Meta-Analysis of Observational Studies in Epidemiology

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Prognostic impact of red blood cell distribution width in pulmonary hypertension patients

A systematic review and meta-analysis

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Abstract

Elevated red blood cell distribution width (RDW) may correlate with a worse prognosis in pulmonary hypertension (PH), though results to date are inconsistent. The goal of this study is to detect the impact of RDW on the prognosis of PH.

PubMed and EMBASE databases were searched from their inception to July 22, 2019 for relevant publications reporting the relationship between RDW and the prognosis of PH. A meta-analysis was performed, and the heterogeneity across the included studies was evaluated using I^2 and Q statistics. We conducted sensitivity and subgroup analyses to detect sources of heterogeneity. In addition, potential publication bias was evaluated by Begg's and Egger's tests.

In total, 1236 publications were retrieved, and 7 eligible publications with 666 PH patients were included in our meta-analysis. The results suggested that increased RDW can predict worse prognosis in PH (hazard ratio (HR) = 1.27, 95% confidence interval (CI) 1.11–1.45). According to subgroup analysis, study design, region, various endpoints, time of follow-up, and patient age were not sources of heterogeneity. In addition, RDW showed prognostic value in retrospective studies (HR = 1.32, 95%CI 1.15–1.51) but not in prospective studies (HR = 1.14, 95%CI 0.78–1.67). Additionally, RDW may serve as a predictive biomarker of PH in Europe (HR = 1.33, 95%CI 1.18–1.49) but not in Asia (HR = 1.20, 95%CI 0.90–1.58). Further analysis indicated that the prognostic value of RDW was influenced by patient age (>44 years: HR = 1.34, 95%CI 1.17–1.55; ≤44 years: HR = 1.20, 95%CI 0.90–1.58) and follow-up (<3 years, HR = 1.36, 95%CI 0.53–3.47; ≥3 years, HR = 1.29, 95%CI 1.14–1.45).

RDW provides important prognostic information for PH patients, and this measure may be used to optimize patient management and guide clinical treatment.

PROSPERO registration number: CRD42019122636.

Abbreviations: CI = confidence interval, CTEPH = chronic thromboembolic pulmonary hypertension, ES = Eisenmenger syndrome, HR = hazard ratio, IPAH = idiopathic pulmonary arterial hypertension, MOOSE = Meta-analysis Of Observational Studies in Epidemiology, NOS = Newcastle-Ottawa Scale, PH = pulmonary hypertension, RDW = red blood cell distribution width, RHC = right heart catheterization.

Keywords: meta-analysis, prognosis, pulmonary hypertension, red blood cell distribution width

1. Introduction

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure greater than 25 mm Hg, as detected by right heart catheterization (RHC) in the resting state at sea level.[1] A previous study found that approximately 1% of the world's population has pulmonary hypertension and that the prevalence among people over 65 increases to 10%.[2] Thus, PH remains a global health threat. Moreover, because it can increase right ventricular (RV) afterload and damage RV systolic function, PH

Editor: Leyi Wang.

JL and JY contributed equally to this work.

This work is supported by grants from the National Natural Science Foundation of China (Nos. 81560694 and 81760015), the "Special and Joint Program" of Yunnan Provincial Science and Technology Department and Kunming Medical University (Nos. 2018FE001(-2-6) and 2017FE467(-094)), Yunnan health training project of high level talents (No. D-201627), and Young Academic and Technical Leaders of Yunnan Province (No. 2017HB053).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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How to cite this article: Liu J, Yang J, Xu S, Zhu Y, Xu S, Wei L, Qian P, Lv Y, Zhang C, Xing X, Deng Y. Prognostic impact of red blood cell distribution width in pulmonary hypertension patients: a systematic review and meta-analysis. Medicine 2020;99:16(e19089).

Received: 27 October 2019 / Received in final form: 3 January 2020 / Accepted: 8 January 2020

http://dx.doi.org/10.1097/MD.0000000000019089

tends to result in right-sided heart failure and has a poor prognosis.[3,4] At present, targeted therapies, such as prostaglandins, phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and soluble guanylate cyclase stimulators, are used to treat PH and improve quality of life, but these vasodilators do not target the key factors of pathogenesis or reduce mortality. To better optimize patient management, a comprehensive prognosis assessment is of great importance. Despite a number of clinical and hemodynamic parameters or technologies for evaluating PH prognosis, such as right heart catheterization, the gold standard,[5] the invasive, subjective, and unstable nature and very high costs of such techniques limit their use.[6] Therefore, a specific, inexpensive, and non-invasive measure to evaluate PH prognosis is urgently needed.

The red blood cell distribution width (RDW) index, a routine parameter reported in the complete blood cell count, shows the size variability of the circulating red blood cell volume.[7] RDW has been widely used to diagnose anemia of different mixed etiologies.[8] Previous studies have reported the value of RDW in predicting adverse outcomes in malignant tumours, such as oesophageal cancer,[9] hematological malignancies,[10] and breast cancer,[11] and in other diseases including congestive heart failure,[12] acute myocardial infarction,[13–15] chronic obstructive pulmonary disease,[16] acute pulmonary embolism,[17] and cardiovascular and thrombotic disorders.[18] Furthermore, recent studies have found that RDW can act as a prognostic marker of adverse outcomes in patients with PH of different etiologies,[19,20] and the novel biomarker RDW may reflect multiple physiological and pathological impairments related to PH, with significant prognostic value for these patients.

Many studies to date have focused on the relationship between RDW and PH prognosis, but the results are inconclusive. Considering the limitations of individual studies, we performed a meta-analysis, a tool for detecting connections that might be easily ignored by individual studies, to identify the association between RDW and PH.

2. Materials and methods

We conducted this systematic review and meta-analysis according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[21] Since our analysis was based on published literature, the study did not need the ethical approval of the ethics committee.

2.1. Data sources

PubMed and EMBASE databases were searched from their inception to July 22, 2019, to identify relevant publications exploring the relationship between RDW and PH prognosis. The search terms used in our study were "erythrocyte indices"[Mesh], "red cell distribution width", "RDW", "hypertension, pulmonary"[Mesh], "pulmonary hypertension", "PH", and "PAH". The detailed strategy is presented in online supplementary Figure 1, http://links.lww.com/MD/E55. In addition, the bibliographies of the identified papers were checked for potential eligible studies.

2.2. Study selection

Eligible articles were screened independently by 2 of the authors (XSL and LJ) by reading the titles and abstracts of all papers retrieved. When the titles and abstracts did not provide enough information or one author thought it might meet our requirements, the full text was reviewed. Any disputes were resolved via consensus.

2.3. Inclusion and exclusion criteria

Studies meeting the following criteria were included in this analysis:

1) patients were diagnosed with PH and were >18 years old;
2) evaluation of the prognostic value of RDW for patients with PH of different etiologies;
3) available RDW hazard ratio (HR) and corresponding 95% confidence intervals (CIs); and
4) available full text.

The exclusion criteria were as follows:

1) reviews, case reports, abstracts, meta-analyses;
2) animal or cell line studies;
3) duplicate literature and duplicate data;
4) insufficient data; and
5) articles published in languages other than English.

2.4. Data extraction

The following data were independently extracted by 2 reviewers (XSY and ZY) from the included studies: first author, country of origin, year published, study design, PH disease type, number of participants, RDW, participants' characteristics, outcomes (all-cause death, death or lung transplantation), and years of follow-up. Disagreements were resolved by consultation with a third author (DYS), who was blinded to the previous assessment. When we did not obtain sufficient information to conduct a meta-analysis, we attempted to contact the authors by email to obtain missing details.

2.5. Quality assessment

Two authors (ZCF and YJ) independently evaluated the quality of the included studies according to the Newcastle-Ottawa Quality Assessment Scale (NOS).[22] The scale was used to evaluate a study from 3 aspects: selection, comparability, and outcome assessment. The components selection and outcome were given a maximum of 1 point; comparability was given a maximum of 2 points. The scores were summed, with the highest score being 9. Studies with NOS scores ≥7 were considered to be high quality.

2.6. Statistical analysis

Hazard ratios (HRs) and 95%CIs were obtained directly from the articles, and pooled HRs and 95%CIs for RDW were calculated using fixed- or random-effects models. Statistical heterogeneity among the included studies was evaluated using the Cochran Q test and I^2 statistic (low = 0.0–25.0%; moderate = 25.0–50.0%; and high = 50.0–75.0%).[23] For the Cochran Q test, a P value ≤.1 or $I^2 \geq 50.0\%$ indicates significant heterogeneity, and the random-effects model was applied to estimate the pooled HR.[24] Otherwise, the fixed-effect model was chosen.[25] To explore the potential source of heterogeneity, subgroup analyses were performed based on the study design (prospective or

retrospective), location of research (Europe or Asia), median or mean age of the included study populations (>44 years or ≤44 years), time of follow-up (median or mean time of follow-up ≥3 years or <3 years), analysis (multivariate or univariate), and various endpoints (death, adverse outcome, and all-cause death).

Sensitivity analysis was also conducted to identify whether excluding each of the included studies would have a significant impact on the final results.[26] If the 95% confidence interval (CI) calculated after excluding a study did not agree with the original 95%CI generated from the collection of all studies, the study was considered for exclusion. In addition, Begg's test and Egger's test were employed to assess potential publication bias.[27] In addition, the trim and fill method was used to adjust the results.[28] All statistical analyses were conducted using STATA statistical software version 12.0 (STATA Corp. LLC, College Station, TX).

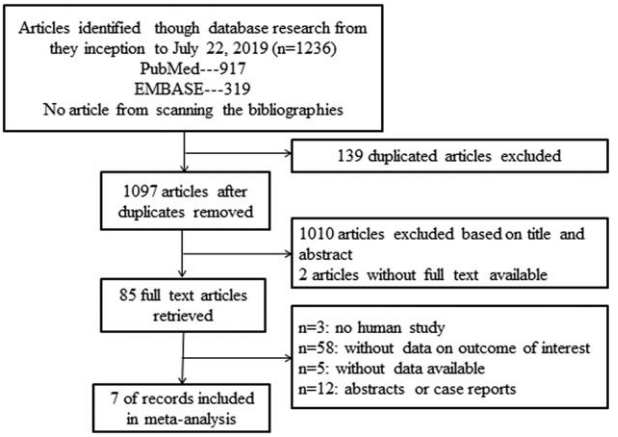

Figure 1. Flowchart of our literature identification process.

3. Results

3.1. Search results and study selection characteristics

Initially, 1236 articles (917 from PubMed and 319 from EMBASE) were identified according to our systematic literature search. No additional articles collected from reference lists of relevant publications were included. Figure 1 shows the flowchart outlining our literature search. After a series of screens, 7 articles[20,29–34] involving 666 patients with PH meeting all the criteria were included in this meta-analysis. PH was diagnosed based on standard criteria, with confirmation by RHC.

The characteristics of the 7 eligible studies included in our meta-analysis are presented in Table 1. Three studies were performed in Europe and 3 in Asia. These studies were published between 2009 and 2019. The sample size of the 7 studies varied from 9 to 145, with more female patients than male patients (73.7% vs 26.3%). Among the studies, 3 were retrospective in nature, and the others were prospective studies. The mean or median of the duration of follow-up varied from 2.1 to 5.4 years. The study populations comprised patients with different types of PH, such as Eisenmenger syndrome (ES), idiopathic pulmonary arterial hypertension (IPAH), and chronic thromboembolic pulmonary hypertension (CTEPH). As shown in Table 2, 2 of the study outcomes were all-cause death, and the primary endpoints of 2 studies were death; for the remainder, the outcome was adverse outcomes. The range of RDW values was 13.7% to 18.1%, as measured using an XE-1800 (Sysmex, Kobe, Japan) or XE-2100 (Sysmex, UK) automated hematology analyzer.

3.2. RDW and endpoints

As shown in Figure 2, the pooled HR for the 7 studies including 666 patients showed that increased RDW was able to predict a worse prognosis in PH (HR = 1.27, 95%CI 1.11–1.45, $I^2 = 50.4\%$, $P = .06$). Due to the high degree of heterogeneity

Table 1

Characteristics of the patients included in this meta-analysis.

Author and year of publication	Study years	Study design	Country (region)	PH included (%)	Females, n (%)	Mean age (yr)	Follow-up (yr)	NOS score
Hampole et al (2009)	2004–2009	P	–	PAH 61.7; PVH 21.0; HPH 3.1; CTEPH 4.3; Others 9.9	126 (78.0)	53.0 ± 15.0	2.1 ± 0.8	8
Nickel et al (2011)	1999–2009	P	Germany (E)	IPAH 100	78 (71.6)	55.0 (42.0–68.0)	3.1 (2.1–5.8)	8
Rhodes et al (2013)	2002–2011	R	England (E)	IPAH 89.7 HPAH 5.5 CHD-PAH 3.4 CTD-PAH 1.4	94 (64.8)	51.1 ± 17.0	3.83 (0.3–8.6)	8
Yang et al (2014)	2005–2009	R	China (A)	ES 100	78 (71.6)	31.0 ± 10.0	4.2 (3.7–5.0)	8
Li et al (2018)	2007–2016	P	China (A)	HHT-PAH 100	7 (77.8)	33.9 ± 10.0	2.70 (1.5–6.4)	7
Smukowska et al (2018)	2008–2016	R	Poland (E)	IPAH 45.5 CHD-PAH24.7 CTD-PAH15.6 CTEPH 13.0 PAH-PoP 1.3	54 (70.0)	52.2 ± 17.5	5.42 (median)	7
Hui et al (2019)	2007–2017	R	China (A)	pSS-PAH 100	54 (98.2)	38.9 ± 9.3	3.4 ± 2.8	7

–=not mentioned, A=Asia, CHD-PAH=congenital heart disease-related pulmonary arterial hypertension, CTD-PAH=connective tissue disease-related pulmonary arterial hypertension, CTEPH=chronic thromboembolic pulmonary hypertension, E=Europe, ES=Eisenmenger syndrome, HHT-PAH=hereditary hemorrhagic telangiectasia-related pulmonary arterial hypertension, HPAH=heritable pulmonary arterial hypertension, IPAH=idiopathic pulmonary arterial hypertension, NOS: Newcastle-Ottawa scale, P=prospective, PAH-PoP=portopulmonary arterial hypertension, PH=pulmonary hypertension, pSS-PAH=primary Sjogren's syndrome with pulmonary arterial hypertension, R=retrospective.

Table 2

Parameters related to cardiopulmonary function of the patients included in this meta-analysis.

Author and year of publication	Cut-off value (%)	RDW (%)	PAPm (mm Hg)	WHO functional class, n (%)		Endpoint population (n/N)	Primary endpoint
				I/II	III/IV		
Hampole et al (2009)	13.9	14.8±3.0 (0–15.0)	48.0±13.0	21 (13.0)	141 (87.0)	22/162	Death
Nickel et al (2011)	–	14.9 (13.7–16.1)	52 (44–60)	–	–	57/109	Adverse outcome
Rhodes et al (2013)	–	15.3±2.3	55.6±13.4	34 (23.4)	111 (76.6)	40/145	Death
Yang et al (2014)	13.9	14.8±3.0	77.8±20.2	71 (65.1)	38 (44.9)	21/109	All-cause death
Smukowska et al (2018)	15.7*	–	53	14 (18.2)	63 (81.8)	28/77	All-cause death
Li et al (2018)	–	14.9±2.9	61.2±19.7	4 (44.4)	5 (55.6)	5/9	Death
Hui et al (2019)	15.0	14.9±2.5	49.9±9.5	29 (52.7)	26 (47.3)	7/55	Adverse outcome

– = not mentioned, 6MWD = 6-min walk distance, mPAP = mean pulmonary artery pressure, NT-proBNP = N-terminal pro-brain bone natriuretic protein, PCWP = pulmonary capillary wedge pressure, RDW = red blood cell distribution width.

* Mean RDW from all hospitalizations during the entire follow-up of the patient.

detected, we conducted subgroup analysis to explore possible sources.

Subgroup analysis based on the study design (prospective vs retrospective) was performed first. For the retrospective studies, the pooled result (HR = 1.32, 95%CI 1.15–1.51, $P = .09$) showed the same association between RDW and increased mortality as that of the original analysis, though the pooled HR (HR = 1.14, 95%CI 0.78–1.67, $P = .13$) for the prospective studies indicated that RDW had little impact on the prognosis of PH. The I^2 values for the prospective and retrospective studies were 50.7% and 53.8%, respectively. In addition, we categorized the studies according to the location (Europe vs Asia), revealing that the prognostic value of RDW was influenced by the location: RDW did not predict PH prognosis in Asia (HR = 1.20, 95%CI 0.90–1.58, $I^2 = 61.3\%$, $P = .08$), whereas a high RDW was associated with increased mortality among patients developing PH in Europe (HR = 1.33, 95%CI 1.18–1.49, $I^2 = 2.7\%$, $P = .36$). Additional analysis based on age suggested that RDW has prognostic value in study populations with mean or median age over 44 years of age (HR = 1.34, 95% CI 1.17–1.55, $I^2 = 21.0\%$, $P = .28$) but lacks this value in those younger than 44 years (HR = 1.20, 95%CI 0.90–1.58, $I^2 = 61.3\%$, $P = .08$). The prognostic value of RDW might be influenced by follow-up time (<3 years, HR = 1.36, 95%CI 0.53–3.47, $I^2 = 75.2\%$; ≥3 years, HR = 1.29, 95%CI 1.14–1.45, $I^2 = 43.6\%$). According to subgroup analyses (Fig. 3), study design, region, patient age, various endpoints, and time of follow-up might not be sources of heterogeneity.

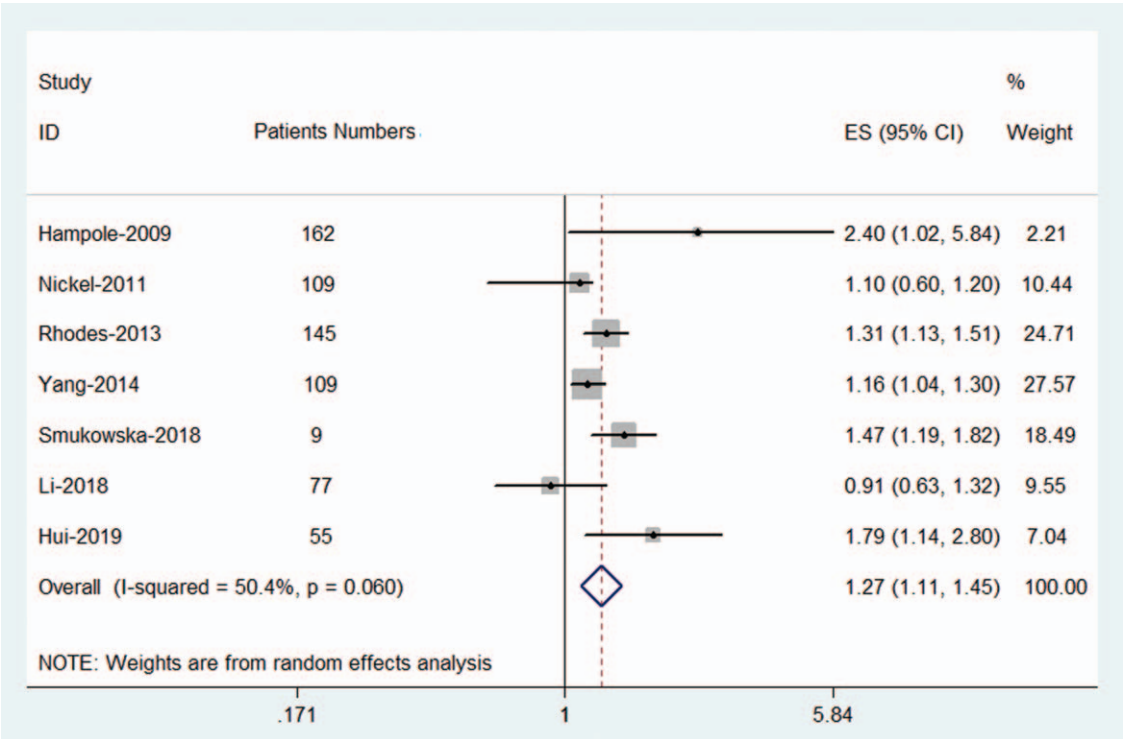

Figure 2. Forest plot of RDW associated with PH prognosis (a random-effects model was applied).

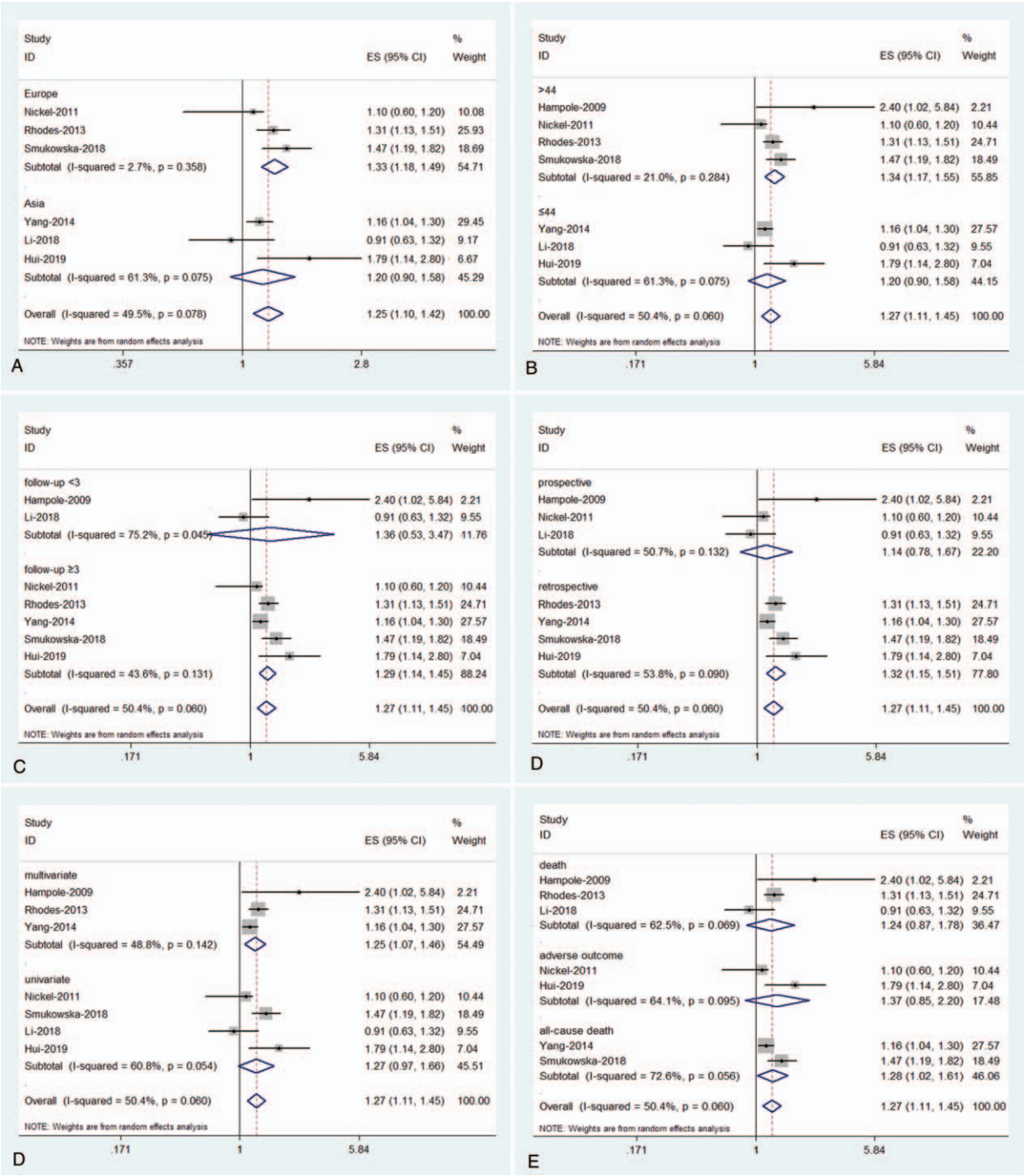

Figure 3. Subgroup analyses of RDW and prognosis of PH (a. based on location of research; b. based on the median or mean age of the included study populations; c. based on time of follow-up; d. based on study design; e. based on multivariate or univariate analysis, and f. based on various endpoints).

3.3. Quality assessment and sensitivity analysis

The scores for the 3 aspects of NOS are shown in Table 1. All 7 articles were of high quality (scores ≥7.00).

To detect whether the results were stable, sensitivity analysis was carried out by sequentially omitting 1 study to obtain a new result and then comparing it with the original result. This sensitivity analysis indicated that none of the studies were outliers and skewed the original result in a specific direction (online supplementary Fig. 2, http://links.lww.com/MD/E56).

3.4. Publication bias

Potential publication bias was also examined (Fig. 4). However, no evidence of publication bias was obtained in Begg's test ($P > |z| = .76$) and Egger's test ($P > |t| = .44$). To make our results more reliable, we performed the trim and filled method and obtained an altered HR (pooled HR = 1.25, 95%CI 1.09–1.44, $P = .002$) that did not show a significant difference from the pooled results (online supplementary Fig. 3, http://links.lww.com/MD/E57).

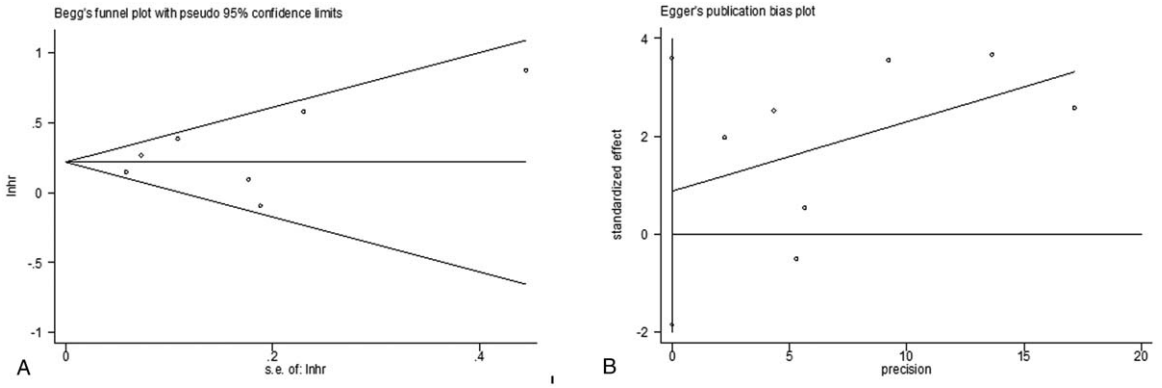

Figure 4. (A) Begg's funnel plot. (B) Egger's publication bias plot.

4. Discussion

In this meta-analysis, we assessed the prognostic value of RDW among PH patients. The pooled data suggested that a higher RDW is closely related to increased mortality, indicating that RDW is a useful prognostic predictor in a mixed and large population of PH patients. In addition, RDW can be employed to guide clinical patient management and individualized treatment decisions. To our knowledge, there is no meta-analysis to date detecting the influence of RDW on PH prognosis.

The results from further analysis showed that among the included retrospective studies, an elevated RDW was associated with a poor prognosis in PH, though RDW had no value regarding PH mortality among prospective studies. In addition, the results might differ due to the different research locations. In fact, RDW was reported as a predictor of a worse prognosis for PH in Europe, but this prognostic correlation was not found when subgroup analysis was conducted in Asia. Differences in altitude between Asia and Europe could be a big reason. Asia has a higher altitude than Europe, and the RDW values of people at high-altitude areas are higher than those at low altitudes.[35] As a result, the normal range of RDW for Asian people may be higher than that for European people. In addition, RDW was found to have a closer association with the prognosis of PH in patients over 44 years of age compared with people under 44 years of age. This finding might be attributed to the change in demographics of PAH – the largest proportion of the study populations: PAH was always found in young people in 1980s,[36] but over the past 30 years, more recent studies suggested a shift toward finding PAH in elderly people.[37,38] RDW had a more pronounced prognostic effect in group with follow-up ≥3 years compared with the group with <3 years follow-up time. It may be that the mortality rate of PH patients would increase with extended follow-up time. Finally, there were more female patients than male patients in our analysis. Many studies suggested a female predominance of approximately 2 to 4 over male patients in developing PAH after adjusting for race and age.[39] Previous studies have reported approximately 4 times higher morbidity among women than men with PAH,[40] consistent with the results of the present study.

Reports in recent years have shown that the relationship between RDW and PH remains controversial. Wang et al found increased RDW to have a diagnostic value in CTEPH,[41] and RDW might be a significant factor in assessing whether systemic sclerosis patients develop PAH.[42] In addition, RDW was reported to be a significant prognostic biomarker in IPAH[43,44] and indicate severity and poor adverse outcomes of CTEPH.[19] Furthermore, a decrease in RDW level with targeted treatment appears to reflect a good treatment response.[20] However, 1 study involving 9 patients with HHT-PAH found that baseline total bilirubin, but not RDW, had a significant association with adverse outcomes,[33] and Nickel et al found that RDW had little predictive value in IPAH patients.[30] These different conclusions might be due to variations in pathogenesis and study design. Certainly, bias caused by an overly insufficient studied population might be a reason.

This analysis suggests that RDW might serve as an indicator of poor prognosis in PH, but the exact mechanism remains unclear. There are several possible explanations. First, inflammation might bridge the association between an elevated RDW and worse PH prognosis. Elevated RDW may be due to inflammatory markers,[45] and inflammation might play a positive role not only in IPAH but also in PH linked to underlying diseases.[46] Another possible mechanism might be associated with iron deficiency, whereby elevated RDW might be due to iron deficiency and ineffective erythropoiesis. It is well documented that iron status in the human body plays an important role in regulating pulmonary vascular tension,[47] and iron deficiency is common in patients with IPAH.[48] As iron status might have an impact on the prognosis of PH patients, iron supplementation may be used as targeted therapy for PH.[47] Third, PH could lead to systemic hemodynamic disorders and tissue hypoxia. Hypoxia promotes the synthesis and release of erythropoietin, which leads to elevated RDW.[35] Therefore, RDW may play an important role in the condition and long-term prognosis of cardiopulmonary vascular diseases. Nonetheless, the role of RDW in the detailed pathogenesis of PH and its influence on PH development and prognosis are worthy of further discussion.

Of note, we conducted this systematic review and meta-analysis according to the MOOSE guidelines.[21] The studies included in our analysis were all of high quality, and our pooled results were stable and robust based on sensitivity analysis. No evident publication bias was observed according to Begg's test and Egger's test, and the trim and fill method makes our results more reliable. Regardless, this meta-analysis has several limitations. First, the number of PH patients included in the analysis was very limited: only 7 publications were included, and the types of PH studied were also not comprehensive. Due to the lack of data, we did not study whether the prognostic effects of RDW were different in various types of PH by subgroup analysis. Second, the cut-off values of RDW varied, which might cause

bias. Third, half of the included studies were retrospective, and differences were present among the study populations. Moreover, many of the PH patients studied also developed other diseases, which may lead to increased mortality and overestimate the prognostic effect of RDW. Finally, the adjustment factors were not exactly the same among the studies, and other potential confounding factors were not excluded.

Despite many limitations, our study still provides a new direction for the assessment of the prognosis of PH patients: RDW, an inexpensive, stable and easily obtained parameter, may be used to evaluate the clinical prognosis in PH patients. However, large-scale prospective studies should be performed to confirm these results. At the same time, we will explore the prognosis of RDW in patients with different types of PH in our future work.

5. Conclusion

This meta-analysis demonstrates that RDW offers important prognostic information for PH patients, and this measure might be applied to better optimize patient management and guide clinical treatment.

Author contributions

XXQ and DYS contributed to the conception and design. LJ, YJ, ZY, XSL, XSY, WL, LYY, QPP, and ZCF contributed to the acquisition, analysis, and interpretation of data. YJ and LJ were involved in the drafting or critical revision of the manuscript. All the authors approved the final version.

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