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RESEARCH ARTICLE

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An updated meta-analysis of hemodynamics markers of prognosis in patients with pulmonary hypertension due to left heart disease

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Abstract

Pulmonary hypertension (PH) is associated with a poor prognosis in left heart disease (LHD). We sought to provide an updated analysis on the association of hemodynamic variables, such as pulmonary vascular resistance (PVR), pulmonary artery compliance (PAC), and diastolic pressure gradient (DPG), with prognosis in PH-LHD, through a systematic literature review. Sixteen articles were identified, including 9600 patients with LHD, heterogeneous in terms of age, sex, and etiology of cardiac disease. In this large population, PVR (hazard ratio [HR], 1.07; 95% confidence interval [CI]: 1.05−1.0), DPG (HR, 1.02; 95% CI: 1.01−1.02) and PAC (HR, 0.76; 95% CI: 0.69−0.84) were associated with an increased risk of adverse outcome, albeit with a less solid performance of DPG. Similar results were found when hemodynamic variables were analyzed according to the thresholds commonly applied in clinical practice, or subdividing cohorts according to the underlying LHD. Furthermore, cumulative metanalysis indicated that these results are consistently stable since 2018. Thus, PVR, DPG and PAC have an established prognostic value in PH-LHD. These results are consistent through the years and unlikely to change with further studies.

KEYWORDS
hemodynamics, pulmonary hypertension, left heart disease, prognosis

BACKGROUND

Pulmonary hypertension (PH) is a common complication and a consequence of left heart disease (LHD). It is defined by a mean pulmonary arterial pressure (mPAP) > 20 mmHg and a pulmonary arterial wedge pressure (PAWP) > 15 mmHg which corresponds to the postcapillary hemodynamic presentation.[1] As such, it can be interpreted as an abnormal biomarker of the underlying cardiac disorder, where the increase in pulmonary artery pressure (PAP) is explained by passive backward transmission of high filling pressure from the left atrium to the pulmonary circulation, defining isolated postcapillary PH (IpcPH).[1]

However, in a minority of patients, a precapillary component of PH may develop[1,2] through several mechanisms that may eventually lead to pulmonary vascular remodeling affecting the structure and function of the pulmonary circulation.[3,4] When present, the hemodynamic phenotype of combined post and precapillary PH (CpCPH) may potentially expose patients to a poorer outcome.[2,4]

Over the past years, several hemodynamic parameters have been proposed to identify this more severe profile, although their association with outcome has led to contrasting results. In a previous meta-analysis on the hemodynamic predictors of outcome ($n = 2513$ patients with PH-LHD), both the diastolic pressure gradient (DPG), pulmonary vascular resistance (PVR) and pulmonary artery compliance (PAC) appeared to be associated with mortality. However, PVR and PAC seemed to be more strongly associated with outcome than DPG.[5]

Accordingly, the new hemodynamic definition proposed at the 6th World Symposium on PH held in 2018, reintroduced PVR alone to differentiate IpcPH to CpcPH. This was thought to better reflect the impact of the right ventricle on outcome,[1] at variance from the previous guidelines' definition, where the PH-LHD profile was defined as "isolated" if DPG < 7 mmHg and/or PVR ≤ 3 WU; and "combined" if DPG ≥ 7 mmHg and/or PVR > 3 WU. Moreover, additional studies were performed to better characterize the severity of PH-LHD since 2018. We therefore sought to assess whether recent data were consistent with previous findings.

METHODS

We followed the PRISMA statement[6] for reporting systematic reviews and meta-analysis. A comprehensive literature research in Pubmed bibliographic database was updated to December 2020, and the search terms included: ("left heart disease" OR "LHD" OR "heart failure with preserved ejection fraction" OR "HFpEF" OR "heart failure" OR "HF" OR "diastolic dysfunction" OR "diastolic heart failure" OR "HFrEF" OR "heart failure with reduced ejection fraction" OR "VHD" OR "valvular heart disease") AND ("PH" OR "pulmonary hypertension" OR "PH-LHD" OR "PHLHD" or "pulmonary hypertension due to left heart disease" OR "post-capillary pulmonary hypertension" OR "IpCPH" OR "CpCPH" OR "isolated post-capillary pulmonary hypertension" OR "combined post- and pre-capillary pulmonary hypertension") AND ("hemodynamics" OR "wedge pressure" OR "PAWP" OR "PCWP" OR "pulmonary capillary wedge pressure" OR "occlusion pressure" OR "right heart catheterization" OR "RHC" OR "cardiac catheterization") AND ("mortality" OR "death"). Each term was considered as both free text and Mesh terms. We only included English-language publications.

We only included cohort studies reporting association measurements (and corresponding 95% confidence intervals [CI] or data allowing the estimation of their standard error) between DPG and/or PVR and/or PAC and death (or heart failure hospitalization) in PH-LHD patients. Relative risk, odds ratio and hazard ratio (HR) were considered adequate association measurements. In case of duplicated data, only the most recent publication was selected. Studies focusing on the effects of specific treatments (including drugs approved for pulmonary arterial hypertension), investigating the outcome after left ventricular assistance device implantation or heart transplantation, or those evaluating short-term follow-up (i.e., less or equal to 1 year) were excluded.

Two authors independently assessed paper's eligibility; disagreements between readers were solved by consensus.

Extraction data

For each included study, we recorded the following variables: country, length of follow-up, sample size, etiology of LHD, age, sex, body mass index (BMI), New York Heart Association functional class, prevalence of comorbidities (arterial hypertension, atrial fibrillation, diabetes, coronary artery disease, and obesity), background treatments (diuretics, betablockers, or angiotensin-converting enzyme inhibitors), N-terminal pro brain natriuretic peptide, glomerular filtration rate, left ventricular ejection fraction, hemodynamic data (heart rate, pulmonary artery pressures, pulmonary artery wedge pressure, right atrial pressure, cardiac output, cardiac index, DPG, transpulmonary pressure gradient, stroke volume, PVR, and PAC), thus including hemodynamic variables tested for association with outcomes, as well as covariates included in multivariate analysis.

Statistics

Sociodemographic and clinical continuous characteristics of each cohort were reported as mean and standard deviation (SD). If the original paper showed median and interquartile range [IQR] we transformed them in mean and SD value following Wan et al.[7] Categorical variables were reported as proportion. Summary of clinical and hemodynamic characteristics of included studies was performed by order statistics (minimum, maximum, median, and IQR). For each hemodynamic variable of interest, we estimated the pooled HR of death and its 95% CI from a fixed model. This was done both for continuous variables and for dichotomized variables according to more frequently used thresholds (PVR > 3 WU, DPG ≥ 7 mmHg, PAC < 2.3 ml/mmHg). A random effect model[8] was applied when the Q-statistic was statistically significant. Moreover, between-studies' heterogeneity was quantified by means of I^2 index.[9] A subgroup analysis was performed based on the presence of adjustment covariates to estimate the original HR. The homogeneity between subgroup pooled HRs was tested. Cumulative meta-analysis was performed to investigate temporal trends in the effects reported in the literature as well as the impact of sample size. An influence analysis was conducted to verify the impact of each estimate on the pooled HR, omitting one study at time. Publication bias presence was evaluated by both funnel plot and Egger test.[10] Moreover, when Egger test resulted statistically significant, a trim and fill approach was applied to correct the funnel plot asymmetry.[11] An exploratory analysis on the association between hemodynamics and outcomes stratifying patients according to the underlying LHD was performed only for the studies that reported the HR for a given hemodynamic variable in a homogeneous patients' cohort. Results were considered statistically significant when two-tailed *p* value was lower than 0.05. All analyses were performed with R version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

Out of 551 manuscripts identified by bibliographic search, 535 did not fulfilled inclusion criteria. Details about exclusion reasons as reported in Figure 1.

The final analysis was conducted on 16 articles, including a total of 9600 patients with LHD in whom

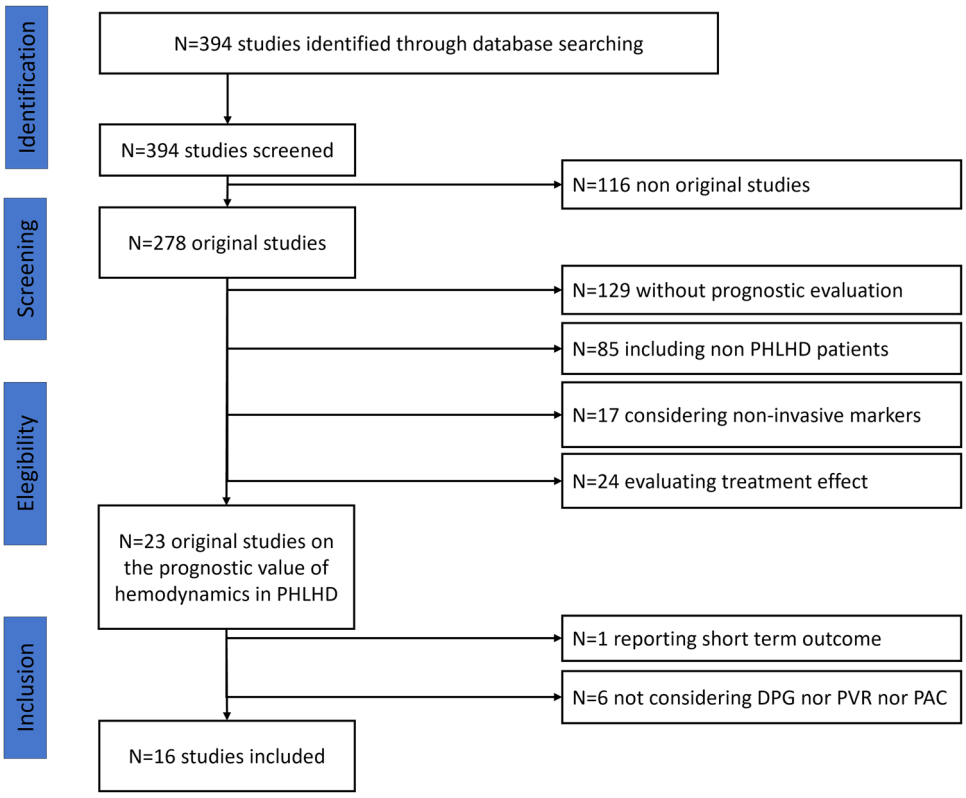

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection. DPG, diastolic pressure gradient; LVAD, left ventricular assistance device; MRI, Magnetic Resonance Imaging; PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PHLHD, pulmonary hypertension due to left heart disease; PVR, pulmonary vascular resistance.

invasive hemodynamics were performed. Characteristics of individual studies are reported in Table 1.

Most of studies included PH-LHD patients independently from the underlying cardiac disease (either heart failure with preserved or reduced left ventricular ejection fraction, or VHD), while six studies focused on one specific etiological subgroup, such as HFpEF,[12,13] HFrEF[14,15] and VHD.[16–18]

The association between hemodynamics (PVR, DPG, and PAC) and outcome was reported on continuous scale in 13 studies,[12–16,19–26] while 13 studies dichotomized PVR, DPG, and PAC according to prespecified cut-offs.[12–17,19,21,23–27]

In most of the studies, a multivariate analysis was performed to adjust the effect on PVR, DPG, and PAC of covariates such as age and sex,[12,15,17–23,27] BMI,[12,17–19,21] comorbidities[15,17,20–23,27] and hemodynamic parameters.[12,18,20,23]

Clinical and hemodynamic characteristics

Analysis of the different populations revealed heterogeneity in terms of age, sex, and etiology of PH-LHD (Table 1). As reported in Table 2, median age was 64 years old, with values varying from 47 to 83 years old. Female sex prevalence varied from 17% to 76% and median BMI was 28 kg/m^2 (from 26 to 30 kg/m^2).

The populations were characterized by a significant burden of comorbidities, including atrial fibrillation, whose prevalence varied from 15% to 71%, and were largely treated with diuretic, betablocker and antihypertensive therapies. However, a complete non-invasive assessment by echocardiography and biological tests was not reported in all studies, while left ventricular ejection fraction was reported in most studies, with a median value of 44.2% (IQR 39%−51%), as well as brain natriuretic peptide, with a median value of 802.7 pg/ml (IQR 464.7−970.0 pg/ml).

Mean PAP had a median value of 38 mmHg (36−42 mmHg). Almost all studies[12–19,21–26] reported PAWP and PVR, whose median values were, respectively, 24 [22−24] mmHg, and 3.9 [2.7−5.1] WU, which corresponds to the CpcPH presentation.

Twelve studies reported DPG[12–14,17–19,21,22,24–27] whose median value was 1.8 [−0.4 to 6.9] mmHg and 11 studies[12,14–17,21,23–27] reported PAC, with a median value of 2.1 [1.8−2.4] ml/mmHg. Thorough hemodynamic characteristics of included patients across studies are reported in Table 3.

Almost all studies defined PH according to 2015 PH Guidelines, except for one[16] in which the definition proposed during the 6th Symposium of PH was adopted.

A major part of authors[12,15,17,18,21–27] stratified the patients on the base of the presence of a precapillary component, mostly considering a DPG ≥ 7 mmHg,[12,17,18,21,22,27] PVR > 3 WU [15,18] or a combination of both,[23–26] while 2 authors considered also a TPG > 12 mmHg.[20,22] Following this heterogeneous classifications of the pre-capillary component, IpCPH cohort was composed of 5234 patients and CpCPH one by 2374 patients.

Association between hemodynamic variables and outcomes

Overall, unitary increase in PVR was significantly associated with outcome in PH-LHD (HR, 1.07; 95% CI: 1.05−1.08) (Figure 2). This held true also when separately analyzing studies where the association between PVR and mortality was either unadjusted or adjusted for relevant covariates. These findings were consistently achieved when 1263 patients were analyzed, or in the year 2015, as suggested by cumulative meta-analysis (Figures 3 and 4).

DPG was associated with mortality in PH-LHD (HR, 1.02; 95% CI: 1.01−1.02). However, such an association was no more significant when considering only the 2 studies performing an adjustment for covariates (Figure 2). Cumulating evidence by publication year noted that the initial statistically significant strong effect of 2013 was not confirmed until 2018 and with weaker pooled HR (Figure 4). Moreover, at the cumulative meta-analysis based on the sample size, the studies demonstrated a high degree of heterogeneity and the overall effect gained stability only after having included 480 patients (Figure 3).

PAC was significantly associated with mortality in PH-LHD (HR, 0.76; 95% CI: 0.69−0.84) (Figure 2). Despite a non-negligible heterogeneity between included studies ($I^2 = 60\%$), results were consistent when only 73 patients were analyzed (Figure 3) or in the year 2015 (Figure 4).

Only 9 out of 16 studies reported the association between PAWP and outcome. Only in 3 of these 9 studies such association was statistically significant.

Influence and publication bias analysis

No study influenced the summary estimates of PVR, DPG and PAC (e-Figure 1). Moreover, Egger test suggested publication bias for both PVR and PAC although in an opposite direction, that is, with an underestimation for PAC and an overestimation for PVR. However, trim and

TABLE 1 Characteristics of included studies

Author (year)	Country	Sample size, *N*	Age, years	Female gender, %	BMI, kg/m^2	HFpEF	HFrEF	VHD	Hemodynamic variables tested for association with outcomes	Covariates in multivariate analysis	Outcome
Gerges et al.[22]	Austria	1094	63 ± 13		26.3 ± 4.5	≈55%	≈45%	Significant VHD ≥ 1/3 of patients (comorbidity)	DPG continuous	Sex, age, GFR < 60, CAD	Death
Miller et al.[15]	USA	337	59 ± 14	25	29.1 ± 6.4	0%	100%	Significant VHD ≥ 1/3 of patients (comorbidity)	PVR dichotomized (>/≤3 WU) PAC continuous and dichotomized (>/≤ 2.3 ml/mmHg)	Risk factors that were significantly different among the groups at baseline and clinically important factors	Death
Dragu et al.[20]	Israel	264	66 ± 12	55		45%	76%	24%	PVR continuous PAC continuous	age, gender, estimated GFR, LV and RV function, RAP, PCWP, and type of PH	Death
Al-Naamani et al.[12]	USA	73	69 ± 12	74	33 ± 10	100%	0%	0%	DPG continuous and dichotomized (≥/<7 mmHg) PVR continuous PAC continuous	Age, sex, ethnicity, BMI, haemodynamic parameters	Death
O'Sullivan et al.[17]	Switz	269	83 ± 5	58	26.3 ± 5			100%	DPG dichotomized (≥/<7 mmHg)	Age, sex, BMI, DM, previous CABG, PVD, previous MI, CAD, LVEF ≤ 30%, COPD	Death after transcatheter aortic valve implantation
Gerges et al.[27]	Austria	668				67%	38%	62%	DPG dichotomized (≥/<7 mmHg)	Sex, age, GFR < 60, CAD	Death

(Continues)

TABLE 1 (Continued)

Author (year)	Country	Sample size, *N*	Age, years	Female gender, %	BMI, kg/m^2	HFpEF	HFrEF	VHD	Hemodynamic variables tested for association with outcomes	Covariates in multivariate analysis	Outcome
Assad et al.[21]	USA	1820	61 ± 14	44	31.2 ± 8.2			Significant VHD ≥ 8% of patients (comorbidity)	DPG continuous and dichotomized (≥/<7 mmHg)	Age, sex, BMI, COPD, ILD, OSA, CAD, AF, VHD, lupus, scleroderma	Death
Palazzini et al.[26]	Italy	276	69 (60–75)	75		41%	9%	50%	DPG continuous and dichotomized (≥/<7 mmHg) PVR continuous and dichotomized (>/≤3 WU) PAC continuous and dichotomized (>/≤2 ml/mmHg)		Death
Brunner et al.[18]	Canada	133	80 ± 8	47	28 ± 7			100%	DPG dichotomized (≥/<7 mmHg) PVR dichotomized (>/≤3 WU)	Age, sex, BMI, PASP	Death after transcatheter aortic valve replacement
Vanderpool et al.[13]	USA	2587	65 ± 38	45	31 ± 9	100%	0%	0%	DPG continuous and dichotomized (≥/<7; >/<4.7 mmHg) PVR continuous and dichotomized (>/≤3; >/<2.3 WU) PAC continuous		Death

TABLE 1 (Continued)

Author (year)	Country	Sample size, *N*	Age, years	Female gender, %	BMI, kg/m^2	HFpEF	HFrEF	VHD	Hemodynamic variables tested for association with outcomes	Covariates in multivariate analysis	Outcome
Tampakakis et al.[19]	USA	1036	57 (45–67)	39	27.7 (23.9–3-3.3)				DPG continuous and dichotomized (≥/<7 mmHg) PVR continuous PAC continuous	Model 1: age Model 2: age, BMI, HR, sex, and cohort	Death
Caravita et al.[24]	Belgium	93	64 ± 13	55	29 ± 5	51 + 45 + 63	49 + 45 + 30	0 + 10 + 7	DPG continuous and dichotomized (≥/<7; >/<2.5 mmHg) PVR continuous and dichotomized (>/≤3 WU) PAC Continuous		Death
Dragu et al.[23]	Israel	393	66 ± 12	56					DPG dichotomized (≥/<7 mmHg) PVR dichotomized (≥/<3 WU)	Age, gender, GFR, Hb, LV and RV function, RAP, PAWP, type of PH	Death or HF admission
Quan et al.[14]	China	92	47 ± 13	17	24 ± 4.7	0%	100%	0%	PVR continuous or dichotomized (>/≤ 3 WU) DPG continuous or dichotomized (≥/<7 mmHg) PAC continuous		Death or transplanta-tion pr hospital-ization
Sugimoto et al.[25]	Japan	243	64 ± 15	44					PVR continuous or dichotomized (>/≤3 WU) DPG continuous and		Cardiac death

(Continues)

TABLE 1 (Continued)

Author (year)	Country	Sample size, *N*	Age, years	Female gender, %	BMI, kg/m^2	HFpEF	HFrEF	VHD	Hemodynamic variables tested for association with outcomes	Covariates in multivariate analysis	Outcome
									dichotomized (≥/<7 mmHg) PAC continuous		
Bermejo et al.[16]	Multicentric	222	72 (66−77)	76		0%	0%	100%	PVR continuous or dichotomized (>/≤3 WU) DPG continuous and dichotomized (≥/<7 mmHg) PAC continuous		Death

Note: Continuous data are reported as mean ± SD or median (interquartile range); proportions are reported as percentage.

Abbreviations. AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CABG, Coronary artery bypass graft; CAD, coronary artery disease; COPD, Chronic obstructive pulmonary disease; DM, diabetes mellitus; DPG, diastolic pressure gradient; GFR, glomerular filtration rate; Hb, hemoglobin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; ILD, interstitial lung disease; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NTproBNP, N-terminal pro brain natriuretic peptide; NYHA FC, New York Heart Association functional class; OSA, obstructive sleep apnea; PAC, pulmonary artery compliance; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricle; USA, United States of America; VHD, valvular heart disease.

TABLE 2 Summary of clinical and hemodynamic characteristics of included studies

Variable	*N* papers	*N* estimates	Minimum	25° pctl	Median	75° pctl	Maximum	% missing data
Age, years	16	27	46.8	60.0	64.3	67.9	82.6	0%
Female sex, %	15	26	17.0	39.0	50.7	56.0	76.0	4%
BMI, Kg/cm^2	11	17	24.0	26.3	28.0	29.9	33.0	37%
NYHA FC III–IV,%	5	6	49.0	61.0	72.3	83.0	100.0	78%
Atrial fibrillation, %	9	17	15.3	32.0	44.0	46.0	71.0	37%
Arterial hypertension, %	8	14	22.0	38.3	64.0	80.0	86.0	48%
Diabetes, %	7	10	23.0	29.0	34.0	41.0	49.0	63%
CAD, %	7	13	19.0	36.7	50.0	57.0	81.0	52%
Diuretics, %	7	13	54.0	67.0	72.0	79.0	97.0	52%
Bblockers, %	8	16	43.0	56.5	71.5	79.0	92.0	41%
ACEi/ARBs, %	8	16	25.0	41.0	57.5	83.0	88.0	41%
BNP, pg/ml	4	7	313.0	464.7	802.7	970.0	1078.0	74%
GFR, ml/min	6	13	50.0	53.0	54.0	64.0	70.0	52%
LVEF, %	8	13	23.0	38.6	44.2	51.2	64.3	52%
HR, bpm	12	20	71.0	74.0	78.0	82.0	90.0	26%
SPAP, mmHg	13	21	30.4	53.7	57.0	62.0	74.0	22%
DPAP, mmHg	12	19	12.6	23.0	25.0	32.0	38.4	30%
MPAP, mmHg	16	27	18.9	36.4	38.0	42.0	50.1	0%
PAWP, mmHg	15	25	11.2	22.0	23.5	24.0	26.7	7%
CI, L/min/m^2	11	18	1.9	2.2	2.5	2.8	2.9	33%
RAP, mmHg	15	24	5.8	10.7	12.0	13.7	15.0	11%
DPG, mmHg	13	20	−3.7	−0.4	1.8	6.9	12.7	26%
PVR, WU	15	24	1.7	2.7	3.9	5.1	9.3	11%
PAC, ml/mmHg	11	20	0.6	1.8	2.1	2.4	3.1	26%

Note: Data are reported as median, 25° and 75° percentile, minimum/maximum value.

Abbreviations: ACEi, Angiotensin-converting-enzyme inhibitors; ARBs, Angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; CI, cardiac index; DPAP, diastolic pulmonary artery pressure; DPG, diastolic pressure gradient; GFR, glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary artery pressure; NYHA FC, New York Heart Association functional class; PAC, pulmonary artery compliance; PAWP, pulmonary artery wedge pressure; PCTL, percentile; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SPAP, systolic pulmonary artery pressure; WU, Wood Unit.

fil approach confirmed findings of the main analysis after controlling for this source of bias (e-Figure 1).

Stratification according to the underlying LHD

We performed an exploratory analysis on the association between hemodynamics and outcomes stratifying patients according to the underlying LHD (HFpEF, HFrEF, and VHD). The results of this exploratory analysis were in line with those obtained in the whole cohort, even though they resulted significant in all the three conditions only for PVR (e-Figure 2).

DPG, PVR, and PAC considered as dichotomous variables

For this analysis, we considered only papers reporting the association measurements when DPG, PVR and PAC were dichotomized using the following cut-off values: PVR > 3 WU; DPG ≥ 7 mmHg; PAC < 2.3 ml/mmHg. DPG > 7 mmHg as well as PVR > 3 WU were both

TABLE 3 Hemodynamics of patients with left heart disease as reported in individual studies

Author	SPAP	DPAP	MPAP	PAWP	RAP	TPG	DPG	HR	SV	CO	CI	PVR	PAC
Gerges et al.[22]	56 ± 16	25 ± 8	37 ± 10	24 ± 8	10 ± 5	13 ± 8	1 ± 7	78 ± 16		4.8 ± 1.4	2.6 ± 0.7	3.0 ± 2.1	
Miller et al.[15]	56 ± 12		38 ± 7		15 ± 7	14 ± 5		77 ± 17	56 ± 19		4.2 ± 1.1	3.7 ± 1.5	2.1 ± 0.8
Dragu et al.[20]	59 ± 14	26 ± 7	39 ± 8	24 ± 6	24 ± 6	15 ± 6			63 ± 25				
Al-Naamani et al.[12]			41 ± 11	21 ± 4	13 ± 5	19 ± 10	5 ± 7	71 ± 14	69 ± 29	4.7 ± 1.5		4.9 ± 3.7	2.1 ± 1.2
O'Sullivan et al.[17]	59 ± 12	24 ± 6	39 ± 8		9 ± 4	14 ± 8	−1 ± 6	80 ± 15	49 ± 15	3.7 ± 1.3	2.1 ± 0.5	4.2 ± 2.8	0.8 ± 0.4
Gerges et al.[27]			38 ± 9	24 ± 7	10 ± 5	14 ± 6	2 ± 5	78 ± 16		4.8 ± 3.4	2.5 ± 0.7	3.2 ± 1.7	2.3 ± 1.2
Assad et al.[21]	56 ± 15	25 ± 6	38 ± 9	24 ± 6	12 ± 6	18 ± 6	2 ± 5	74 ± 16		2.7 ± 0.9		3.2 ± 2.0	2.6 ± 1.7
Palazzini et al.[26]	60 (48–76)	22 (18–29)	37 (31–46)	20 (18–23)	12 (8–16)	16 (12–24)	1 (−2 to 7)	75 (65–85)			2.6 (2.2–3.1)	3.6 (2.3–5.6)	1.8 (1.2-2.2)
Brunner et al.[18]	59 ± 15	24 ± 6	38 ± 8	24 ± 7	11 ± 5	14 ± 8	0 ± 7	4.0 ± 3.1		3.9 ± 1.1			
Vanderpool et al.[13]	58 ± 18	23 ± 8	38 ± 10	24 ± 15	14 ± 7	12 (9-18)	−1 (−4-3)	77 ± 18	79 ± 36	5.7 ± 2.1	2.9 ± 0.9	2.3(1.5–3.6)	
Tampakakis et al.[19]	53(45–63)	27(22–31)	35(30–42)	25(20–35)	13(9–18)	11 (7–14)	1(−1 to 5)	81 (69–97)			2.3 (1.7–2.7)	2.3(1.4–3.5)	
Caravita et al.[24]	68 ± 18	28 ± 8	39 ± 10	23 ± 5	13 ± 6	16 ± 8	5 ± 5	71 ± 13	59 ± 19		2.2 ± 0.6	4 ± 3	2.1 ± 1.1
Dragu et al.[23]	60 ± 16	27 ± 6	40 ± 9	24 ± 6	13 ± 6	15 ± 6			62 ± 25	4.5 ± 1.4		3.45 ± 1.9	2.3 ± 1.2
Quan et al.[14]	55 ± 13		38 ± 9	25 ± 6	10 ± 6		4 ± 6	82 ± 15			1.9 ± 0.7	4.3 ± 2.8	1.93 ± 1.1
Sugimoto et al.25	47 ± 10	23 ± 5	32 ± 6	23 ± 6		10 ± 5	0 ± 3		73 ± 17		2.6 ± 0.7	2.5 ± 1.1	2.8 ± 1.3
Bermejo et al.[16]			37 (32–44)	22 (18–26)	12 (9–16)	15 (11–21)	2 (0–7)				2.8 (2.4–3.3)	3.2 (2.1–4.8)	2.0 (1.4–2.7)

Note: Data are reported as mean ± SD or median (interquartile range).

Abbreviations: CI, cardiac index; CO, cardiac output; DPAP, diastolic pulmonary artery pressure; DPG, diastolic pressure gradient; HR, heart rate; MPAP, mean pulmonary artery pressure; PAC, pulmonary artery compliance; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SPAP, systolic pulmonary artery pressure; SV, stroke volume; TPG, transpulmonary pressure gradient; WU, Wood Unit.

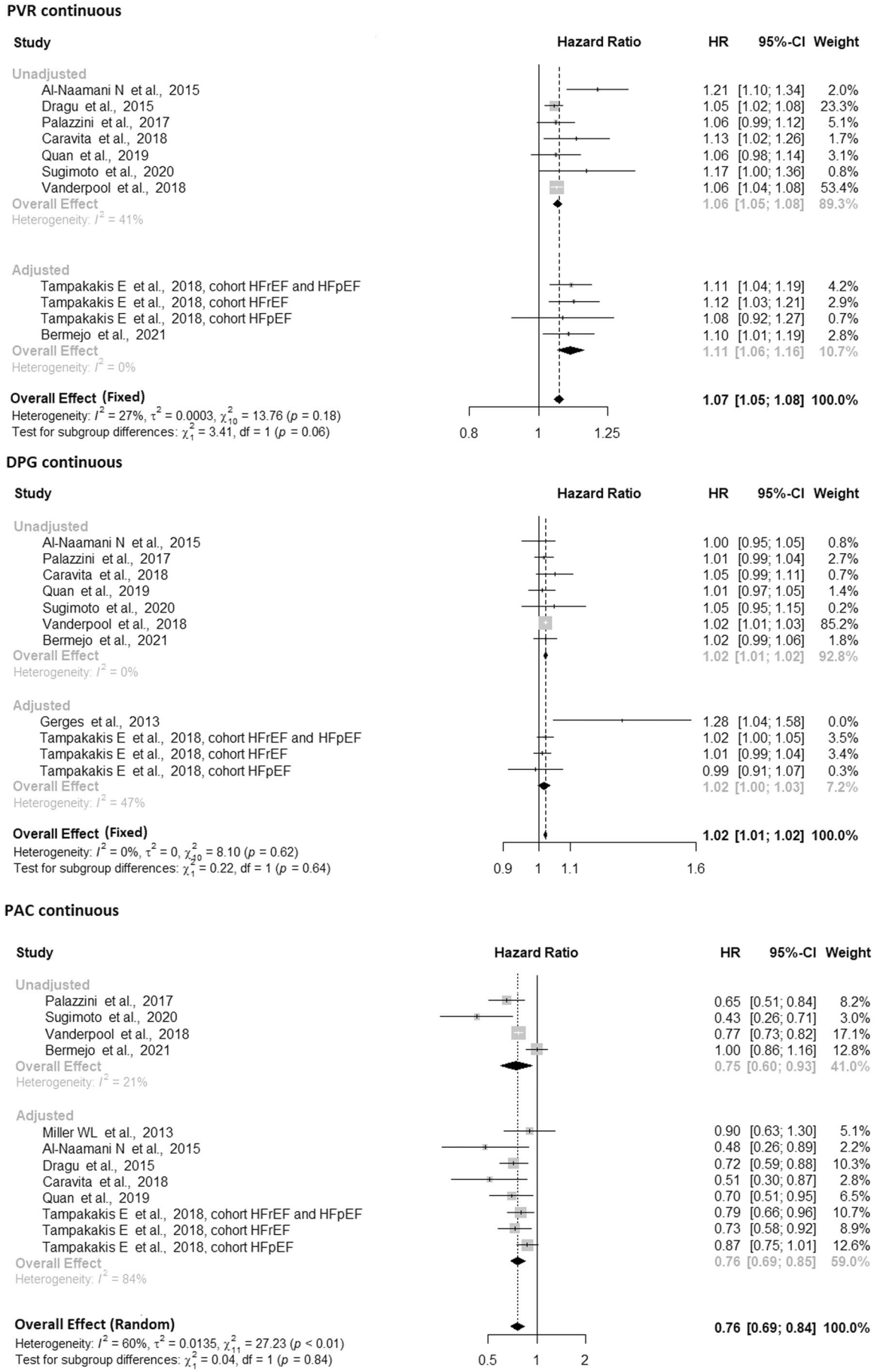

FIGURE 2 (See caption on next page)

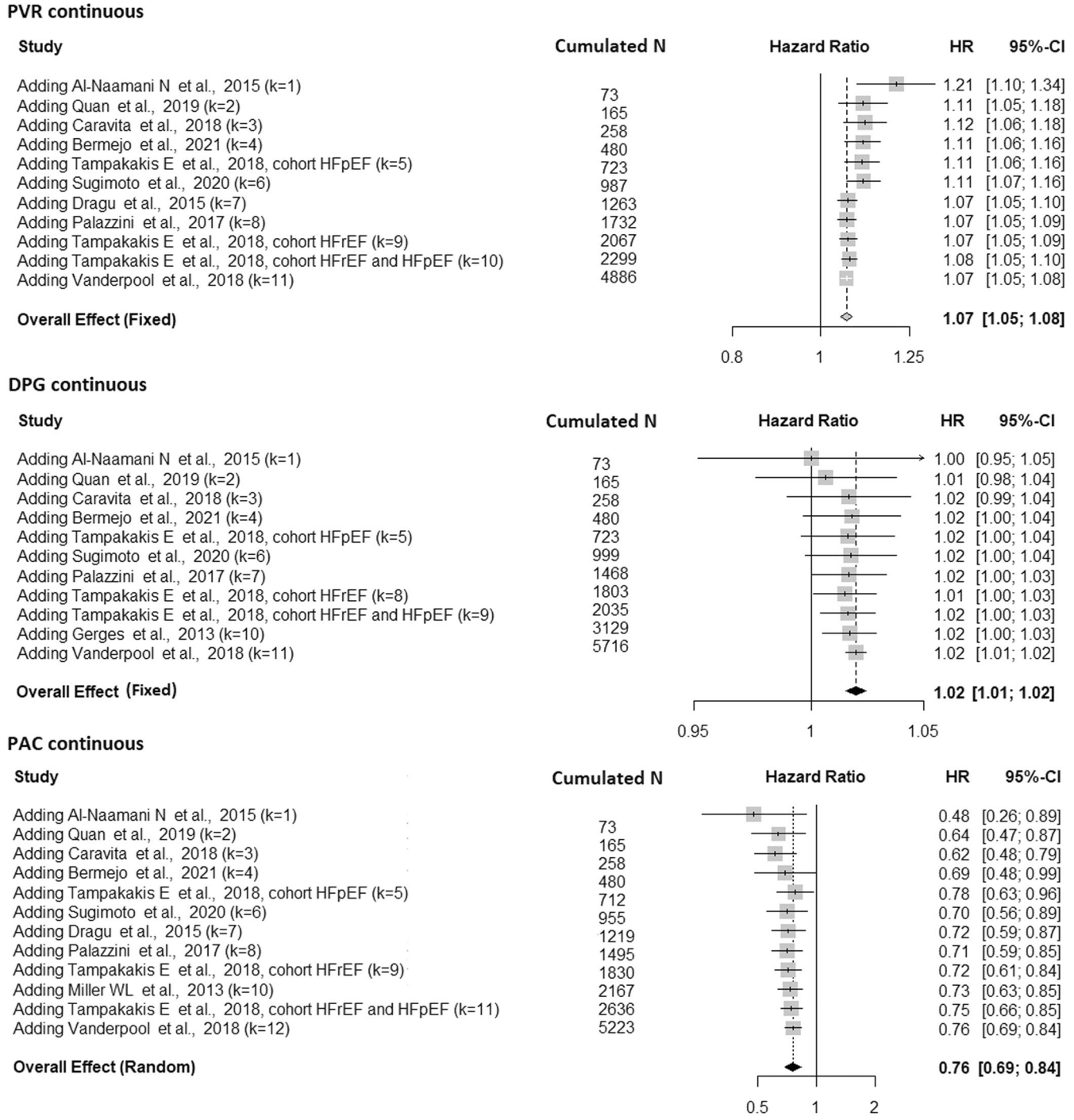

FIGURE 3 Cumulative metanalysis according to sample size for each hemodynamic variable. CI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

FIGURE 2 Forest plots with pooled standardized hazard ratio for hemodynamic variables reported in a continuous way. For each variable, unadjusted and adjusted analysis are reported. CI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

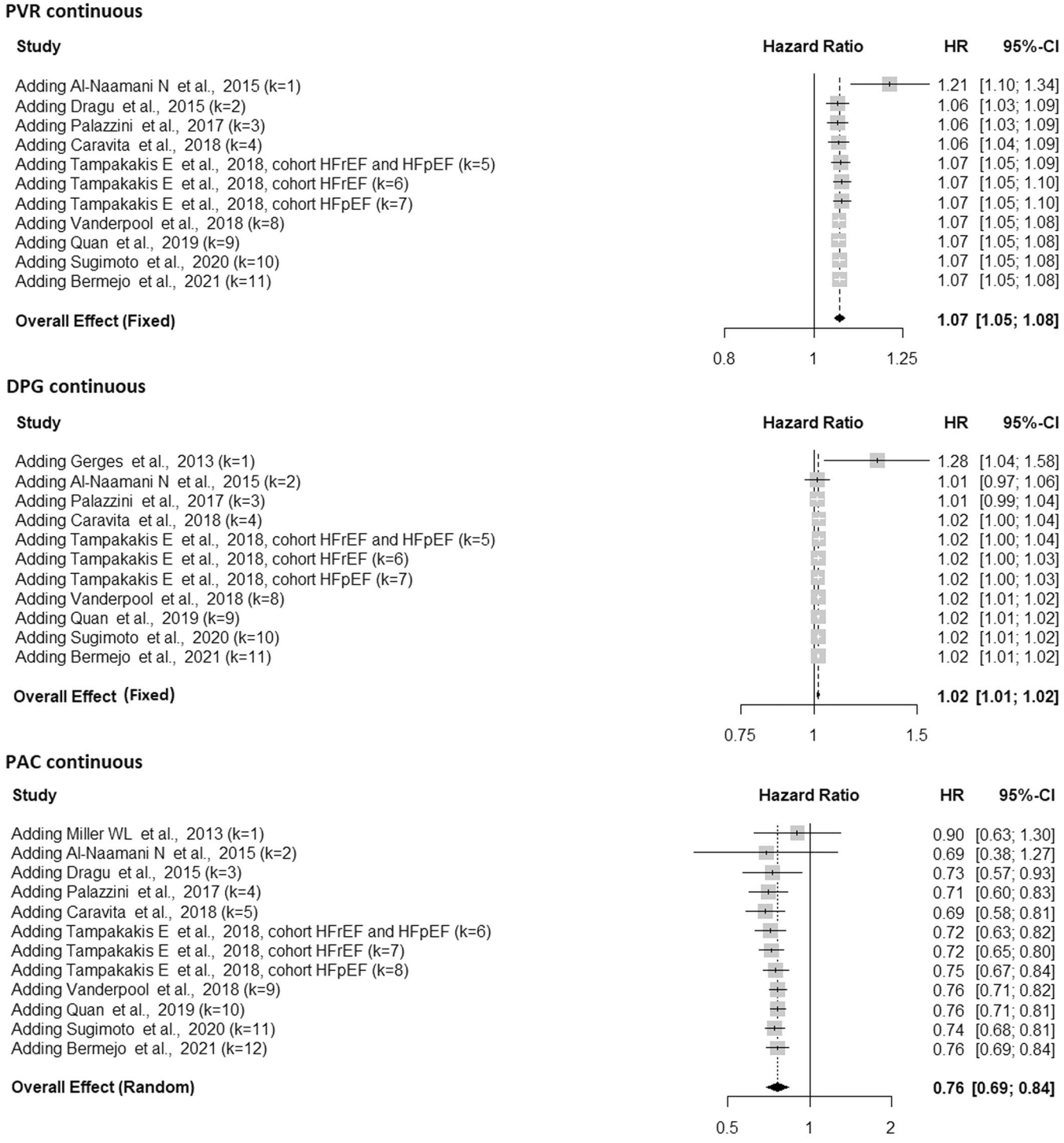

FIGURE 4 Cumulative metanalysis according to year of publication for each hemodynamic variable. CI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

associated to a higher risk for mortality, with HR of 1.36 (95% CI: 1.24–1.49) and 1.53 (95% CI: 1.40–1.67), respectively. Furthermore, a PAC < 2.3 ml/mmHg carried the highest risk of mortality (HR 2.14, 95% CI: 1.62–2.84) (Figure 5).

DISCUSSION

From pooling data from more than 9000 LHD patients with PH from various etiologies, our meta-analysis confirms and reinforces the established association of

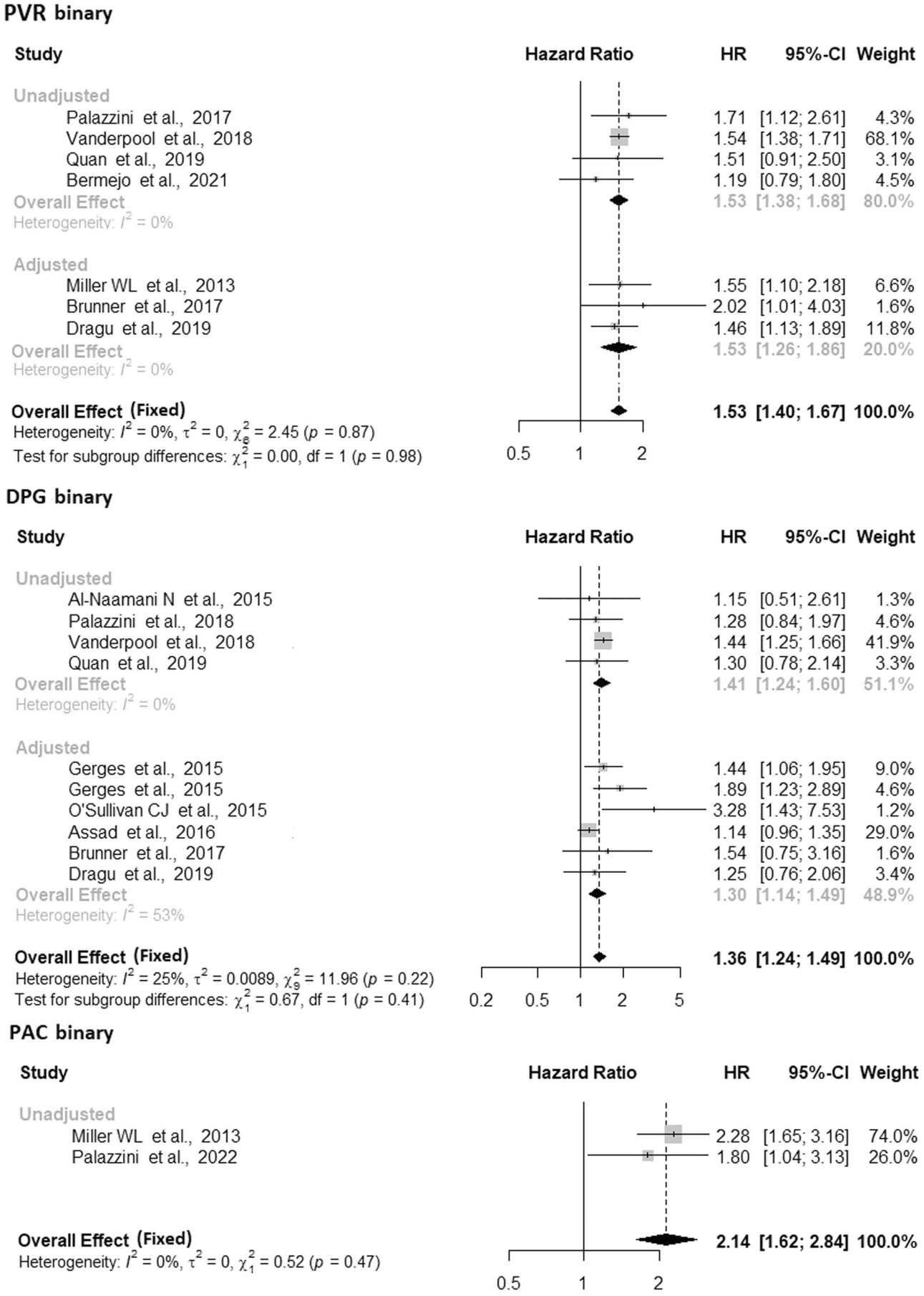

FIGURE 5 (See caption on next page)

PVR and PAC with prognosis, providing a synthesis of the evidence collected in the last 8 years also in term of cumulative meta-analysis. While the results for DPG appeared somehow less solid, at least when DPG was intended in a continuous way, PVR and PAC appear to be stronger predictor of outcome, both when dichotomized or when used as continuous variables. PVR proved capable to predict outcome independently of the underlying LHD (HFpEF, HFrEF, or VHD).

The heterogeneity of the populations included in the analysis mirrors the broad spectrum of LHD,[1] composed of HFrEF, HFpEF, and VHD. However, independently from the underlying LHD, the pooled cohort was an elderly one, characterized by a quite large burden of comorbidities including a high rate of atrial fibrillation. The average hemodynamic profile was quite typical, combining an elevated PAWP (>20 mmHg), a mildly elevated mPAP (25–40 mmHg), a normal DPG (<3 mmHg) and PVR ranging from 3 to 4.9 WU.[1]

In this large population, the unitary increase in PVR resulted associated with a 7% of increase in risk of adverse outcome, while a unitary increase in DPG carried a smaller increase in risk (+2%). At variance, a unitary increase in PAC was associated with a 24% mortality risk reduction.

Accordingly, evidence have not changed substantially since 2018.[5] Additional studies reinforced the consistency of results, which should be considered sufficiently stabilized and unlikely to change in the future. Furthermore, when variables were expressed in a binary way using high and commonly applied thresholds in clinical practice, the results were even more stable and consistent across hemodynamic variables, with similar HR between PVR and DPG.

Traditionally, PVR is a practical and widely accepted and used variable in clinical practice. On a physiological perspective, it normalizes the characteristics of the pulmonary circulation (mPAP−PAWP) for a marker of cardiac performance (CO). Accordingly, our analysis could confirm available data on its robust prognostic discriminative potential in PH-LHD,[5] even when the cohorts were subdivided based on the underlying etiology of PH.

DPG was similarly found to be associated to outcome, but with a small increase in risk for a unitary increase. Moreover, the meta-analysis results were not extremely solid when separately analyzing studies in which the association of DPG with mortality was either adjusted or unadjusted. As it has been repeatedly remarked, the DPG is a small number and exposed to measurement error, potentially explained also by the relative inaccuracy of the used catheters ("fluid filled" rather than "high fidelity"), the lack of standardization in the measure of PAWP across laboratories (mean PAWP vs. mid-A PAWP; end-expiratory vs. respiratory-averaged values), and the fact that the two terms of the subtraction, that is, the diastolic PAP and PAWP are not simultaneously measured in the same heartbeats and over the same breaths. Accordingly, a relevant proportion of negative DPGs was found in the studies under analysis.

PAC has been proposed as predictor of outcome in LHD [12–16,19,20,24,25] given its presumed pathophysiological meaning, even if the estimated PAC could overestimate its real value by 60%−80%.[2,28] Given the inverse relationship between PAC and PVR, the former has been advanced to be a better fit as prognostic marker when PVR are still "in the normal range" or when mean PAP is below 25 mmHg. However, the recent evidence linearly linking PVR with outcome since a lower cut-off than 3 WU might change current threshold to define diseases, potentially overcoming this previous limit of PVR. Finally, the strong association of PAC with mortality reflects its dimension: it is an even smaller number than DPG, and similarly subject to measurement errors. Additionally, we still do not know which changes should be considered clinically meaningful, and thus it is probably impractical to assess fine changes in pulmonary vascular properties and right ventricular afterload.

Thus, even though these three variables carry prognostic significance, a pragmatic approach aiming at simplifying and rendering clinical practices and communication more homogeneous across laboratories,[1,4,29,30] PVR alone may suffice as a hemodynamic marker for risk stratification. Finally, PAC might be used to strengthen the prognostic assessment.

Thus, the prognostic role of PVR is undisputed. It is still uncertain whether it might represent a therapeutic target in PH-LHD. Indeed, the great majority of studies testing drugs targeting the pulmonary circulation in PH-LHD have provided neutral or even negative results,[1,4,29,30] so that these compounds should not be used in patients with PH-LHD.[1] More favorable results have been obtained with the inodilator levosimendan in patients with HFrEF[31–34] and in patients with VHD[35] in

FIGURE 5 Forest plots with pooled standardized hazard ratio for hemodynamic variables reported in a dichotomous way. For each variable, unadjusted and adjusted analysis are reported. ACI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

whom this compound was demonstrated to improve PVR and RV function. Its effects in HFpEF are less studied, but it might at least decrease PAWP in a subgroup of such patients.[36] Finally, PVR might be useful for the selection of HFpEF patients candidate to the placement of an interatrial septal device: in the REDUCE LAP-HF II trial,[37] patients with high PVR during exercise (>1.74 WU) had an increased incidence of HF events as compared with those with low PVR, who seemed to have more benefit from this device.

LIMITATIONS

The literature search was done using only the Pubmed database, however screening nearly 400 studies. Hemodynamic predictors of prognosis in LHD may be influenced by the study characteristics (single center vs. multicentric; RHC methodology), timing of data collection (elective RHC vs. acute decompensation, changes under therapy), the characteristics of the referral center as well as of the population (HFrEF, HFpEF, and VHD). However, the large sample size may at least in part overcome such limitation.

There was an overlap of studies between our previously published meta-analysis[5] and this study. However, since studies on this topic doubled since the publication of our previous work, we thought appropriate to re-run an updated analysis, including additional information, such as a cumulative meta-analysis based on the sample size of the individual studies and the year of publication, expressing variables not only in continuous but also in a binary way (dichotomized according to currently used thresholds) and performing a sub-analysis stratifying the populations according to the underlying etiology of LHD (HFrEF, HFpEF, and VHD).

We only included studies published since 2013, with the aim to maintain a homogeneity in the definition of PH, to focus on contemporary patients' populations, and to better focus on more attractive hemodynamic variables with supposed prognostic value in this context. Indeed, in 2013 DPG was revived,[38] and suggested as diagnostic criterion to define a precapillary component to postcapillary PH,[39] then combined with PVR in the guidelines on PH.[40] Always in 2013, the prognostic value of PAC was similarly suggested for the first time.[15]

We did not explore the association between PAWP and outcomes in these studies. However, only in 3 of the studies reporting it, the association between PAWP and outcome resulted statistically significant. Indeed, all cohorts included in the analysis had, by definition, a high PAWP. Thus, we preferred to focus our study on hemodynamic markers more likely reflecting the presence of a precapillary component to postcapillary PH.

We could not explore the association of a lower threshold of PVR (e.g., 2 WU) with outcome since we did not perform an individual patients' data meta-analysis. However, since a unitary increase in PVR was associated with a 7% of risk, our data may indirectly suggest that the link of PVR with outcome may start from a lower threshold.

CONCLUSIONS

Despite the heterogeneity of PH-LHD group and the intrinsic limitations of each variable, PVR, DPG, and PAC are all associated with outcome. The strongest correlation with PVR and PAC supports their use in defining disease severity and identifying a subgroup of patients at higher risk of adverse outcome. We believe this evidence is robust enough for sufficient time to make it unlikely to change with the addition of similar studies. Nevertheless, further studies are needed to assess how these hemodynamic markers perform in predicting outcome in more homogeneous PH-LHD phenotypes, and how time- or treatment-induced changes may influence outcome.

AUTHOR CONTRIBUTIONS

Claudia Baratto: Conceptualization, data curation, investigation, methodology, writing–original draft. **Sergio Caravita**: Conceptualization, methodology, supervision, writing–review and editing. **Davide Soranna**: Methodology, formal analysis, writing–review and editing. **Céline Dewachter**: Conceptualization, data curation, methodology, supervision, writing–review and editing. **Antoine Bondue**: Supervision, writing–review and editing; **Antonella Zambon**: Methodology, formal analysis, writing–review and editing; **Luigi P. Badano**: Supervision, writing–review and editing. **Gianfranco Parati**: Supervision, writing–review and editing. **Jean-Luc Vachiéry**: Conceptualization, methodology, supervision, writing–review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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