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Research article

The feasibility in estimating pulmonary vascular resistance by cardiovascular magnetic resonance in pulmonary hypertension: A systematic review and meta-analysis

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ABSTRACT

Purpose: Cardiac magnetic resonance (CMR) is a substitute technique for noninvasively assessing pulmonary hemodynamics. Some preliminary studies have shown that CMR has the potential to quantify pulmonary vascular resistance (PVR). However, the evaluative value has not been well established. The purpose of the systematic review is to assess the feasibility of CMR in the measurement of PVR in patients with pulmonary hypertension (PH).

Methods: Studies were retrieved from multiple databases. Methodological evaluation of CMR and right heart catheterization (RHC) in estimating PVR were obtained from included studies. The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used to assess the quality of studies. The results of comparisons of continuous variables are reported as weighted mean difference (WMD), together with the corresponding 95% confidence intervals (CIs). Summary correlation coefficient (r) values were extracted from each study, and 95% CIs were calculated after Fisher's z transformation. Sensitivity analysis was conducted to investigate potential heterogeneity.

Results: A total of 15 studies were included in the systematic review, and 6 of these studies were included in the meta-analysis. The pooled WMD with fixed-effects analysis revealed no statistical significance between PVR-CMR and PVR-RHC in patients with PH (WMD = 0.278 WU; 95% CI: −0.415 to 0.972; p = 0.431). The pooled r value for all studies was 0.85 (95% CI: 0.81, 0.89), and notable heterogeneity was evident. The pooled r value after the exclusion of one heterogeneous article was 0.81 (95% CI: 0.74, 0.87) and was not significantly heterogeneous.

Conclusions: CMR and RHC have good consistency in the testing of PVR in the meta-analysis. The systematic review shows that completely noninvasive evaluation of PVR with CMR in patients with pH is feasible.

1. Introduction

Pulmonary hypertension (PH) is a disease of the pulmonary arteries that is characterized by pulmonary arteriolar proliferation and vascular remodeling [1], which results in a progressive increase in pulmonary vascular resistance (PVR), heart failure, and ultimately death. With the growing availability of effective therapy [2], long-term mortality remains high [3]. PVR partly reflects right ventricle (RV) afterload, which was demonstrated to be predictive of mortality in prior study [4]. The early assessment of PVR plays a crucial role in PH patients, notwithstanding those with defective arteries. Right heart catheterization (RHC) is an invasive procedure and is the current golden standard for the diagnosis and monitoring of PH. Moreover, RHC provides hemodynamic information, including the assessment of PVR. The pressure difference over the pulmonary blood flow measurements is required to calculate PVR, but accurately measuring blood flow parameters in the clinical setting may be difficult [5]. Given the radiation exposure and small but real risk of mortality and morbidity associated with RHC [6], there is an urgent need for more accurate, alternative and convenient approaches to estimate PVR. Doppler echocardiography has become a routine tool to noninvasively evaluate RV function and mean pulmonary arterial pressure (mPAP). However, the estimation of PVR via echocardiography has several drawbacks, such as user dependency, oftentimes unfavorable echo windows, and controversial data in the estimation of pulmonary hemodynamics [7,8]. Cardiac magnetic resonance (CMR) is reported as a substitute in assessing

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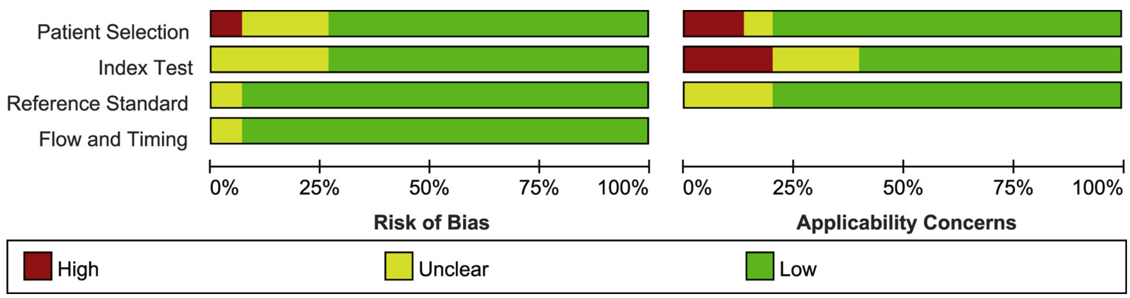

Fig. 1. Quality analysis of the included studies based on QUADAS-2 criteria.

pulmonary hemodynamics noninvasively [9–11]. Although some preliminary studies have shown that CMR has the potential to quantify PVR and there is a significant correlation between some CMR-related parameters and PVR [12–14], the evaluative value has not been well-established. Several studies have reported mixed results, and these studies have generally included small sample populations and various calculation models [20,23,25]. A quantitative evaluation and synthesis of data is necessary to elucidate the role of CMR in PH. A systematic review and meta-analysis of studies was conducted to assess the feasibility in estimating PVR by CMR in patients with PH.

2. Methods

The systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA guidelines) [15]. The medical ethical committee waived ethical approval for this study given that data were obtained from previous publications.

2.1. Eligibility and exclusion criteria

The included studies assessing patients with PH who underwent CMR imaging to estimate PVR. Eligibility criteria comply with the PICOS principle as follow:

Patients (P): Patients with known or suspected PH.

Intervention (I): CMR.

Comparison/Control (C): RHC.

Outcome (O): (A) These studies included some key parameters: PVR, mPAP or other relative hemodynamic findings; (B) The corresponding data about PVR could be extracted directly or calculated from raw data (e.g., the concrete values of PVR derived from CMR or assessing patterns for PVR by CMR; correlation coefficients); (C) The time interval between CMR and RHC is less than 4 weeks without any change in patient management during the time interval.

Study design (S): Prospective or retrospective cohort studies.

Exclusion criteria: (A) Patients with unstable clinical condition, arrhythmia, and/or significant forms of valvular heart disease were not included; (B) Corresponding PVR results via CMR cannot be extracted from the studies; (C) Abstracts, case reports, reviews, or editorial materials; (D) Nonoriginal research or animal research.

2.2. Search strategy

Two reviewers (H.C. and J.Z.) independently searched for studies estimating PVR by CMR in patients with PH. The selections of two reviewers (H.C. and J.Z.) were compared and discussed to obtain consensus in case of disagreement. Studies were identified using PubMed/Medline, Embase, the Cochrane Library, Web of Science, VIP database and China National Knowledge Infrastructure (CNKI) in the field. There were no any language restrictions, and the last search was conducted on September 13, 2018. The following search words were applied to PubMed: Pulmonary vascular resistance or PVR, Pulmonary arterial hypertension or PH and Cardiovascular magnetic resonance or CMR. The actual search strategy was adjusted to the corresponding database and combined with manual retrieval to minimize the possibility of missing any studies.

2.3. Data extraction

Data were extracted from each study and recorded on an electronic spreadsheet. Among included studies, the following data were collected by two investigators (H.C. and C.H.L.) independently: the first author, year of publication, country, study design (prospective or retrospective), study population, age, percentage male, demographic characteristics, the time interval between CMR and RHC, RHC cut-off value for diagnosing PH, PVR variables measured using CMR and RHC (mean ± SD), the methods of PVR assessment by CMR and RHC, the main CMR variables in estimating PVR, the patterns of CMR and RHC, and type of CMR images. Moreover, the correlation coefficient (r) for assessing the strength of the correlation between PVR-CMR and PVR-RHC was obtained directly from eligible papers. Any discrepancy was resolved by consensus of all authors.

2.4. Quality assessment

The quality (risk of bias) assessment for included articles was conducted independently by two investigators (H.C. and B.X.) using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (Fig. 1). The full QUADAS-2 tool is available from the QUADAS Web site (www.quadas.org). The QUADAS-2 tool contains four key domains: (1) Patient Selection, (2) Index Test, (3) Reference Standard and (4) Flow and Timing [16]. The risk of bias and applicability concerns for each domain were rated based on the following grades: low, high and unclear. The descriptive results of the quality assessment were used to provide an estimation about the overall quality and to probe into potential heterogeneity of all articles included. Discrepant comments of domains for each article were discussed and arbitrated by reaching consensus among three investigators (H.C., J.Z. and B.X.). The methodological quality summary is shown in Supplemental Fig. S1.

2.5. Statistical analysis

To assess the feasibility in estimating PVR by CMR, we estimated the meta-analytic values of PVR after first undertaking a descriptive analysis of the studies. Then the results of comparisons of continuous variables are reported as weighted mean difference (WMD) together with the corresponding 95% confidence intervals (CIs). In addition, an evaluation of the pooled r with its 95% CI between PVR-CMR and PVR-RHC was calculated by combining the r recorded in each study. If the sampling of r was not normally distributed, Fisher's transformation of r to z values and z values to r was performed to obtain variance-stabilized correlation coefficients and 95%CIs such that the data were utilized preferably before meta-analysis [17,18].

Data heterogeneity across pooled studies was tested using Cochrane Q statistic and Chi^2 test and quantified with the I^2 value. I^2 values of 25%, 50%, and 75% indicate heterogeneity rated as mild, moderate,

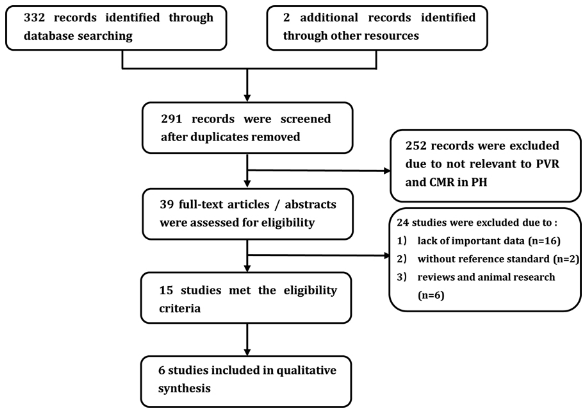

Fig. 2. Flow diagram showing the screening process for included publications. Note: PVR, pulmonary vascular resistance; CMR, cardiac magnetic resonance; PH, pulmonary hypertension.

and notable, respectively, and $P < 0.05$ was deemed statistically significant [30]. For heterogeneity analysis in the study showing a lack of significant heterogeneity for the WMD, the inverse variance(I-V) statistical method with fixed-effects was used as analysis model for the pooled WMD [31]. Heterogeneity of the r values between studies was notable; thus, random-effects meta-analysis was conducted to combine the data [32]. Furthermore, a sensitivity analysis was performed for included studies to further inspect the study heterogeneity. Begg's adjusted rank correlation test [33] and Egger's test [34] were calculated to investigate possible publication bias. The statistical software Stata (version 15.1; Stata Corp, College Station, TX,USA) and Revman (version 5.3; Cochrane Collaboration, Software Update, Oxford, UK) were used to perform the meta-analysis.

3. Results

3.1. Study selection

The details of the study selection are shown in Fig. 2. A total of 334 publications were identified using PubMed/Medline, Embase, the Cochrane Library, Web of Science, VIP database and CNKI, and 2 additional records were obtained using other resources. In total, 291 records remained after the removal of 43 duplicates. Then, 252 records were excluded after a first screening given that these studies did not focus on PVR and CMR in PH patients. After further screening of the remaining 39 publications, 24 publications were excluded: (1) 16 articles due to the lack of important data; (2) 2 articles without reference standard and (3) 6 articles that involve reviews and animal research. A total of 15 studies [9,14,19–29,39,40] were included in the systematic review, and 6 papers [19,21,23,25,26,28] were included in the meta-analyses.

3.2. Characteristics of the included studies

The included articles were published from 1999 to 2017, and the number of study participants ranged from 7 to 115 patients with PH. Eight studies involved prospective cohorts, whereas 6 articles [9,21–23,29,40] which involved retrospective cohorts. The mean age ranged from 6.4 to 62.9 years, and the percentage of male patients ranged from 7% to 58%. The time interval between CMR and RHC was less than 2 weeks in all studies. Most of studies included reported cut-off values for diagnosing PH. Most of included studies were performed on 1.5-T CMR systems, the study by Skrok et al. [39] was conducted by 3.0-T CMR and one [21] additional was performed using both 1.5-T and 3.0-T CMR. Table 1 summarizes the detailed information about the characteristics of the included studies.

3.3. Methodologic characteristics in assessing PVR

Considerable variability was noted in the methodologic characteristics in assessing PVR in the included studies (Table 2). Phase contrast (PC) CMR imaging, which is regarded as the most common method to obtain blood flow images, was used to estimate PVR in recent research reports. Kheyfets et al. [27] used 4D flow cardiac MRI (4D CMR) with interleaved 3D velocity encoding to estimate PVR. The studies by Skrok et al. [39] and Swift et al. [40] both correlated dynamic contrast-enhanced (DCE) parameters with PVR. Two studies [14,26] performed velocity-encoded MR or scout/cine MR to obtain the required data. The most of the included studies assessed PVR by CMR via model or equation, and 4 articles [9,14,39,40] adopted nonquantitative approaches to evaluate PVR and assess the relationship between PVR-CMR and PVR-RHC. All included studies used RHC as the gold standard to quantify PVR. PVR was determined using the Thermodilution technique in the majority with the exception of 3 studies [19,26,28] that used the Fick principle. PVR-RHC was mostly determined based on the following equation: PVR = (mPAP – PCWP)/CO.

3.4. The main CMR variables in estimating PVR

Table 3 provides details on the main CMR variables in evaluating PVR of included studies. These CMR metrics could be divided into two parts: pulmonary artery variables or hemodynamic variables and right ventricle variables. Most of the studies used pulmonary artery flow metrics (such as the average velocity, the peak diastolic velocity, and the peak systolic velocity) to reflect PVR. And just as important, right ventricle variables, such as end-diastolic volume (EDV), ejection fraction (EF), and end-systolic volume (ESV), do play an important role, directly and indirectly to the evaluation of RV function and PVR.

3.5. Comparison of methodology results

Table 4 shows the data (directly acquired from articles without any adjustment or calculated from initial articles) of PVR determined by CMR and RHC extracted from 6 publications [19,21,23,25,26,28]. Moreover, these data were derived from baseline conditions, excluding CMR, which was derived from measurements during nitric oxide (NO) inhalation. In the meta-analysis, the test for heterogeneity revealed $I^2 = 0.0\%$ and $P = 0.537$. No evidence of significant heterogeneity was noted across 6 studies that reported PVR values. Hence, the overall pooled results of WMD with fixed-effects analysis showed revealed no statistical significance between PVR-CMR and PVR-RHC in patients with PH (WMD = 0.278 WU; 95% CI: −0.415 to 0.972; $P = 0.431$). No significant differences were noted between the two methods used to determine PVR. See Fig. 3 for detailed pooled data.

3.6. The correlation between PVR-CMR and PVR-RHC

The r values were obtained from 5 studies [19,21,25,26,28], and detailed data are presented in Table 5. A random-effects model was applied to compute a pooled r for all studies (Fig. 4), and the pooled r was 0.85 (95% CI: 0.81, 0.89) and exhibited notable heterogeneity ($I^2 = 87.2\%$, $P = 0.000$). After sensitivity analysis, one [26] of the five studies was excluded, and the remaining studies were considered to be generally homogeneous. The pooled r after one heterogeneous article was excluded (Fig. 5) was 0.81 (95% CI: 0.74, 0.87), and no significant heterogeneity was noted ($I^2 = 34.9\%$, $P = 0.203$).

3.7. Publication bias

Begg's funnel plot of effect size did not show any major plot asymmetry with respect to possible publication bias (Fig. 6), and the results of the Egger's test to assess this bias was not significant ($t = 0.68$; $p = 0.536$).

Table 1
Characteristics of studies included in the systematic review.

Author	Year	Country	Population	Blind	Study design	Mean age, years *	Male sex, (n%) †	Time interval between CMR and RHC	RHC cut-off value for PH	Field strength
Mousseaux et al. [14]	1999	France	19 Subjects with suspected PH	+	PC	38	11 (58)	28 h	NR	1.5-T
Muthurangu et al. [19]	2004	UK	24 patients with either suspected PH or CHD (4 patients were excluded)	+	PC	6.4	NR	The same time(RHC was guided under MR)	NR	1.5-T
Kuehne et al. [20]	2005	Germany	10 patients had PH and 5 controls	+	PC	42 ± 11 (5 controls) and17 ± 6 (10 patients)	NR	Simultaneously	NR	1.5-T
Sanz et al. [9]	2007	USA	42 patients with PH and 17 suspected PH	+	RC	46.1 ± 14	10 (17)	Within 2 weeks	mPAP > 25mmHg	1.5-T
Garcı´a-Alvarez et al. [21]	2011	USA	100 patients with known or suspected PH	NR	RC	53 ± 16	27 (27)	The same day	mPAP > 25 mmHg or increased PVR > 3 WU	1.5-T and 3.0-T
Skrok et al. [39]	2012	USA	43 patients who were known to have or who were suspected of having PH	+	PC	58.7	7(16)	The same day	mPAP > 25 mm Hg, PCWP ≤ 15 mm Hg	3.0-T
Swift et al. [22]	2012	UK	115 Patients with PH and 19 control subjects	+	RC	59 ± 18 (no PH) and 64 ± 14 (PH)	16 (12)	Within 2 days	mPAP > 25mmHg	1.5-T
Kreitner et al. [23]	2013	Germany	19 patients with suspected CTEPH	NR	RC	51	11 (58)	20 – 35 minutes	mPAP ≥ 25mmHg at rest	1.5-T
Swift et al. [24]	2013	England	64 patients with suspected PH in derivation cohort and 64 patients with suspected PH in validation cohort	+	PC	62.9 ± 13.5 (derivation cohort) and 62.8 ± 12.8 (validation cohort)	22 (34.4) in derivation cohort and 29 (44.7) in validation cohort	Within 12 h	mPAP ≥ 25mmHg at rest	1.5-T
Swift et al. [40]	2014	UK	79 patients diagnosed with PH	+	RC	62 ± 16	31(39)	within 48 h.	mPAP ≥ 25mmHg,and PCWP < 15 mm Hg	1.5-T
Bane et al. [25]	2015	USA	7 patients with suspected PH	+	PC	NR	NR	1 – 10 days	mPAP ≥ 25mmHg	1.5-T
Yan et al. [26]	2015	China	77 patients with PH	+	PC	32.42 ± 11.01	17 (22)	Within 2 days	mPAP > 25 mm Hg and PCWP ≤ 15mmHg at rest	1.5-T
Kheyfets et al. [27]	2016	USA	17 patients with PH and 5 controls	+	PC	58.6 ± 9.9	8 (36)	Within 24 h	mPAP ≥ 25mmHg	1.5-T
Rogers et al. [28]	2017	USA	102 patients with and without PH	NR	PC	53 ± 14	54 (53)	Real-time CMR guided RHC	mPAP ≥ 25mmHg	1.5-T
Zhang et al. [29]	2017	China	50 patients with PH	+	RC	38.56 ± 12.76 (derivation cohort) and 40.78 ± 11.34 (validation cohort)	5 (10)	Within 1 week	mPAP ≥ 25mmHg, PCWP ≤ 15 mmHg, PVR > 3WU	1.5-T

Note: CHD, congenital heart disease; CMR, cardiac magnetic resonance; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; MR, magnetic resonance; NR, not reported; PC, prospective-cohort; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RC, retrospective cohort; RHC, right heart catheterization; WU, wood units.

* Continuous variables are presented as mean ± standard deviation (SD).

† Categorical variables are presented as percentages.

Table 2
Methodologic characteristics in assessing PVR of publications included in the systematic review.

First author, year	PVR assessment by CMR	Pattern of PVR-CMR*	CMR images	PVR assessment by RHC	Pattern of PVR-RHC*
Mousseaux, 1999	Hemodynamic parameters	Linear correlations	Velocity-encoded MR	Thermodilution	PVR = (mPAP-PCWP)/CO
Muthurangu, 2004	PVR was calculated by the use of MR flow and invasive pressure measurements	PVR = (mean pulmonary artery pressure-pulmonary wedge or left atrial pressure) ÷ (Qmr / BSA)	Velocity-encoded phase-contrast MR	Fick	PVR = (mPAP-pulmonary wedge or left atrial pressure) ÷ (Qfick/BSA)
Kuehne, 2005	PVR was assessed from PA flow volumes and simultaneously determined invasive PA pressures	PVR = mean PA pressures / PA forward flow	Velocity encoded cine (VEC) MRI	Thermodilution	PVR = (mPAP–PCWP)/CO
Sanz, 2007	Hemodynamic parameters	Correlations	Phase contrast MR imaging	Standard procedures	PVRI = (mPAP–PCWP)/CI
Garcı´a-Alvarez, 2011	PA velocity and RVEF	PVR = 19.38 – (4.62 × ln PA velocity) – (0.08 × RVEF)	CMR cine and phase-contrast images	Thermodilution	PVR = (mPAP–CWP) / RV-CO
Skrok, 2012	Correlations of first-pass bolus kinetic parameters with hemodynamic parameters	Correlations of PTT, LV FWHM, and LV TTP with PVR	CE MR imaging	Thermodilution	PVRI = 80 × (mPAP–PCWP)/CI
Swift, 2012	Pulmonary artery AC, RAC	an inverse linear model	Phase contrast imaging	NR	PVR = (mPAP–PCWP)/CO
Kreitner, 2013	PVR was estimated using equation	PVR_cal = (mPAP_cal – CWP) × 80/RV-CO_MR †	Phase-contrast MRI (PC-MRI)	Thermodilution	PVR = (mPAP–CWP) × 80/RV-CO
Swift, 2013	PVR was calculated from the CMR-derived measurements	PVR = (CMR-predicted mPAP – CMR-predicted PCWP)/ CMR phase contrast CO	Phase contrast Q-flow CMR	Thermodilution	PVR = (mPAP–PCWP)/CO
Swift, 2014	Correlations and receiver operating characteristic analysis	Diagnostic accuracy of FWHM and PTT for detection of PVR	DCE time-resolved MR imaging	Thermodilution	PVR = (mPAP–PCWP)/CO
Bane, 2015	PVR was calculated from MRI-derived mPAP, PCWP and RV-CO	PVR = (mPAP–PCWP)/ RV-CO	2D phase-contrast flow images	Thermodilution	PVR = (mPAP–PCWP)/ RV-CO
Yan, 2015	According to a formula	PVR = TTE derived (mPAP –PCWP) / CMR-derived CO	Scout images and cine images	Fick	PVR = (mPAP–PCWP)/CO
Kheyfets, 2016	4-parameter multivariate linear regression model	A function of vorticity in the MPA (ωMPA), RPA (ωRPA), CO, and the RAC in the MPA	4D flow cardiac MRI with interleaved 3D velocity encoding	Thermodilution or Fick	PVR = (mPAP–PCWP)/CO
Rogers, 2017	PVR was calculated using a formula	PVR = (mPAP-PCWP)/CO-MRI	Phase contrast CMR	Fick	PVR = (mPAP–PCWP)/CO-Fick ‡
Zhang, 2017	CMR-PVR was calculated with an equation	PVR-CMR = mPAP-CMR/RVCI	Fast cine phase-contrast	Thermodilution	PVR-RHC = (mPAP–PCWP)/CO

Note: AC, area change; BSA, body surface area; contrast material-enhanced, CE; CMR, cardiac magnetic resonance; CI, cardiac index; CO, cardiac output; CWP, capillary wedge pressure; DCE, dynamic contrast-enhanced; FWHM, full width at half maximum; LV, left ventricular; MPA, main pulmonary artery; mPAP, mean pulmonary artery pressure; MR, magnetic resonance; NR, not reported; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PTT, right-to-left ventricle pulmonary transit time; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; Qmr, pulmonary blood flow calculated with PC-MRI; RAC, relative area change; RHC, right heart catheterization; RPA, right pulmonary artery; RV-CO, right ventricular cardiac output; RVCI, right ventricular cardiac index; RVEF, right ventricular ejection fraction; TTE, transthoracic doppler-echocardiography; TTP, time to peak; WU, wood units.
2D, two dimensional; 3D, 3 dimensional; 4D, Four dimensional.
*PVR-CMR indicates the values of PVR derived from CMR and PVR-RHC indicates PVR as measured during RHC.
†Where PVR_cal is the calculated PVR, mPAP_cal is the calculated mPAP derived from velocity-encoded parameters, and RV-CO_MR, the RV-CO as determined by PC-MRI.
‡CO-Fick indicates cardiac output, averaged measurement by Fick principle.

Table 3
The main cardiac magnetic resonance variables in estimating PVR in the systematic review.

Author	Year	Pulmonary artery variables/Hemodynamic variables	Right ventricle variables
Mousseaux et al.	1999	Acceleration time, Acceleration volume, Maximal change in flow rate during ejection, Maximal change in flow rate during ejection	NR
Muthurangu et al.	2004	Averaged pulmonary blood stroke volume, The pulmonary flow	NR
Kuehne et al.	2005	PA flow volume, Quantitative pulmonary blood flow	NR
Sanz et al.	2007	Average velocity, The minimum PA area	NR
Garcı´a-Alvarez et al.	2011	PA peak velocity, PA average velocity, PA net forward volume	RV EDV, RV ESV, EF
Skrok et al.	2012	PTT, LV FWHM, LV TTP	RVEDVI, RVESVI, RVSVI, CI, EF, RVEDMI, Ventricular mass index
Swift et al.	2012	AC, RAC	TAPSE, RVEDMI, RVEDVI, RVSVI
Kreitner et al.	2013	CO, Ata, MV, AV, dQ/dt	NR
Swift et al.	2013	RAC, Average PA velocity, Interventricular septal angle, Interventricular septal angle ratio	RVEDVI, RVSVI, EF, RVSVI, RV mass index, Ventricular mass index (ratio)
Swift et al.	2014	FWHM, PTT	NR
Bane et al.	2015	The peak early diastolic mitral inflow velocity(E), The peak early diastolic mitral annular velocity (e′), MPAP, PCWP	RV systolic/diastolic ventricular volumes, RV CO, EDV/EF ratio
Yan et al.	2015	NR	RV EDV, RV ESV, EF, CO
Kheyfets et al.	2016	Maximum spatial peak systolic vorticity, RAC	CO, SV
Rogers et al.	2017	MPAP, Mean PAWP	RV EDV, RV ESV, EF, CI
Zhang et al.	2017	QP, AVP, Maximal and minimal pulmonary arterial areas	RV volume, RV EDV, RV ESV, EF, SV, CI, IVS, MM

Note: AC, pulmonary artery area change; Ata, absolute acceleration time; AV, volume of acceleration; AVP, average pulmonary arterial velocity; CI, cardiac index; CO, cardiac output; dQ/dt, maximal flow acceleration; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; FWHM, full width at half maximum; IVS, interventricular septum; MM, myocardial mass; MPAP, mean pulmonary artery pressure; MV, maximum of mean velocities; LV, left ventricular; NR, not reported; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PTT, right-to-left ventricle pulmonary transit time; QP, positive pulmonary arterial flow; RAC, pulmonary artery relative area change; RV, right ventricle; RVEDMI, RV end-diastolic mass index; RVSVI, RV stroke volume index; RVEDVI, RV end diastolic volume index; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; TTP, LV time to peak.

4. Discussion

Pulmonary artery hypertension develops from a series of physiological changes in the lung vasculature. The review by Saouti et al. [4] has described the mechanism of PH, as an increase in vascular resistance and the right ventricular load due to the narrowing of the distal portions of the pulmonary arterial vasculature, which in turn leads to the decrease in pulmonary arterial compliance. The combination of increased PVR and reduced vascular compliance exacerbates the load on the right ventricle and hemodynamic dysfunction, ultimately leading to right ventricular failure. Thus, the metrics of hemodynamic changes in part reflect vascular resistance and the right ventricular load.

To date, RHC has facilitated our understanding of hemodynamic dysfunction in critically ill patients. The Fick and Thermodilution methods are generally conducted to quantify flow. PVR can be measured by invasively estimating pulmonary artery pressure and flow. The Fick method for determining CO was not sufficiently precise given the wide ranges observed in clinical practice based on its dependency on multiple measurements, [35] the reliability of Thermodilution method also decreases in the context of valvular diseases or various cardiac operations [36]. Importantly, RHC is associated with a range of risks and complications. As a noninvasive modality, CMR plays a critical role in measuring hemodynamic indexes and monitoring and detecting the progress of chronic pulmonary hypertension. The approaches used to estimate PVR based on the pathophysiologic basis via CMR are largely empirical. As explained earlier, the included studies obtained pulmonary artery variables or hemodynamic variables and right ventricle variables to evaluate PVR directly and indirectly. Mousseaux et al. [14] reported that velocity encoded MRI (VE-MRI) imaging can provide new hemodynamic parameters that are inversely or directly proportional to PVR, and PVR exhibits a significant correlation with acceleration time, acceleration volume, and the ratio of maximal change in flow rate during ejection to acceleration volume ($r = 0.65$, 0.78, and 0.89, respectively). Sanz et al. [9] showed a significant correlation between average velocity and PVRI ($r = 0.86$; $P < 0.001$). Swift et al. [22] conducted a nonquantitative method to predict PVR and reported that pulmonary artery area change (AC) and relative area change (RAC) exhibited sensitivity for the detection of mild increases in PVR. Furthermore, the metrics of pulmonary artery AC and RAC, which are noninvasively assessed via CMR, are predictive of adverse outcomes in patients with PH. The 2 studies [37,38] above and prior investigations have shown that CMR could provide noninvasively pulmonary vascular hemodynamic parameters and excellent correlations between several CMR-derived indexes and RHC-quantified PVR. Garcı´a-Alvarez et al. [21] demonstrated that noninvasive CMR-quantified PVR is feasible despite some acceptable limits and accurately detects increased PVR. Nevertheless, differences are noted. Kreitner et al. [23] showed that the

Table 4
The data of PVR tested by CMR and RHC reported in the publications included in the meta-analysis.

First author, year	PVR-MRI*†, WU	PVR-RHC*†, WU	No. of patients	Raw data: PVR-MRI/PVR-RHC
Muthurangu [19] 2004	4.6 ± 3.5	4.7 ± 4.6	15	
Garcı´a-Alvarez [21] 2011	6.0 ± 3.5	6.5 ± 4.9	20	
Kreitner [23] 2013	6.94 ± 2.52	5.84 ± 1.69	19	562 (427; 679) / 427 (398; 567) †
Bane [25] 2015	6.66 ± 3.37	5.04 ± 2.3	7	
Yan [26] 2015	14.75 ± 6.83	13.86 ± 7.05	77	
Rogers [28] 2017	4.5 ± 3.5	4.8 ± 3.9	102	

Note: CMR, cardiac magnetic resonance; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WU, wood units.
*PVR-CMR indicates the values of PVR derived from CMR and PVR-RHC indicates PVR as measured during RHC.
†Continuous variables are presented as mean ± SD or median (Q1; Q3).
Mean and standard deviation are combined value of different PVR level.

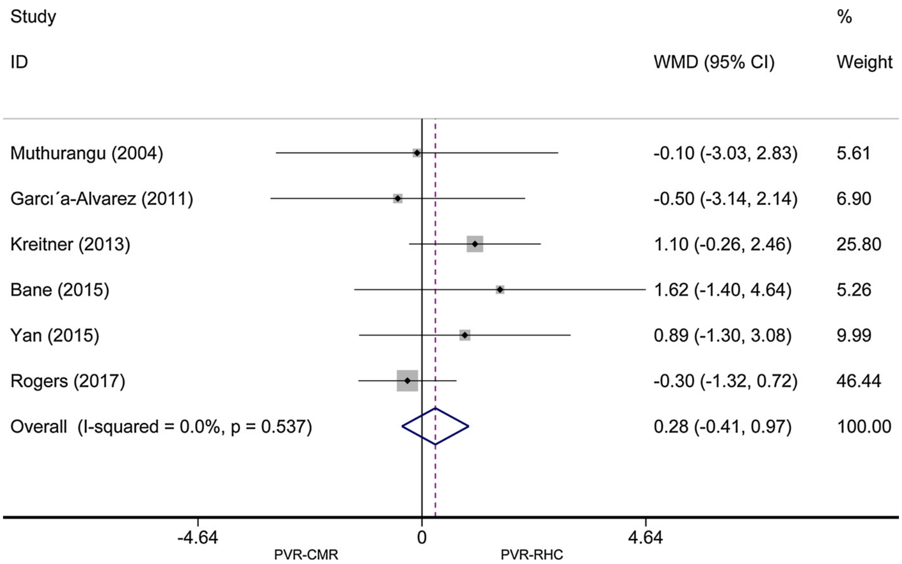

Fig. 3. Comparison of the results in estimating PVR between CMR and RHC.
Note: PVR, pulmonary vascular resistance; CMR, cardiac magnetic resonance; RHC, right heart catheterization; WMD, weighted mean difference.
*PVR-CMR indicates the values of PVR derived from CMR and PVR-RHC indicates PVR as measured during RHC.

PVR-CMR presented a noteworthy overestimation compared with PVR values obtained from RHC.

This systematic review and meta-analysis was performed to demonstrate the feasibility in estimating PVR by CMR in patients with PH on two fronts: comparison of PVR values derived from different methods and the correlation between PVR-CMR and PVR-RHC. In the meta-analysis, the pooled WMD (pooled WMD = 0.278 WU; 95% CI: −0.415 to 0.972) for PVR suggests no significant difference between PVR-CMR and PVR-RHC ($P > 0.05$) and that PVR-CMR is accurate. This conclusion was consistent with previous studies [19–23]. Sanz et al. [37] demonstrated a potential contributory role of PA stiffness and vascular resistance in the development and progression of PH that was crucial for clinical evaluation of patients with PH.

Regarding the correlation between PVR-CMR and PVR-RHC, Bane et al. [25] reported a modest correlation between the RHC and CMR-derived values (Spearman r = 0.43). However, other studies with a large number of patients reported more significant correlation in both modalities. In the validation cohort from the study by Garcı´a-Alvarez et al. [21], the correlation between RHC quantified invasively and CMR-estimated PVR was 0.84. Swift et al. [24] also reported that CMR- and RHC-derived PVR exhibited good correlation in the derivation and validation cohorts ($R^2 = 0.67$, $P < 0.0001$; $R^2 = 0.76$, $P < 0.0001$, respectively). The small sample sizes may yield inconstant results. Thus, a meta-analysis was conducted to calculate the pooled r and acquire a more stable result. The result (pooled r = 0.85; 95% CI: 0.81, 0.89) showed reasonable agreement between CMR and the invasive method of PVR quantification. The pooled r with notable heterogeneity and the study of Bane et al. [25] were the only outliers in the meta-analysis. Removal of this study resulted in r = 0.86 and 95% CI 0.83 to 0.90, but the heterogeneity remained significant ($I^2 = 86.4\%$, p = 0.000). Variations in study results cannot exclusively be attributed to this study. Variations can also be introduced by other sources, including various technical characteristics of the PVR measurements and the time interval between RHC and CMR. In addition, given that certain parameters were measured by Doppler echocardiography (TTE) in the study by Yan et al, [26] the data derived from TTE might represent a confounding factor in the correlation between PVR-CMR and PVR-RHC. Thus, sensitivity analysis was performed after excluding this study. The results revealed no notable variation between the remaining studies ($I^2 = 34.9\%$, P = 0.203), and PVR-CMR method correlated well with the PVR-RHC method (Pooled r = 0.81; 95% CI: 0.74, 0.87). Future research will provide more evidence to further investigate variations in both methods.

5. Study limitations

Although meta-analysis is a valuable tool for synthesizing the published literature, there are always some limitations to such analyses. First, the PVR values retrieved from the included studies were all obtained at baseline. Rogers et al. [25] observed different correlations between the two PVR quantified methods after inhalation of 100% oxygen and 40 ppm NO compared with that reported by Muthurangu et al. [19] These differences may be due to a range of factors, such as an increased number of paired calculations in different studies and narrow arteriovenous oxygen difference. In the future, more studies should focus on assessing PVR by CMR after inhaling 100% oxygen and 40 ppm NO. Second, the enrolled patients in the meta-analyses were heterogeneous regarding etiology and range of PVR severity. Thus, the conclusions from this study cannot be applied to all patients with PH. Finally, the subject group included in this analysis is small, which

Table 5
The correlation coefficients (r) between PVR-CMR and PVR-RHC.

First author, year	No. of patients	Raw r	Fisher's z* (95%CI)	SE(z) †	r(95%CI) ‡
Muthurangu 2004	15	0.91	1.53(0.96,2.09)	0.2887	0.91(0.744,0.97)
Garcı´a-Alvarez 2011	20	0.84	1.22(0.75,1.7)	0.2425	0.84(0.635,0.935)
Bane 2015	7	0.43	0.46(−0.52,1.44)	0.5	0.43(−0.478,0.894)
Yan 2015	77	0.931	1.67(1.44,1.89)	0.1162	0.93(0.894,0.955)
Rogers 2017	102	0.81	1.13(0.93,1.32)	0.1005	0.81(0.731,0.867)

Note: * Fisher's z values were calculated from Raw r values after Fisher's r to z transformation.
†SE(z) was the standard error (SE) of the Fisher's z values.
‡Correlation coefficients (r) and corresponding 95% confidence intervals (CIs) were calculated depending on the.
Fisher's z values after Fisher's z to r transformation.

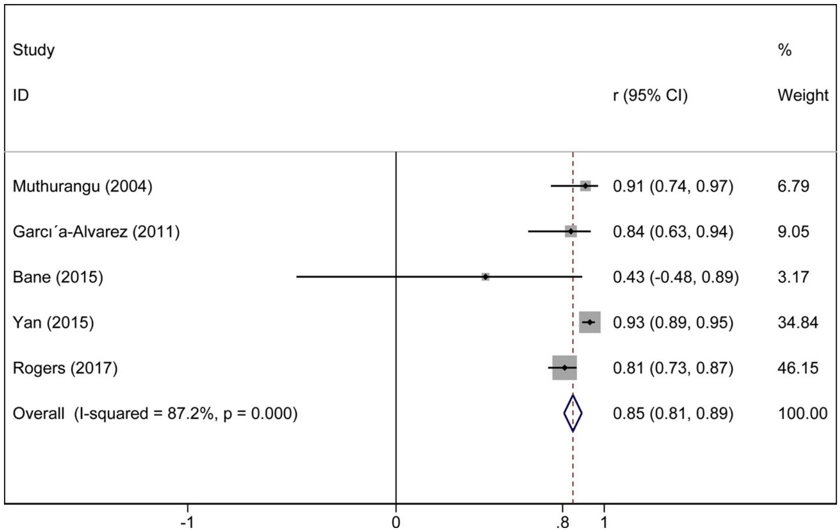

Fig. 4. Forest plot of the pooled correlation coefficient (r) with corresponding 95% CIs for the correlation between PVR-CMR and PVR-RHC from all eligible studies.

represents a limitation to the interpretation of applying this technique. Given the limited number of studies included in the analysis, the findings from our systematic review and meta-analysis should be confirmed in future research.

6. Conclusions

Although abovementioned limitations potentially detrimentally affected the performance of our study, all currently available evidence supports an excellent correlation between PVR values derived from CMR and RHC in patients with pH and the meta-analysis demonstrates that CMR and RHC exhibit good consistency in the testing of PVR. The systematic review shows that completely noninvasive evaluation of PVR with CMR is feasible.

Conflict of interest

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

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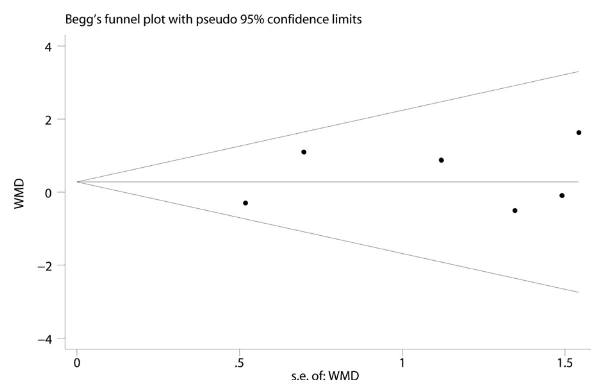

Fig. 6. Begg's funnel plot of the meta-analysis.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.03.014.

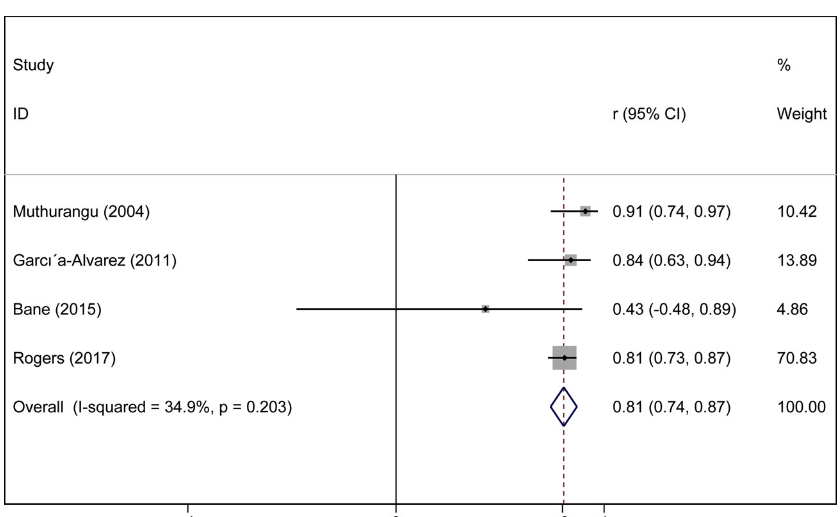

Fig. 5. Forest plot of the pooled correlation coefficient (r) with corresponding 95% CIs for the correlation between PVR-CMR and PVR-RHC after sensitivity analysis.

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