) OR outcome) OR risk) OR prognosis) OR discrimination) OR c statistic)

For Scopus:

((((pulmonary hypertension) OR pulmonary pressure)) AND (((heart failure) OR left heart disease) OR valvular heart disease)) AND ((((((predict) OR outcome) OR risk) OR prognosis) OR discrimination) OR c statistic) AND (LIMIT-TO(SUBJAREA, "MEDI")) AND (LIMIT-TO(EXACTKEYWORD, "Heart failure") OR LIMIT-TO(EXACTKEYWORD, "Mortality") OR LIMIT-TO(EXACTKEYWORD, "Prognosis") OR LIMIT-TO(EXACTKEYWORD, "Echocardiography") OR LIMIT-TO(EXACTKEYWORD, "Risk Factors") OR LIMIT-TO(EXACTKEYWORD, "Heart Failure") OR LIMIT-TO(EXACTKEYWORD, "Pulmonary hypertension") OR LIMIT-TO(EXACTKEYWORD, "Treatment Outcome") OR LIMIT-TO(EXACTKEYWORD, "Follow up")) AND (LIMIT-TO(SUBJAREA, "MEDI")) AND (LIMIT-TO(LANGUAGE, "English") OR LIMIT-TO(LANGUAGE, "French"))

Online table: Scoring algorithm developed by de Jonge et al[6] to strengthen the discriminative capacity of the QUIPS*

Criteria**	Score		
	+	+/-	-
1. Study participation			
• Target population	3	1.5	0
• Sampling frame	3	1.5	0
• Inclusion criteria	3	1.5	0
• Baseline study population	3	1.5	0
• Adequate study participation	3	1.5	0
2. Study attrition			
• Proportion of population available for analysis	5	2.5	0
• Outcome and prognostic factor information on	5	2.5	0
• Reasons and potential impact of subjects lost to	5	2.5	0
3. Measurement of prognostic factors			
• Definition of prognostic factor	5	2.5	0
• Valid and reliable measurement of prognostic	5	2.5	0
• Method and setting of prognostic factor	5	2.5	0
4. Measurement of outcomes			
• Definition of outcome	5	2.5	0
• Valid and reliable measurement of outcome	5	2.5	0
• Method and setting of outcome measurement	5	2.5	0
5. Statistical analysis and presentation			
• Presentation of analytical strategy	5	2.5	0
• Model development strategy	5	2.5	0
• Reporting of results	5	2.5	0

* QUIPS: Quality In Prognosis Studies

** Used (adapted) QUIPS list for scoring methodological quality of prognosis studies

All five domains were given a maximum of 15 points each, equally distributed across all items per category. For four items we assigned 5 points in case of low risk of bias and 2.5 and 0 in case of moderate and high risk of bias, respectively, except for category 1 (patient selection bias) containing five instead of three items, for which we assigned 3 points in case of low risk of bias and 1.5 and 0 in case of moderate and high risk of bias, respectively. A total score, with a maximum of 75 points, was calculated by summing up the scores per item. A priori, we chose to consider ≥60 points (≥80% of the maximum attainable score) as high quality, between 45 and 60 points (≥60% of the maximum attainable score) as moderate/high quality and <45 points as low quality studies.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6,7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, 40
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7,8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8,9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	24-38
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	25,25
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	26-38
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	24,25
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15,16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

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