

The prognostic value of red blood cell distribution width for mortality in intracranial hemorrhage

A systematic review and meta-analysis

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Abstract

Background: Some studies have reported conflicting results regarding the prognostic value of red blood cell distribution width (RDW) for patients with intracranial hemorrhage (ICH). This meta-analysis aims to investigate the association between RDW and all-cause mortality in ICH.

Methods: We systematically searched the following databases, including PubMed, EMBASE, Cochrane library, and Web of Science, for all studies assessing the prognostic value of mortality in patients with ICH from inception to December 2023. We calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs).

Results: A total of 7 studies evaluated the association of RDW and all-cause mortality. A higher RDW levels were significantly associated with all-cause mortality (OR = 1.52; 95% CI = 1.22 to 1.89; $P = .0002$; $I^2 = 76\%$).

Conclusion: Therefore, RDW is a valuable prognostic marker for the risk of all-cause mortality in patients with intracranial hemorrhage.

Abbreviations: CI = confidence intervals, CRP = C-reactive protein, GCS = Glasgow Coma Scale, ICH = intracranial hemorrhage, NOS = Newcastle-Ottawa Quality Assessment Scale, OR = odds ratio, RDW = red blood cell distribution width.

Keywords: intracranial hemorrhage, mortality, prognosis, red blood cell distribution width

1. Introduction

Spontaneous intracranial hemorrhage (ICH) is the second most common cause of stroke.^[1,2] It is a serious and acute neurological disease with a high morbidity and mortality rate.^[3] ICH has a multifactorial pathogenesis, including hypertension, genetics, and lifestyle.^[4] Although the treatment of ICH has made rapid developments in recent years, the prognosis of some patients is still poor.^[5,6] However, despite the efforts made to improve therapeutic interventions and risk stratification, accurately predicting the prognosis of ICH remains unclear. The Glasgow Coma Scale (GCS) is a common neurological scale used in the classification of ICH.^[7,8] However, several studies have demonstrated that the predictive value of GCS is modest.^[9] Therefore, accurate biomarkers that accurately predict disease severity and prognosis are urgently needed.

Some studies have reported that the identification of serum biomarkers may help identify the pathophysiological mechanisms and potential therapeutic targets.^[10–12] Laboratory tests are heavily used in prognosis assessment due to cheap, convenient and reliable. Red blood cell distribution width (RDW) is a simple and cheap hematologic parameter and represents the heterogeneity in the sizes of red blood cell.^[13–15] RDW is used as a common indicator of erythrocyte volume heterogeneity and is traditionally used in laboratory hematology for differential diagnosis of anemias.^[16,17] RDW have considered to be a biochemical marker of pre-inflammatory state, and a high RDW may be a potential negative predictor in patients with cardiovascular diseases, cerebrovascular diseases, autoimmune diseases, or tumors.^[18–21] Cao et al suggested that elevated RDW was significantly associated with poor prognosis. However, there are still conflicting results regarding the prognostic value

PZ, YC, and JZ contributed equally to this work.

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We are consent for publication.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Our meta-analysis was not prospectively registered in the PROSPERO database. However, the study was strictly carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

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of RDW for ICH.^[22] Currently, no meta-analysis has separately analyzed the association between RDW and mortality in ICH. Therefore, we aim to assess whether RDW values can predict mortality in ICH patients using a systematic literature review and meta-analysis.

2. Materials and methods

This study was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.^[23]

2.1. Search strategy

We systematically searched the following databases, including PubMed, EMBASE, Cochrane library, and Web of Science, for all studies assessing the prognostic value of mortality in patients with ICH from inception to December 2023. The search terms were as follow (File S1, Supplemental Digital Content, <http://links.lww.com/MD/O523>): (“red cell distribution width” OR “red blood cell distribution width,” OR “RDW”) AND (“intracranial hemorrhage” OR “intracerebral hemorrhage” OR “ICH”). We also manually reviewed the reference lists of identified review articles to avoid missing relevant studies.

2.2. Selection criteria

The inclusion criteria were as follows: patients were diagnosed with spontaneous ICH; data assessing the association between RDW and mortality were enough to be extracted; full-text was provided to evaluate the quality.

The exclusion criteria were as follows: not written in English; unrelated studies, animal experiment, comments, letters, meta-analysis, or case reports; patients not diagnosed as with spontaneous ICH; duplicated publications; and incomplete or deficient data.

2.3. Study selection and data extraction

Two researchers independently performed study selection and data extraction. They searched and reviewed eligible trials based on the selection criteria. The data from the full-text version of each selected publication were extracted into a detailed data spreadsheet using a standard data extraction form. This meta-analysis extracted data including first author names, publication year, study country, study design, number of patients, mean or median age of patients, sampling time, follow-up period, and cutoff values of RDW.

2.4. Quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to evaluate the quality of all included studies. Two researchers independently evaluated the quality of all included studies, and disagreements were solved by discussion or a third researcher. The NOS scale contains 9 items measuring 3 domains: participant selection (four items for 4 points), group comparability (1 item for 2 points), and exposure/outcome (3 items for 3 points). The total NOS score was 9, and studies with NOS scores ≥ 6 were considered as having a high quality (File S2, Supplemental Digital Content, <http://links.lww.com/MD/O524>).

2.5. Statistical analysis

The statistical analysis was completed using RevMan software (version 5.4.1). Pooled ORs and 95% CIs were calculated to assess the strength of this relationship between RDW and ICH. Cochrane Q test and I^2 test were calculated to assess the

heterogeneity among included studies. If there was obvious heterogeneity among studies ($P < .1$ or $I^2 > 50$), a random-effects model was adopted to combine the data; otherwise, a fixed-effects model was adopted. To identify the source of heterogeneity, sensitivity and subgroup analyses were performed. Sensitivity analysis was performed by excluding each study individually and observing for change in heterogeneity. We evaluated the publication bias drawing a funnel plot. A symmetrical funnel plot indicated no publication bias.

3. Results

3.1. Study selection

The 2 reviewers found 130 articles in the initial literature search. There are no additional articles from other sources. After excluding 54 duplicate articles, 76 were screened on the basis of titles and abstracts, which identified 32 articles of interest. Full-text versions were reviewed for the remaining 32 articles, and 7 were selected for inclusion in this study^[24–29] (Fig. 1).

3.2. Baseline characteristic of the included studies

The main characteristics of the included studies are shown in Table 1. This study included 7 studies (including 6322 patients) that reported the association between RDW and all-cause mortality. Six of the included studies were retrospective studies and one is prospective studies. Four studies were conducted in Asia, 2 in Europe and 1 in North America. The study sample sizes ranged from 46 to 4233, and the mean age ranged from 58 to 71 years. The follow-up duration varied from until hospital discharge to more than 1 year. All of our included studies had a high quality with NOS scores ≥ 7 points.

3.3. Association between RDW and all-cause mortality

Seven studies, including 6322 patients, evaluated the association between RDW and all-cause mortality. The pooled results indicated that higher RDW levels were significantly associated with all-cause mortality (OR = 1.52; 95% CI = 1.22 to 1.89; $P = .0002$; Fig. 2). There was significant heterogeneity among these studies ($I^2 = 76\%$; $P = .0003$).

3.4. Subgroup analyses for the association of RDW and all-cause mortality

We conducted subgroup analyses based on ethnicity, sample size, study design and RDW cutoff value (Table 2).

The subgroup analysis based on ethnicity showed a significant association between RDW and all-cause mortality in both Asian (OR, 1.76; 95% CI, 1.47 to 2.11; $P = .03$), and non-Asian (OR = 1.24; 95% CI = 1.04 to 1.49; $P < .00001$).

A significant association was observed between RDW and all-cause mortality in studies with sample size ≥ 300 (OR = 1.70; 95% CI = 1.20 to 2.41; $P = .003$), with sample size < 300 (OR = 1.75; 95% CI = 0.86 to 3.59; $P = .12$).

RDW was significantly associated with all-cause mortality in retrospective observational study (OR = 1.83; 95% CI = 1.32 to 2.55; $P = .0003$).

RDW was significantly associated with all-cause mortality in both studies with high (OR = 2.96; 95% CI = 1.81 to 4.83; $P < .0001$) and low (OR = 1.32; 95% CI = 1.09 to 1.59; $P = .004$) RDW cutoff values.

In the subgroup analysis, we found no obvious heterogeneity in Asian group ($I^2 = 13\%$; $P = .33$), and in low RDW cutoff values group ($I^2 = 0\%$; $P = .72$). Obviously, it suggested that ethnicity and cutoff value might be the heterogeneity source. In addition, we found that RDW is not related to mortality in subgroup with sample size < 300 .

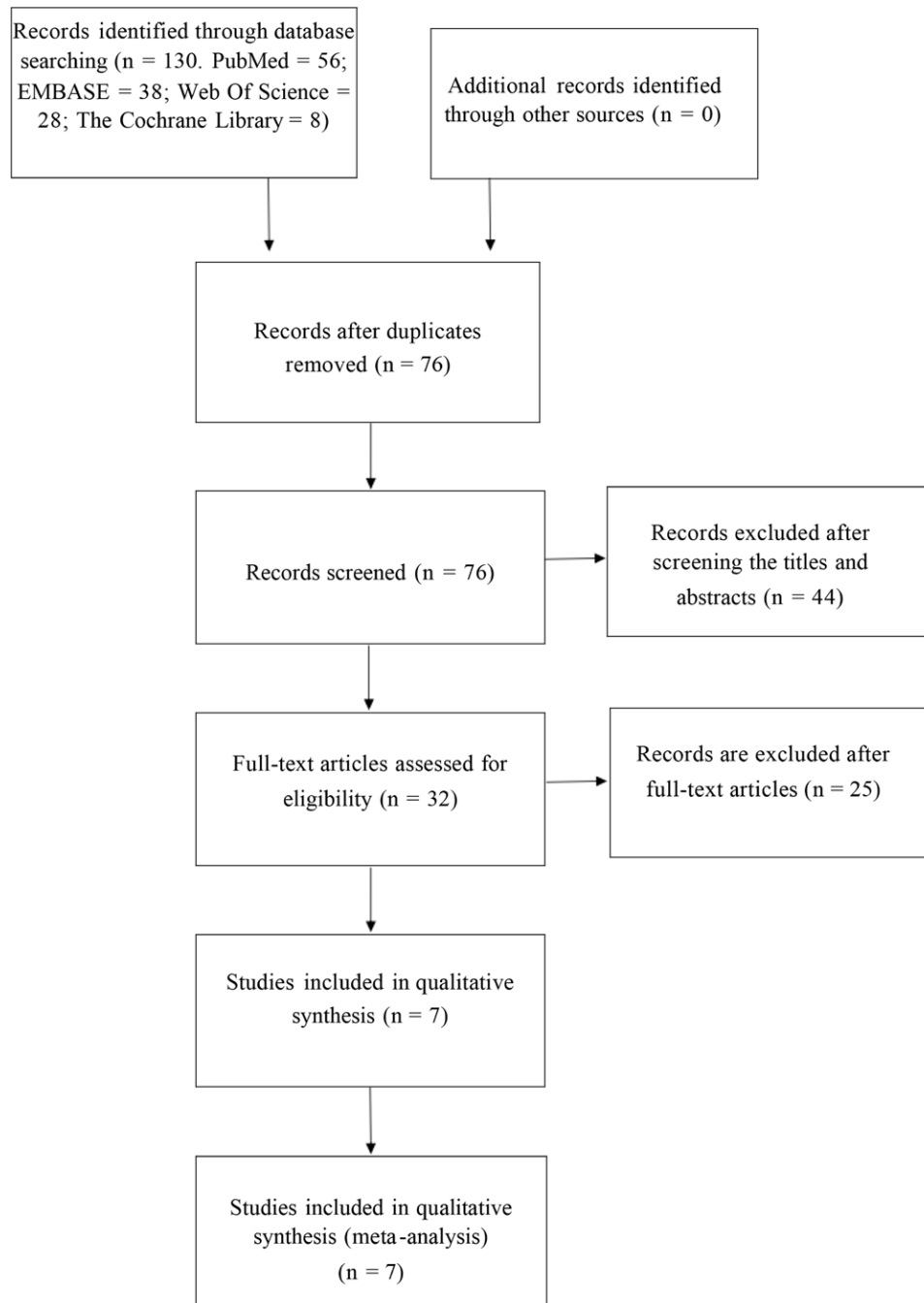


Figure 1. Flow diagram of the study selection process.

Table 1

Basic characteristics of all included studies.

Study	Country	Design	Number (M/F)	Age	FUP	Outcome	Cutoff value
He 2023 ^[24]	China	R	4233 (2829/1404)	58.0 ± 14.8	4.7 yr	3-mo poor outcome	13.35
Xu 2023 ^[25]	China	R	393 (255/138)	63.6 ± 14.0	1 yr	3-mo poor outcome	45.9
Hu 2023 ^[26]	USA	R	940 (553/387)	67.41 ± 15.28	At discharge	poor outcome/mortality at discharge	13.5
Cao 2022 ^[27]	China	R	46 (33/13)	60.04 ± 10.67	At discharge	6-mo poor outcome	14.9
Pinho 2021 ^[28]	Portugal	R	358 (198/160)	71 (60 to 80)	3 mo	Hospital mortality/ 3-mo poor outcome	14.1
Cui 2020 ^[22]	China	R	235 (156/279)	64.5 (20 to 90)	30 d	3-mo mortality	14.0
Lorente 2020 ^[29]	Spain	P	117 (76/41)	59 (52 to 67)* 68 (56 to 75) [†]	30 d	Hospital mortality/1-yr mortality	10.0

F = female, FUP = follow-up period, M = male, P = prospective, R = retrospective.

*The age of survivors.

[†]The age of deceased.

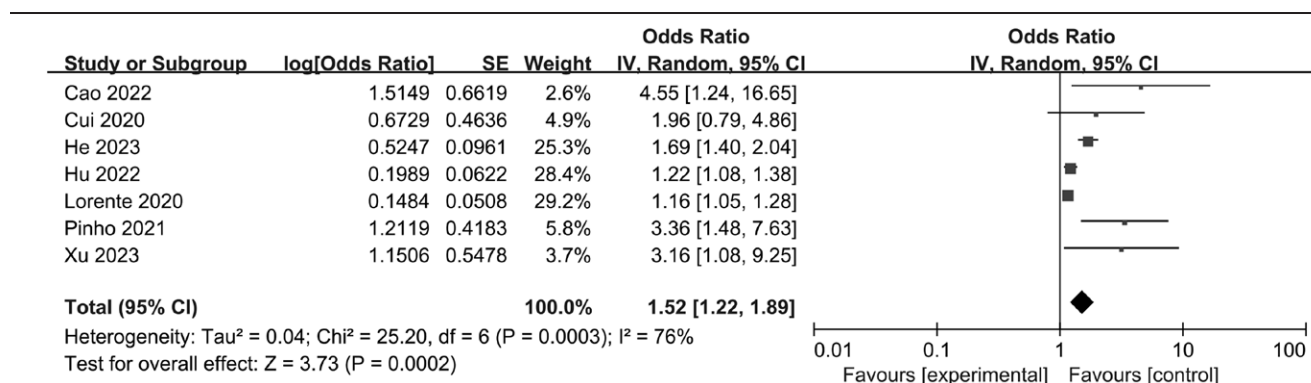


Figure 2. Meta-analysis of the association between RDW and mortality. RDW = red blood cell distribution width.

Table 2

Subgroup analysis of the association of RDW with all-cause mortality.

Subgroup	No. of studies	I ²	P value	Model	OR (95% CI)	P value
RDW and all-cause mortality						
Total	7	76%	.0003	Random	1.52 (1.22 to 1.89)	.0002
Ethnicity						
Asian	4	13%	.33	Fixed	1.76 (1.47 to 2.11)	.03
Non-Asian	3	70%	.04	Random	1.24 (1.04 to 1.49)	<.00001
Sample size						
<300	3	63%	.07	Random	1.75 (0.86 to 3.59)	.012
≥300	4	80%	.002	Random	1.70 (1.20 to 2.41)	.003
Study design						
retrospective	6	74%	.002	Random	1.83 (1.32 to 2.55)	.0003
Cutoff value						
<14.0	3	84%	.002	Fixed	1.32 (1.09 to 1.59)	.004
≥14.0	4	0%	.72	Fixed	2.96 (1.81 to 4.83)	<.0001

RDW = red blood cell distribution width.

3.5. Sensitivity analysis

We further performed a sensitivity analysis to test the reliability of the meta-analysis results through omitting studies 1 by 1 (Table 3). Hence, the results of this sensitivity analysis were robust and reliable because exclusion of any individual study did not significantly change the overall results.

3.6. Publication bias

We produced a funnel plot for the all-cause mortality to assess the publication bias, and observed no obvious publication bias (Fig. 3).

4. Discussion

We assessed the prognostic value of RDW in ICH patients in this study. The results suggested that higher RDW values at baseline were more significantly related to all-cause mortality than lower RDW values. Therefore, RDW value may be used as a new tool to predict the prognosis in ICH patients.

RDW, as a routine hematology parameter, shows the variability of red blood cell size. Typically, RDW has been used to explore the causes of anemia. RDW has built up an inextricable link with the adverse prognosis of various diseases including cardiovascular diseases. However, the exact mechanism of this relationship has not been thoroughly understood. There are several potential mechanisms. Inflammation plays an important role in the pathophysiology of ICH with higher levels of inflammatory markers predicting poor prognosis after the onset of the acute hemorrhage.^[30] Following ICH, the autoimmune response in the CNS is activated, resulting in

Table 3

Sensitivity analysis of the association of RDW with all-cause mortality.

Removed study	OR	95% CI	P for test	I ² (%)	P for heterogeneity
He 2023 ^[24]	1.41	1.13 to 1.77	.003	66	.01
Xu 2023 ^[25]	1.47	1.18 to 1.82	.0005	78	.0004
Hu 2023 ^[26]	1.85	1.29 to 2.65	.0008	80	.0002
Cao 2022 ^[27]	1.46	1.16 to 1.80	.0004	77	.0007
Pinho 2021 ^[28]	1.42	1.16 to 1.75	.0007	75	.001
Cui 2020 ^[22]	1.50	1.20 to 1.89	.0004	79	.0002
Lorente 2020 ^[29]	1.83	1.32 to 2.55	.0003	74	.002

RDW = red blood cell distribution width.

pro-inflammatory and anti-inflammatory phases. Innate immunity is activated after following ICH, leading to the release of inflammatory cytokines such as TNF- α and IL-1 β . Elevated RDW may serve as a marker of inflammation, as inflammatory cytokines such as TNF- α and IL-1 β also inhibit the bone marrow and delay erythropoietin-induced erythrocyte maturation and proliferation.^[31,32] Some studies have reported that RDW is significantly related to inflammation indices, such as erythrocyte sedimentation rate and C-reactive protein (CRP), suggesting that RDW can be used as an inflammatory index.^[33,34] Li et al (2010) elucidated that the elevated RDW was closely linked to CRP, which strongly supports that RDW is an important marker of the inflammation.^[35] Therefore, elevated RDW may indicate inflammation, which leads to disease progression in the early stage of ICH. In addition, an increased RDW is commonly related to anemia with nutritional deficiency, such as iron, folate, or vitamin B12 deficiency.^[36] This may be another

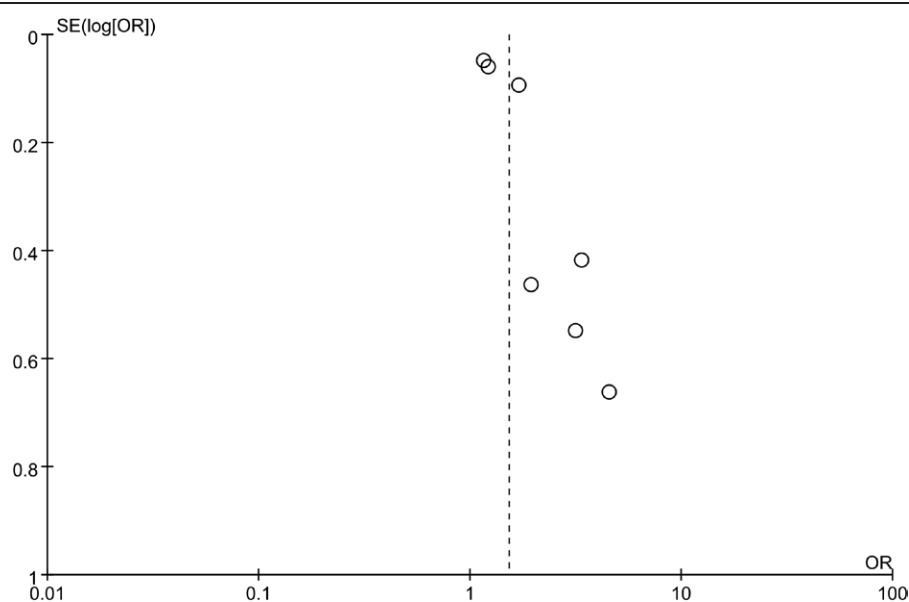


Figure 3. Funnel plot of RDW and mortality. RDW = red blood cell distribution width.

mechanism underlying the association between RDW and poor prognosis of ICH. In the end, oxidative stress has an important role in the development of ICH. Oxidative stress directly damages erythrocyte homeostasis and survival. Therefore, oxidative stress and low antioxidant levels may result in increased RDW levels.

In our study, the pooled results of this meta-analysis prove that elevated RDW levels are a negative prognostic factor after ICH. There was substantial heterogeneity across the studies of all-cause mortality. In the subgroup analysis, we found no obvious heterogeneity in the subgroup with Asian and cutoff value ≥ 14.0 . that Based on subgroup analysis, we assumed that the source of heterogeneity might be ethnic and RDW cutoff value. In addition, some clinical characteristics, comorbidities, complications, and other confounding factors may also lead to the heterogeneity.

In the current study, RDW was significantly related to all-cause mortality. This result is partially consistent with was partially support those of previous studies. Pinho et al demonstrated that RDW can be a negative predictor of mortality in ICH.^[28] More high-quality studies are still needed in the future to further investigate the association between RDW and prognosis.

There were several highlights in the study. First, this is the first meta-analysis to investigate the prognostic significance of RDW in patients with ICH. Second, we searched as many eligible studies as possible and carried out a strict quality evaluation strategy to ensure the credibility and precision of the results. Third, subgroup and sensitivity analyses were conducted, which provided adequate evidence on this topic. In the end, this study enrolled 6322 patients, and the relatively large sample size could strengthen the current evidence base on the prognostic value of RDW in ICH.

However, some limitations should be considered in the study. First, most of studies are related to its observational and retrospective design, which may have led to selection bias. Second, most of studies are conducted in China, and it might be difficult to generalize the results to other countries. Third, despite our efforts to control for several potential confounders, residual confounding might have affected the results, such as different brain regions of ICH. Fourth, sampling times differed across studies, which may have contributed to the heterogeneity. In the end, many factors might affect the prognosis of ICH patients, such as the initial severity of ictus, treatments and so on. Despite the above

limitations, this study provides valuable insight into the association between RDW and mortality in ICH. In the future, multicenter, prospective studies with larger sample sizes are required to confirm our findings.

5. Conclusions

In conclusion, higher RDW value was consistently associated with an increased risk of mortality after RDW. RDW can serve as a biomarker to rapidly stratify SAH patients at risk of mortality. However, its ability to predict poor prognosis needs to be further supplemented and verified. In addition, the mechanism by which RDW is involved in the pathogenesis of ICH needs to be understood further.

Author contributions

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