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Association between right atrial area measured by echocardiography and prognosis among pulmonary arterial hypertension: a systematic review and meta-analysis

Ke Liu ,[1] Chunhua Zhang,[2] Bingyu Chen,[3] Mingfeng Li,[4] Peican Zhang[4]

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KL and CZ contributed equally.

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[1]Department of General Surgery, Zhengzhou People's Hospital, Zhengzhou, Henan, China
[2]Department of Emergency, Shangcai People's Hospital, Shangcai, Henan, China
[3]Department of Internal medicine, Nanjing University of Traditional Chinese Medicine, Nanjing, China
[4]Department of Emergency, The First Affiliated Hospital of Henan University, Kaifeng, Henan, China

Correspondence to
Dr Ke Liu;
liukedoctor77@163.com

ABSTRACT

Objective The purpose of this meta-analysis was to evaluate the association between enlarged right atrial area (RAA), as measured by echocardiography, and prognosis of patients with pulmonary arterial hypertension (PAH).

Design Systematic review and meta-analysis.

Data sources To identify potential publications, a comprehensive literature search through MEDLINE, the Cochrane database and the Embase database was performed up to December 2019.

Eligibility criteria for selecting studies Studies were included if they reported Cox regression based-HRs with 95% CIs for all-cause mortality or composite endpoint consisting of death and PAH-related events for echocardiography measurements of the RAA or the right atrial area index (RAAI) in patients with PAH.

Data extraction and synthesis The unadjusted HR with 95% CI was extracted for the final pooled analysis. A random-effects model was used to determine the value of RAA/RAAI in the prognosis of patients with PAH. The data heterogeneity among the studies was estimated by the I^2 statistic and the Cochran Q-statistic.

Results Twelve studies with a total of 1085 patients with PAH were finally included in the meta-analysis. These studies had a mean follow-up time ranging from 9.2 months to 5.0 years. Their findings showed that patients with PAH with enlarged RAA/RAAI were associated with poor prognosis. The risk of all-cause mortality in patients with PAH was found to statistically increase by 50% for every 5-unit increase in RAA/RAAI (HR 1.50, 95% CI 1.28 to 1.75, p<0.001). Similarly, the risk of the composite endpoint also significantly increased by 53% for every 5-unit increase in RAA/RAAI (HR 1.53, 95% CI 1.23 to 1.89, p<0.001). Subgroup analyses in which the patients were stratified by RAA and RAAI were consistent with the main results.

Conclusion The meta-analysis suggested that enlarged RAA/RAAI were associated with increased risk of poor prognosis in patients with PAH.

Strengths and limitations of this study

- This meta-analysis is the largest study to date examining the association between right atrial area/right atrial area index as measured by echocardiography and poor prognosis in patients with pulmonary arterial hypertension.
- The heterogeneity between included studies concerning the primary endpoint was relatively low, which enhanced the robustness of this meta-analysis.
- Only univariable HRs were pooled, due to the heterogeneous multivariable adjustment models used in the different studies.
- The studies included were observational, and mostly single centred, with small study populations.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a pathophysiological disorder caused by the progressive narrowing of small pulmonary arteries, which can lead to increased pulmonary vascular resistance and right-sided heart failure.[1 2] Despite the availability of modern treatments, the disastrous prognosis (5-year mortality expectation approaching 30%–50%) of patients with PAH shows the urgent need for amelioration of this condition.[3 4] To achieve optimal clinical management for each patient, risk assessment plays a pivotal role in determining clinical practice by multidisciplinary teams. Current guidelines recommend categorising patients with PAH' risk of severity as low, intermediate or high on the basis of certain prognostic determinants to guide therapeutic decisions.[2] Echocardiography is a well-established and widely available technique that is routinely used during the initial screening, follow-up assessment and evaluation of treatment responses for patients with PAH.[5–7] Despite advances in other imaging modality techniques such as MRI or CT, echocardiography remains a convenient and valuable option for assessing cardiac morphology and function.

A number of echocardiographic parameters has been recently shown to be associated with prognosis in patients with severe PAH.[8 9]

At diagnosis, the right ventricular and right atrial areas (RAAs) are commonly increased in size.[10] Theoretically, the right atrium (RA) is involved in the pathophysiological process of PAH.[11 12] Both right atrial reservoir and conduit functions are impaired and these impairments are associated with right ventricular (RV) pump dysfunction.[13] An enlarged RAA, which reflects right ventricle overload in PAH, is recognised as a risk factor for adverse outcome.[14] However, different studies have reported controversial results regarding the predictive value of this parameter, especially considering the imprecision of the echocardiographic measuring method.[15 16] These various studies have reported a broad range of sample sizes, patient treatments, follow-up durations, outcome parameters and pulmonary hypertension (PH) groups, yielding a challenge to establish the potential prognostic role of RAA in patients with PAH. Hence, the purpose of this systematic review and meta-analysis was to evaluate the association between RAA/right atrial area index (RAAI) measured by echocardiography and prognosis in patients with PAH.

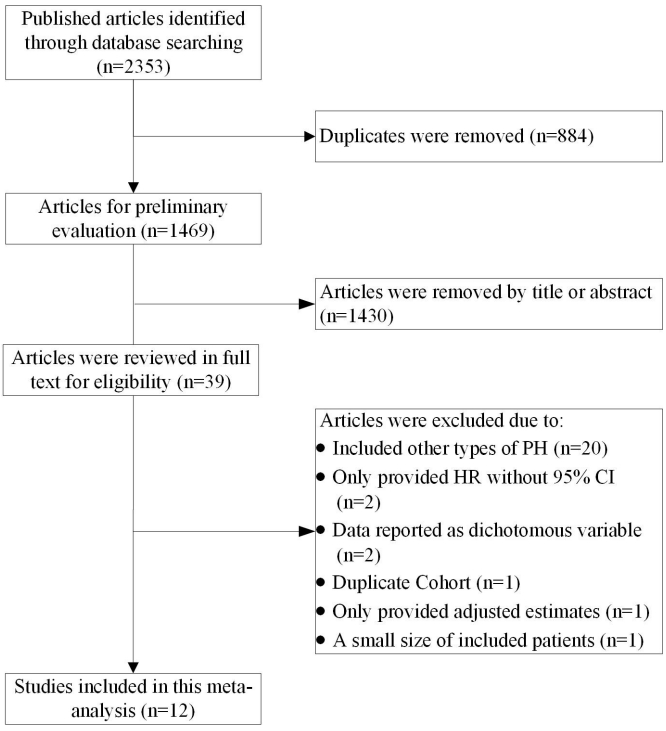

Figure 1 The schematic representation of article searching and screening. PH, pulmonary hypertension.

METHODS

Patient and public involvement statement

Only the authors listed in this study were involved in the design and planning of the study, and neither the patients nor other members of the public influenced that process.

Search strategy

A comprehensive literature search through MEDLINE, the Cochrane database and the Embase database was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] To identify potential studies up to 1 December 2019, the following keywords were adopted: 'pulmonary hypertension', 'pulmonary arterial hypertension', 'echocardiography', 'right heart' 'right atrium', 'right atrial size', 'right atrial area', 'right atrial area index' and 'prognosis'. The details of the search strategy were presented in online supplemental file. The search was restricted to English-language publications. When several publications included the same group of patients (duplicate data), only that one with the most complete data or largest sample size was included. All of the eligible publications were evaluated independently for inclusion criteria by the two reviewers, and discordances were resolved by consensus with a third reviewer. The schematic representation of the article searching and screening process is presented in figure 1.

Study selection criteria and endpoint definitions

The included studies had to meet all of the following criteria: (1) designed as cohort studies; (2) investigated the effects of RAA or RAAI on all-cause mortality or the composite endpoint; (3) patients diagnosed with PAH according to standard guideline-based diagnostic criteria[18]; (4) HRs with 95% CIs reported using RAA or RAAI as the continuous variable; (5) sample sizes of no less than 40 patients.

The primary endpoint was all-cause mortality and the secondary endpoint was a composite endpoint of death and PAH-related events. PAH-related events were heterogeneous between the various studies, included lung transplantation, rehospitalisation due to worsening heart failure, initiation of prostanoids or need for new PAH drug treatment, and clinical worsening of a reduction in the 6 min walking test or WHO functional class.

Data extraction and quality assessment

The data were extracted independently by two investigators, and discrepancies were resolved by consensus with a third investigator. The following features of each eligible study were extracted using a standardised form: study design and population characteristics, PAH targeted therapies, echocardiographic findings, study endpoint and follow-up durations. The unadjusted HR with 95% CI was extracted for the final pooled analysis. Initially, we harmonised group-level exposure estimates to per 5-unit changes, thereby allowing for integration of the estimated effects of RAA/RAAI differing in distinct studies. If the intensity of RAA/RAAI changing was not reported, we assumed that the intensity was one-unit change.

A dedicated tool designed for prognostic study assessment was adopted to evaluate the methodological quality of the included publications.[19 20] This tool consists of the following six methodological domains to assess potential

Table 1 The general characteristics of publications included in the meta-analysis

Authors	Study design	Patients (n)	Age (years)	Women (%)	PH specific therapy	Primary outcome	Follow-up period
Raymond *et al*[14]	Prospective	81	40±15	73	Prostacyclin (n=40)	All-cause mortality	36.9±15.4 months
Moceri *et al*[15]	Prospective	181	39.1±12.8	67.4	Bosentan (n=34); sildenafil (n=32); bosentan+sidenafil (n=8)	All-cause mortality	16.4 (7.1–45.5) months
Mathai *et al*[24]	Prospective	50	61±11	98	Targeted therapy without details	All-cause mortality	15.7 (8.7–38.5) months
Haddad *et al*[25]	Prospective	95	43±11	79	Prostanoid (n=43); PED-5i (n=31); ERA (n=39)	Composite endpoint of death or lung transplantation	5.0±2.4 years
Park *et al*[26]	Retrospective	51	48±14	78	CCB (n=9); PED-5i (n=29); ERA (n=26); prostacyclines (n=32)	A composite of death, cardiac hospitalisation due to worsening of heart failure and lung transplantation	45±15 months
Murata *et al*[27]	Retrospective	86	50±17	72	PDE-5i (n=60); ERA (n=51); prostanoids (n=24); CCB (n=9)	Clinical events of deaths, hospitalisations, PEA and BPA for deteriorating right-sided heart failure	Mean 423 days
Badagliacca *et al*[28]	Prospective	102	52±14	60.8	ERA, PDE-5i and prostanoids (n=102)	Clinical worsening of a reduction in the 6MWT, plus worsening of WHO FC, or non-elective hospitalisation for PAH or all-cause mortality	528±304 days
Mazurek *et al*[29]	Prospective	70	55±15	78.6	PDE5-i (n=58); ERA (n=48); inhaled PG (n=14); parenteral PG (n=14)	All-cause mortality	384 days, (range, 201–753 days)
Amsallem *et al*[30]	Prospective	228	49±14	78.1	Treatment naïve (n=82); prostanoids (n=80); PED-5i (n=100); ERA (n=63)	Composite endpoint of death, lung transplantation or hospitalisation for acute right heart failure	3.9±2.4 years
Stepnowska *et al*[31]	Prospective	47	39±17	63.8	Sildenafil (n=19); bosentan (n=27); iloprost (n=5); treprostinil (n=3)	All-cause mortality	2.6±1.7 years
Bai *et al*[32]	Prospective	53	42±12	96.2	ERA (n=14); PDE-5i (n=16); ERA +PDE-5i (n=7)	Adverse events defined as death, initiation of prostanoid therapy or worsening of PAH	19.3±10.9 months
Kawamukai *et al*[33]	Retrospective	41	48.9±17.3	76	Prostanoids (n=9); ERA (n=7); PDE5i (n=5); triple combination therapy (n=3)	Composite endpoints of cardiovascular death and hospitalisation for PAH and/or right ventricular failure	9.2±8.7 months

Data were presented with mean with SD, median with IQR or % unless other statement.
BPA, balloon pulmonary angioplasty; ERA, endothelin receptor antagonist; 6MWT, 6 min walking test; NYHA, New York Heart Association; PAH, pulmonary artery hypertension; PDE-5i, phosphodiesterase 5 inhibitor; PEA, pulmonary thromboendarterectomy; PG, prostaglandin; PH, pulmonary hypertension.;

Table 2 Values of right atrial area or right atrial area index and HR with 95% CI from the publications included in the meta-analysis

Authors	Right atrial size	Changing amplitude	Events (n)		HR (95% CI)	
			All-cause mortality	Composite endpoint	All-cause mortality	Composite endpoint
RAA (cm^2, m±SD)						
Moceri *et al*[15]	21.1±6.1	Per 10 cm^2	19	NA	3.59 (1.92 to 6.72)	
Park *et al*[26]	22.5±9.4	Per 9.4 cm^2	12	20	1.36 (0.85 to 2.18)	1.45 (1.02 to 2.05)
Murata *et al*[27]	18±5	Per 1 cm^2	NA	19	NA	1.20 (1.06 to 1.34)
Badagliacca *et al*[28]	31±10	Per 1 cm^2	NA	54	NA	1.04 (1.01 to 1.06)
Stepnowska *et al*[31]	29±11(died) vs 19±6 (survival)	Per 1 cm^2	9	NA	1.08 (1.02 to 1.14)	NA
Bai *et al*[32]	28.2±7.3 (with events) vs 17.9±4.2 (without events)	Per 1 cm^2	NA	20	NA	1.13 (1.08 to 1.18)
Kawamukai *et al*[33]	18.0±8.0 (with events) vs 19.8±6.9 (without events)	Per 1 cm^2	NA	18	NA	0.97 (0.90 to 1.02)
RAAI (cm^2/m, m±SD)						
Raymond *et al*[14]	19.9±6.6	Per 5 cm^2	20	41	1.54 (1.13 to 2.10)	1.33 (1.06 to 1.66)
Mathai *et al*[24]	14.0±5.5	Per 1 cm^2	25	NA	1.11 (1.02 to 1.19)	NA
Haddad *et al*[25]	NA	Per 5 cm^2	NA	27	NA	1.81 (1.44 to 2.28)
Mazurek *et al*[29]	13.0±4.4	Per 1 cm^2	18	NA	0.98 (0.62 to 1.56)	NA
Amsallem *et al*[30]	12.1±4.7	Per 4.7 cm^2	NA	88	NA	1.37 (1.20 to 1.57)

NA, not available; RAA, right atrial area; RAAI, right atrial area index.

biases among included studies: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account and statistical analysis and reporting. After assessment, every methodological domain was labelled as good, adequate or unclear in each study.

Statistical analysis

STATA software (V.14.0; StatCorp) was used to perform statistical analysis. Separate analyses were conducted for (1) all-cause mortality and (2) composite endpoint of death and PAH-related events. The DerSimonia and Laird random effect models with the inverse variance-weighted mean of the logarithms of HR with 95% CI are used to pool HR estimates.[21] A two-sided p<0.05 was considered statistically significant. Data heterogeneity among the studies was estimated by the I^2 statistic and the Cochran Q-statistic, with p<0.10 indicating significant heterogeneity.[22] Sensitivity analysis was carried out using the leave-one-out approach and meta-regression was used to explore the potential moderators of effect size. Publication bias was assessed by the Egger's test using the effect size with upper and lower limits for each trial, with p<0.05 considered statistically significant.[23]

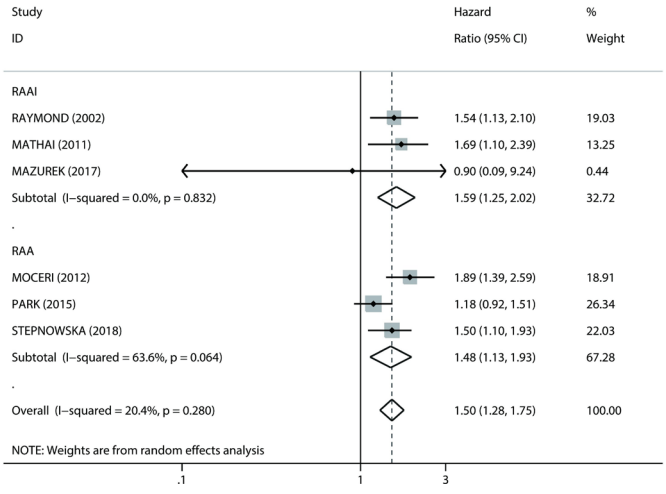

Figure 2 Forest plot comparing the unadjusted HRs of RAA/RAAI for all-cause mortality pooled from included studies. RAA, right atrial area; RAAI, right atrial area index.

RESULTS

Search selection and study characteristics

We totally identified 2353 publications by initial search strategy. After removing 884 duplicates, 1469 publications are remained for further assessment. Among them, 1186 were excluded after review of their titles and abstracts, and 39 publications were then considered for potential inclusion. Through carefully reading full text, 12 studies[14 15 24–33] were finally included in the meta-analysis. The mean follow-up times of these studies ranged from 9.2 months to 5.0 years. In terms of study design, all of the 12 publications were cohort studies, with 9 prospective studies and 3 retrospective studies. Four studies only provided results on all-cause mortality,[15 24 29 31] and five studies only reported results for the composite

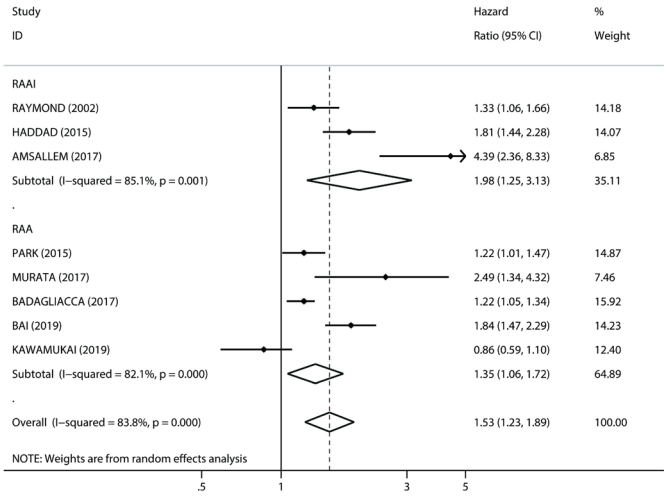

Figure 3 Forest plot comparing the unadjusted HRs of RAA/RAAI for the composite point pooled from included studies. RAA, right atrial area; RAAI, right atrial area index.

endpoint.[25 27 28 32 33] Two studies[14 26] reported separate data for all-cause mortality and composite endpoint, and therefore were eligible for both analysis.

Patient characteristics

A total of 1085 patients with PAH were included in this meta-analysis, of which female patients were predominant (ranging between 60.8% and 98.0%), with mean age varying from 39 to 61 years. With respect to PAH targeted drugs therapies, the proportion of patients who received treatment and the types of drug used were fairly heterogeneous. Two publications reported the proportions of patients receiving a calcium channel blocker, 10 the proportion receiving a phosphodiesterase-5 inhibitor and an endothelin receptor antagonist and 9 the proportion receiving a prostacyclin analogue. In the one remaining study,[24] a demonstrated targeted therapy was prescribed, but no details were given. The key characteristics of the included studies are presented in table 1.

Table 2 summarised the echocardiographic measures of right atrial size (RAS) and the changes in numbers of units in the HRs referred to in included studies. The RAA was presented as an estimated parameter in eight studies,[15 26–28 30–33] whereas RAAI was presented in the other four studies.[14 24 25 29] Moreover, all studies reported the numbers of events and the corresponding HR for primary and secondary endpoints.

Endpoints and quality assessment

The results revealed that the risk of all-cause mortality statistically increased by 50% for every 5-unit increase in RAA/RAAI (HR 1.50, 95% CI 1.28 to 1.75, p<0.001, see figure 2). Subgroup analyses showed the consistency between RAA (HR 1.48, 95% CI 1.13 to 1.93, p=0.004) and RAAI (HR 1.59, 95% CI 1.25 to 2.02, p<0.001). Similarly, the risk of composite endpoint also significantly increased by 53% for every 5-unit increase in RAA/RAAI (HR 1.53, 95% CI 1.23 to 1.89, p<0.001, see figure 3). In addition, the pooled unadjusted HRs in different subgroups were in line with the main results, which was 1.35 in RAA (95% CI 1.06 to 1.72, p=0.016) and 1.98 in RAAI (95% CI 1.25 to 3.13, p=0.003).

Quality assessment of included publications indicated a relatively low to moderate risk of bias. This assessment was performed using a QUIPS tool for prognostic studies, as described by Hayden *et al*.[19] The results are presented in online supplemental table S1.

Sensitivity analysis and publication bias

Relatively low heterogeneity was found among the included studies with regard to the primary endpoint (I^2=20.4%, p=0.280). Subgroup analyses showed that heterogeneity mainly originated from the RAA group. Sensitivity analysis by removing one study per time showed that the study by Park *et al* was as the source of heterogeneity. Exclusion of this study from the analysis markedly reduced the heterogeneity (I^2=0%, p=0.805), and the pooled results were similar to the main finding. Similarly, we conducted sensitivity analysis at secondary endpoint, but we could not identify the key contributor to overall heterogeneity. Hence, possible association between the net effects of RAA/RAAI on the prognosis of patients with PAH and putative moderators (ie, the compositions of composite endpoint, study design, sample size, age, female proportion and duration of follow-up) were assessed using random effect meta-regression analysis. However, none covariates showed direct associations with the results (p>0.05).

Funnel plots with Egger's test showed no significant publication bias toward RAA/RAAI for primary endpoint and secondary endpoint, respectively (Egger's regression test p=0.169 and p=0.262, respectively) (see figure 4).

DISCUSSION

To date, our meta-analysis is the largest study of patients with PAH to examine the relationships between RAA/RAAI and all-cause mortality, as well as the composite endpoint of death and PAH-related events. The main findings suggested that RAA/RAAI derived from echocardiography was significantly associated with the increased risk of poor prognosis in patients with PAH.

To adequately assess the risk of patients with PAH for achieving more acceptable prognosis, accurate prognostication is highly important. Echocardiographic assessment of right ventricular longitudinal strain[26] and tricuspid annular plane systolic excursion[34] have been established as important prognostic factors in determining disease severity and prognosis in patients with PAH. Nevertheless, only a few studies have investigated whether RAS or function were associated with prognosis for PAH, partly due to morphological complexity of RA and the inconsistency of appraisal procedure. Regarding to RAS, Bustamante-Labarta *et al*[35] first reported this parameter was an independent risk factor of transplantation and death in primary PH, although with a small sample. Likely, Fukuda *et al*[36]

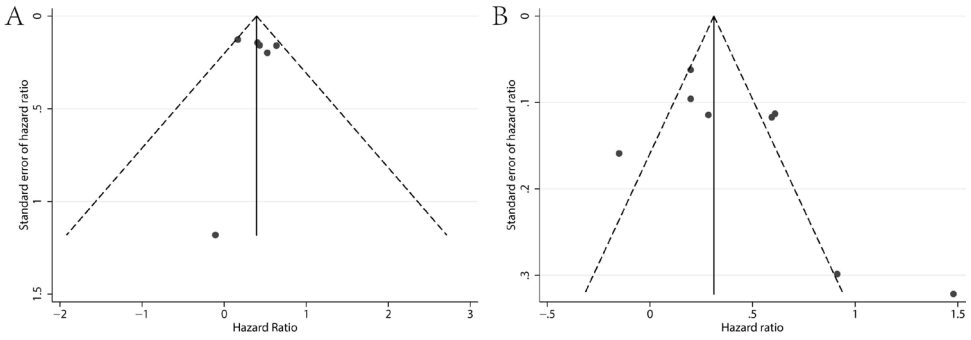

Figure 4 Funnel plot for all-cause mortality (A) and composite endpoint (B).

also found that combined assessment of impaired right ventricular systolic function and increased RAA resulted in more accurate prediction of long-term outcome.

Generally, the mechanics of the RA maintains cardiac function are complex.[10] It has been recognised that the three components of atrial function are reservoir function, conduit function and contractile function.[37] RA is an anatomically dynamic structure, which is able to assist with filling of the RV at low pressure and responsible for up to 30% of normal RV output by contraction. RAS and pressure reflect right ventricular function. Gaynor *et al* demonstrated that the RA conduit-to-reservoir ratio is directly related to the RV pressure-RA pressure gradient.[10] In contrast to primary left ventricular disease that causes elevation of left atrial pressure, PAH causes an elevation of right atrial pressure, which is inversely related to cardiac output.[38] In healthy subjects, short elevations of RV pressure lead to stretching and enlargement of the RA, resulting in higher reservoir volume. This mechanism has been identified as compensating for short-term RV overload.[39] One significant observation has been that PAH is followed by enlargement and remodelling of the RA with hypertrophy and reduced contractility.[40 41] However, right atrial compensation for the increased RV afterload has a limit. Once RA compensation for RV dysfunction is impaired, a scenario inevitably occurs that a decrease of cardiac output with the onset of severe right-side heart failure and rapid deterioration until death occurs.[42 43] Additionally, right atrial enlargement due to increase in right atrial pressure could be a predisposing factor for the development of atrial arrhythmias, thus affecting the risk of hospitalisation and likely the prognosis in PAH.[44]

Currently, the algorithm of risk assessment of 2015 European Society of Cardiology(ESC)/European Respiratory Society(ERS) guidelines for the diagnosis and treatment of PH,[2] suggests only one echo parameter, namely RAA, for use in multimarker risk stratification approach in patients with PAH. However, the evidence level of RAA for predicting prognosis in patients with PAH is low, and most importantly, the prognostic utility was only recommended for idiopathic PAH.[2] Therefore, there is still insufficient solid evidence to demonstrate the prognostic value of RAA/RAAI for patients with PAH. The findings of this meta-analysis imply that enlarged RAA is a useful echocardiographic marker to predict mortality or composite endpoint in patients with PAH, which is largely concordant with the guideline. Moreover, these results remind us that although other imaging examinations, such as MRI which may provide more accurate assessment of cardiac parameters, it is undeniable that echocardiography still has great advantages due to its easy availability and relatively cheapness.

Our meta-analysis revealed a lower capacity of RAA/RAAI for predicting all-cause mortality and composite endpoint. This result may be explained partly by the fact that the studies included in the analysis provided the estimated effect of RAA/RAAI as a continuous variable. This analysis may underestimate the discriminating capacity of the parameters to predict prognosis in patients with a larger RAA. In addition, the composite endpoints in our meta-analysis were heterogeneous. Several studies have prespecified some clinical events, such as initiation of prostanoids or need for new PAH drug treatment, as a composite endpoint, which were objectively determined by physicians' consideration to a great extent. Accordingly, the diversity in clinical events consisting the composite endpoint might contribute to heterogeneity and reduce the capacity of RAA/RAAI to predict the risks of composite endpoint in patients with PAH.

This meta-analysis had several limitations. First, we presented only univariable HRs, because of the wide variety of multivariable adjustments between different studies (regarding the types and numbers of predictors per event used). Second, the included studies were observational, most of them involved a single centre with a small study population, and several were retrospective. Third, clinical inclusion and exclusion criteria used by the individual studies were variable and there was a wide variety of endpoints. This might explain the significant heterogeneity found between the included studies. Finally, we did not perform subgroup analysis based on ethnic groups in the selected studies due to insufficient data. Therefore, a complete picture of the impact of ethnicity on patients could not be obtained.

CONCLUSION

This present meta-analysis suggested that RAA/RAAI was associated with increased risk of poor prognosis in

patients with PAH, as is currently indicated in the guidelines on RAA for the risk stratification of these patients.

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Contributors KL and CZ designed the study and provided critical reviews of the manuscript. BC and ML reviewed the articles and extracted the data. KL and CZ conducted the data analysis. KL wrote the first draft of the manuscript and PZ critically revised it. All authors have reviewed and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The datasets generated during and/or analysed during this study are available in the manuscript.

ORCID iD

Ke Liu http://orcid.org/0000-0003-1450-910X

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