


RESEARCH ARTICLE

Association between red blood cell distribution width and mortality and severity among patients with COVID-19: A systematic review and meta-analysis

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Abstract

Emerging evidence has underscored the potential usefulness of red blood cell distribution width (RDW) measurement in predicting the mortality and disease severity of COVID-19. This study aimed to assess the association of the plasma RDW levels with adverse prognosis in COVID-19 patients. A comprehensive literature search from inception to September 2020 was performed to harvest original studies reporting RDW on admission and clinical outcomes among patients hospitalized with COVID-19. RDW levels were compared between cases (patients who died or developed more severe symptoms) and controls (patients who survived or developed less severe symptoms). A total of 14,866 subjects from 10 studies were included in the meta-analysis. Higher levels of RDW were associated with adverse outcomes in COVID-19 patients (mean differences = 0.72; 95% CI = 0.47–0.97; $I^2 = 89.51\%$). Deceased patients had higher levels of RDW compared to patients who survived (mean differences = 0.93; 95% CI = 0.63–1.23; $I^2 = 85.58\%$). Severely ill COVID-19 patients showed higher levels of RDW, as opposed to patients classified to have milder symptoms (mean differences = 0.61; 95% CI = 0.28–0.94; $I^2 = 82.18\%$). Elevated RDW levels were associated with adverse outcomes in COVID-19 patients. This finding warrants further research on whether RDW could be utilized as a simple and reliable biomarker for predicting COVID-19 severity and whether RDW is mechanistically linked with COVID-19 pathophysiology.

KEYWORDS

biomarkers, COVID-19, erythrocyte indices, red blood cell distribution width, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

Red blood cells (RBC) serves as the vehicle for delivering oxygen to peripheral tissues in the human body. Unequal size of RBCs in the circulation, termed anisocytosis, is observed in several conditions,

such as nutritional deficiencies, anemias, sickle cell anemia, hemolytic anemia, myelodysplastic syndrome, and other hematological disorders.^{1,2} As such, characteristics of human RBCs are utilized in the differential diagnosis of various clinical settings.³ The coefficient of variation of RBC distribution width (RDW), calculated from

Abbreviations: CAD, coronary artery disease; CBC, complete blood count; CI, confidence interval; COVID-19, coronavirus disease 2019; ED, emergency department; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBC, red blood cell; RDW, red blood cell distribution width; ROC, receiver operating characteristic; SD, standard deviation.

dividing the standard deviation (*SD*) of corpuscular volume by the mean corpuscular volume, is a commonly used measure to quantify the variation of individual RBC volumes as it circulates during the approximate lifespan of 115 days.⁴ An increase in RDW can be attributed to several factors. First, increased RDW may reflect an imbalance between hematopoiesis and RBC survival.⁵ Specifically, delayed clearance of senescent RBCs from the circulation leading to RBC underproduction, resulting in an increase in the plasma levels of RDW.^{5,6} Second, elevated RDW may suggest an underlying inflammation through multiple mechanisms. For instance, proinflammatory cytokines, such as interferon γ and tumor necrosis factor α , may affect iron metabolism and the capacity of RBC production by the bone marrow, which leads to anemia and increased RDW.⁷ Alternatively, RDW may increase due to shortened RBC lifespan and premature release of RBCs from the bone marrow in the presence of increased oxidative stress associated with inflammation.⁸ Third, RDW could also increase in other physiologic events, such as aging, pregnancy, or following erythropoietin stimulation and exercise.¹

In practice, elevated RDW levels are utilized as a diagnostic tool for differentiating an early stage of nutritional deficiency or megaloblastic anemias from thalassemia. The potential value of RDW as a rapid and easy prognostic tool among high-risk patients, if effective, will vastly benefit timely intervention because RDW levels are measured as part of routine measures of complete blood count (CBC) by automated instruments in hematology laboratories. In the pre-coronavirus disease 2019 (COVID-19) era, a large-scale prospective cohort study indicated that RDW was a predictor for all-cause mortality independent of the presence of inflammation.⁹ Nevertheless, inflammation may, at least in part, interact with the association of RDW with mortality. In the context of the COVID-19 pandemic, emerging evidence supports the usefulness of biomarkers (e.g., C-reactive protein, troponin, D-dimer) in predicting mortality, disease severity, or thrombotic complications among patients hospitalized for COVID-19.^{10,11} However, the association of RDW with adverse prognosis in COVID-19 has not been well-established.

The current meta-analysis aimed to review and synthesize the current evidence on the association of RDW levels with COVID-19 mortality and severity. We hypothesized that among patients with laboratory-confirmed COVID-19 infection, those who died or were severely ill would have higher levels of RDW compared to those who survived or were mildly ill.

2 | METHODS

2.1 | Search strategies and selection criteria

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the protocol was registered in PROSPERO (registration number: CRD42020211560).¹² A systematic literature search was performed in PubMed, supplemented by a hand search of references from relevant publications, to collect eligible studies from

inception to September 2020. The search for identifying qualifying studies was initiated by constructing sets of relevant keywords (i.e., RDW and COVID-19) and their synonyms. These search terms were expanded and organized in thematic building blocks, as provided in Table S1. To be included in the meta-analysis, published studies needed to be (1) conducted in human subjects, (2) original research articles (including letters and abstracts), (3) reported RDW levels in COVID-19 patients, where there were two or more groups of patients with mortality status (i.e., deceased or survived) or severity (e.g., mild, moderate, or severe cases of COVID-19), and (4) published in English. Nonoriginal publications (e.g., narrative review, systematic review, meta-analysis, editorial) and studies that did not report RDW or adverse outcomes in COVID-19 patients were excluded. Reference lists of relevant studies and review articles were screened for potentially eligible studies. Additional searches were performed in medRxiv to identify preprints (i.e., preliminary reports of work that have not been certified by peer review) that were qualified for the analysis.¹³ Duplicated publications were removed after confirming identical publication information.

2.2 | Data extraction

Data extracted from each study included study design, study population, setting, patient characteristics (age, sex, body mass index, coronary artery disease [CAD], hypotension, smoking status, type 2 diabetes mellitus, cancer, chronic kidney disease), length of hospital stay, methods for RDW measurement, RDW levels (mean and *SD* and/or median and 25th and 75th percentiles), follow-up visits and adverse outcomes (i.e., disease severity or mortality status). Two investigators (Jane J. Lee and Gerald Chi) independently performed the database search and completed article screening and study selection based on a prespecified standardized approach. A third investigator (Adeel Jameel) adjudicated disagreement in extracted articles. A PRISMA flow diagram depicting the process of literature search and screening is provided in Figure 1.

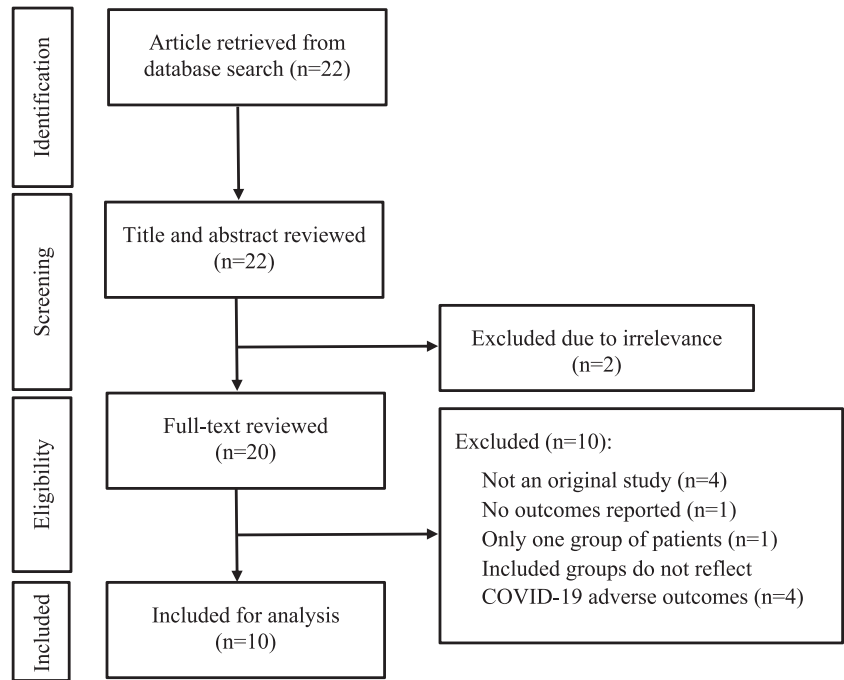
2.3 | Quality assessment

Two independent investigators (Sahar M. Montazerin and Jolanta Marszalek) assessed the quality of the included studies in accordance with the Newcastle–Ottawa Scale. Disagreement in the quality assessment was resolved by discussion and consensus. The quality assessment criteria and scores are provided in Tables S2 and S3.

2.4 | Study endpoints and RDW measurements

The study endpoint was adverse clinical outcomes, defined as the composite of mortality or severe COVID-19. If a study classified patients into three groups (i.e., mild, moderate, and severe) based on the clinical severity of COVID-19, the group with the most severe

FIGURE 1 Flowchart presenting the literature search process according to the PRISMA Statement



symptoms was compared with the group with the mildest symptoms. The coefficient of variation of RDW, expressed as percentages were assessed upon hospital admission as part of the standard complete blood test from each study for assessment of association with adverse clinical outcomes.

2.5 | Statistical analysis

The statistical analysis for this meta-analysis included primary and subgroup analyses. The primary analysis was performed to compare the mean levels of RDW between cases (patients with adverse outcomes, defined as those who died or developed more severe symptoms) and controls (patients without adverse outcomes, defined as those who survived or developed less severe symptoms). In the subgroup analyses, the difference in RDW levels was calculated by comparison between (1) nonsurvivors versus survivors and (2) patients with more severe symptoms versus patients with milder symptoms. In addition, a sensitivity analysis was performed to compare the effects of RDW stratified by geographic regions (China vs. non-China [including the United States and the Netherlands]).

RDW levels were uniformly expressed in percentage for all included studies. For analysis purposes, RDW levels reported in median and 25th and 75th percentiles were converted to mean and SD.¹⁴ For each study, the mean level of RDW was used as an effect size statistic, and the inverse variance of the mean RDW levels was used as study weight. Confidence intervals (CIs) of RDW levels were calculated by normal approximation. The summary effect size was then computed by fitting a random-effects model using the DerSimonian and Laird method.¹⁵ Heterogeneity across the studies was assessed using the Cochran's Q test (with the threshold of

$p < .10$, indicating the presence of heterogeneity) and I^2 statistic ($I^2 > 50\%$: significant heterogeneity; $I^2 \leq 50\%$: insignificant heterogeneity). Funnel plots were used for visual inspection of publication bias, and the Egger test was used for detecting small-study effect for endpoints with a study number of 10 or more.¹⁶

All the analysis was performed using the *metan* and *metaninf* packages in the STATA software of version 16.1 (Stata Corporation).

3 | RESULTS

A total of 14,866 subjects from 10 studies were included in the meta-analysis. Summary of study characteristics and patient characteristics were provided in Tables 1 and 2.^{17–25} The mean age ranged from 38 to 77 years. The proportion of males ranged from 42.4% to 69.2%. The status of CAD, hypertension, and diabetes ranged from 0% to 28%, 2.9%–68.8%, and 5.7%–70.6%, respectively. The majority of the included studies were retrospective and observational. The quality of the studies was generally high, with scores ranging from 6 to 9, as evaluated with the Newcastle-Ottawa Scale (Tables S2 and S3).

3.1 | Association between RDW and adverse outcomes among COVID-19 patients

Higher levels of RDW were significantly associated with severely ill COVID-19 patients (pooled mean differences: 0.72; 95% CI, 0.47 to 0.97; Figure 2). The I^2 value of 89.51% suggested the existence of heterogeneity. No sign of publication bias was detected based on visual inspection of the funnel plot, which was symmetrically shaped (Figure 3). No small-study effect was observed, as determined by

TABLE 1 Summary of study characteristics

Author, Year	N	Country	Study design	Study Population	Setting	Length of hospital stay (days)	RDW measurement	Follow-Up	Comparisons	When was the CBC obtained?
Foy et al., 2020 ¹⁷	1641	United States	Retrospective observational	Adults diagnosed with COVID-19 and admitted	Ward	16.7 (15.5) versus 11.8 (11)	Complete blood counts (including RDW) were performed on an XN-9000 Automated Hematology System (Sysmex Corporation).	Between March 4, 2020, and April 28, 2020	Survivors (N = 1376) versus nonsurvivors (N = 276)	At the time of admission
Gong et al., 2020 ¹⁸	189	China	Retrospective observational	Nonsevere COVID-19 hospitalized patients	Ward	-	-	>15 days after admission	Nonsevere (N = 161) versus severe (N = 28)	On admission
Henry et al., 2020 ¹⁹	49	United States	Prospective observational	Adults (≥18 years of age) presenting to the ED with COVID-19 confirmed by RT-PCR	ED	-	The CBC with differential was performed using a Beckman UniCel DxH 800 Coulter Cellular Analysis System.	30 days	Maximum severity within 30 days of presentation (Mild [N = 16] vs. Moderate [N = 17] vs. severe [N = 16]) ED disposition severity (mild [N = 16] vs. moderate [N = 27] vs. Severe [N = 6])	During the index visit to the ED
Jans et al., 2020 ²⁰	261	The Netherlands	Retrospective observational	Patients who presented with PCR-proven COVID-19	Ward	-	-	From March 5, 2020, until May 7, 2020	Nonsevere (N = 162) versus severe (N = 92)	During the index visit to the ED
Levy et al., 2020 ²¹	11,095	United States	Retrospective and prospective cohort study	Adult patients hospitalized with a confirmed diagnosis of COVID-19	Ward	5.97 (3.16–10.20) versus 7.81 (3.86–14.18)	-	7 days	Survivors (N = 8499) versus nonsurvivors (N = 2596)	Obtained while the patient was in the ED
Lu, 2020 ²⁶	151	China	-	Intensive care patients admitted with confirmed COVID-19	ICU	-	-	From January 25 to February 25, 2020	Type D (favorable prognosis) (N = 42) versus Type C (intermediate prognosis) (N = 27) versus Type B (poor prognosis) (N = 45) versus Type A (extremely poor prognosis) (N = 37)	On the day of admission

TABLE 1 (Continued)

Author, Year	N	Country	Study design	Study Population	Setting	Length of hospital stay (days)	RDW measurement	Follow-Up	Comparisons	When was the CBC obtained?
Lusche et al., 2020 ²²	1022	United States	Retrospective observational	COVID-19 patient (PCR-positive COVID-19 test) admissions from 14 Midwest US hospitals	Ward/ICU	-	-	≥14 days after admission	Clinical phenotype III (N = 173) versus phenotype II (N = 613) versus phenotype I (N = 236)	Collected within 72 h of admission
Nicholson et al., 2020 ²³	1042	United States	Retrospective observational	Adult patients with confirmed COVID-19 who were admitted for illness related to COVID-19	Ward	-	-	Up to July 20, 2020	Survivors (N = 829) versus nonsurvivors (N = 211)	Performed on or within 24 h of hospital admission
Wang et al., 2020 ²⁴	45	China	Retrospective observational	Hospitalized patients with confirmed COVID-19	Ward	-	Complete blood counts (BC-6900, Mindray) were collected from the laboratory information system.	Between January 23, 2020, and February 13, 2020	Moderate (N = 35 [131 samples]) versus severe (N = 10 [30 samples])	Collected from the laboratory information system
Wu et al., 2020 ²⁵	71	China	-	Hospitalized patients with confirmed COVID-19	Ward	-	-	-	Mild (N = 32) versus severe (N = 39)	Obtained from electronic medical record

Abbreviations: CBC, complete blood count; ED, emergency department; RT-PCR, reverse transcription-polymerase chain reaction.

TABLE 2 Summary of patient characteristics

Author, year	Age (years)	Men (%)	BMI (kg/m ²)	CAD (%)	Hypertension (%)	Smoking (%)	Diabetes (%)	Cancer (%)	CKD (%)
Foy et al., 2020 ¹⁷	59.6 (17.6) versus 74.6 (13.4)	53 versus 59	30.8 (6.8) versus 30.2 (7.2)	8 versus 16	23 versus 36	-	17 versus 22	-	8 versus 21
Gong et al., 2020 ¹⁸	45.0 (33.0–62.0) versus 63.5 (54.5–72.0)	44.7 versus 57.1	23.4 (21.4–25.7) versus 23.4 (22.3–24.4)	-	-	-	-	-	-
Henry et al., 2020 ¹⁹	44 (32–50) versus 59 (39–68) versus 66 (53–71)	68.8 versus 44.4 versus 62.5	28 (25–33) versus 26 (25–36) versus 29 (25–32)	0 versus 23.5 versus 18.8	18.8 versus 64.7 versus 68.8	25.0 versus 23.5 versus 31.3	18.8 versus 70.6 versus 31.3	0 versus 5.9 versus 18.8	0 versus 17.6 versus 18.8
Jans et al., 2020 ²⁰	60.3 (16.6) versus 68.2 (16.8)	52.4 versus 63.4	30.2 (5.7) versus 28.4 (5.4)	11.3 versus 16.1	35.7 versus 46.2	-	13.7 versus 23.7	6.0 versus 15.1	2.4 versus 7.5
Levy et al., 2020 ²¹	-	57.2 versus 63.7	28.30 (25.10–32.60) versus 27.40 (23.90–31.70)	8.2 versus 15.4	49.6 versus 61.8	-	29.6 versus 35.5	-	6.5 versus 2.0
Lui, 2020 ²⁶	53 (43–58) versus 65 (51–74) versus 62 (52–70) versus 77 (70–81)	-	-	-	-	-	-	-	-
Luszczyk et al., 2020 ²²	58.6 (34.8–71.3) versus 60.9 (45.9–75.4) versus 67.2 (52.9–79.0)	42.4 versus 46.6 versus 58.4	30.4 (13.4) versus 30.8 (8.2) versus 29.5 (8.9)	-	-	10.4 versus 7.2 versus 3.8	-	9.2 versus 11.9 versus 12.3	21.4 versus 27.7 versus 39.0
Nicholson et al., 2020 ²³	61 (50–71) versus 75 (66–82)	54.1 versus 66.4	-	14.8 versus 28.0	53.6 versus 67.3	-	39.8 versus 52.6	13.6 versus 25.1	13.8 versus 28.0
Wang et al., 2020 ²⁴	38 (16–62) versus 43 (28–62)	48.6 versus 60.0	-	-	2.9 versus 30.0	-	5.7 versus 20.0	0 versus 10.0	2.9 versus 10.0
Wu et al., 2020 ²⁵	56 (38–66) versus 62 (54–72)	56.2 versus 69.2	-	9.4 versus 23.4	12.5 versus 30.8	-	18.8 versus 20.5	3.1 versus 12.8	-

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease.

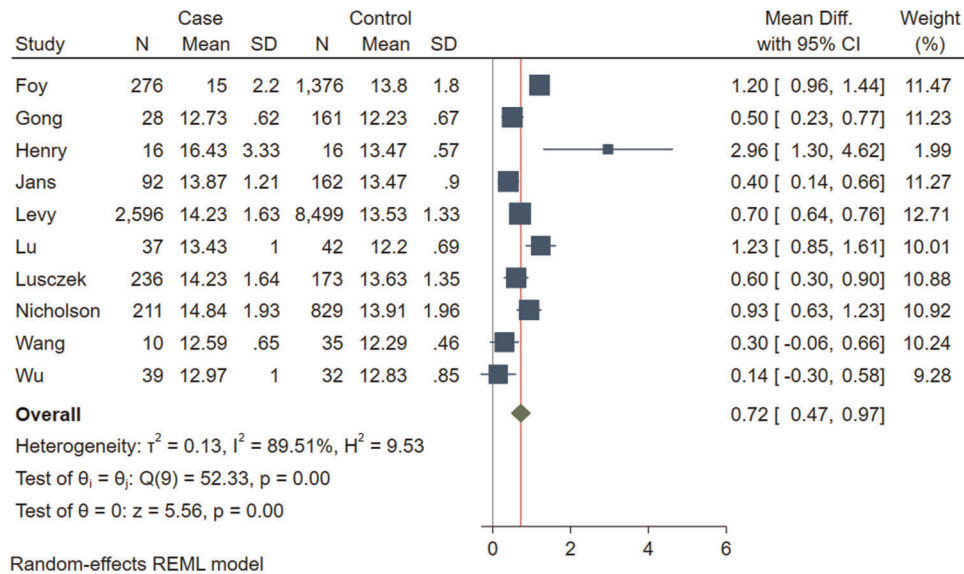


FIGURE 2 Red blood cell distribution width and adverse outcomes in COVID-19 patients

Egger's test ($Z = 1.94$, $p = .052$). In the sensitivity analysis, elevated RDW was associated with adverse outcomes in Chinese populations (pooled mean differences: 0.55; 95% CI, 0.09–1.01) and in non-Chinese populations (pooled mean differences: 0.83; 95% CI, 0.53–1.12). The test for subgroup difference was not significant ($p = .31$) (Figure S1).

3.2 | Subgroup analysis

Results of the subgroup analysis on the associations with two subsets of the study participants (mortality and COVID-19 severity) are shown in Figure 4. On the basis of three studies included in the mortality subgroup analysis, deceased patients had higher levels of RDW compared to survived COVID-19 patients (pooled mean differences: 0.93; 95% CI, 0.63–1.23).

According to the seven studies included in the COVID-19 severity subgroup analysis, severely ill COVID-19 patients showed higher levels of RDW, as opposed to patients classified to have mild symptoms (pooled mean differences: 0.61; 95% CI, 0.28–0.94). There was significant heterogeneity across subgroups (I^2 for mortality subanalysis = 85.58%; I^2 for severity subanalysis = 82.18%). There was no significant difference between the subgroups ($p = .17$), indicating a consistent association between RDW and adverse outcomes.

4 | DISCUSSION

In this meta-analysis, higher levels of RDW were associated with unfavorable outcomes among COVID-19 patients. Furthermore, nonsurvivors and patients with more severe symptoms had a

significantly greater RDW as compared to survivors and those with less severe symptoms. Taken together, these findings suggest that RDW measurement on hospital admission provided prognostic insights among patients hospitalized for COVID-19.

RDW has been reported as an independent marker of mortality regardless of demographic characteristics and underlying clinical conditions¹ and also in the context of COVID-19.^{17,20,21} Elevation of the RDW level has also been associated with higher mortality, such as sepsis.²⁷ Consistent with our findings, Henry et al.¹⁹ demonstrated that elevated RDW at the time of emergency department visit was associated with a nine-fold increased odds of COVID-19 severity. This was further confirmed by another report, suggesting that RDW can be incorporated into a prediction model consisting of advanced age, lactate dehydrogenase, C-reactive protein, blood urea nitrogen,

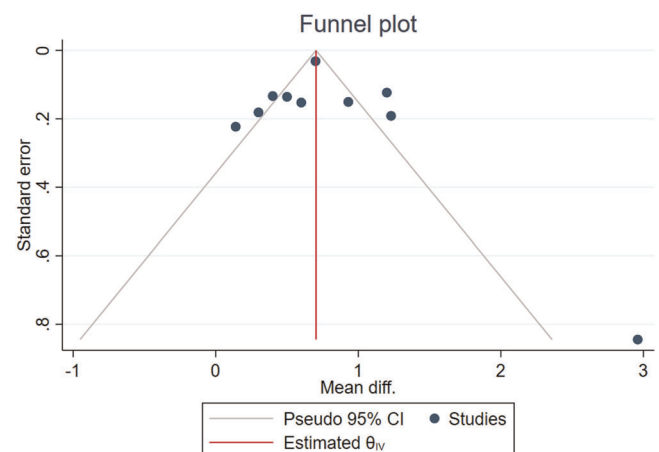


FIGURE 3 Funnel plot of red blood cell distribution width and adverse outcomes in COVID-19 patients

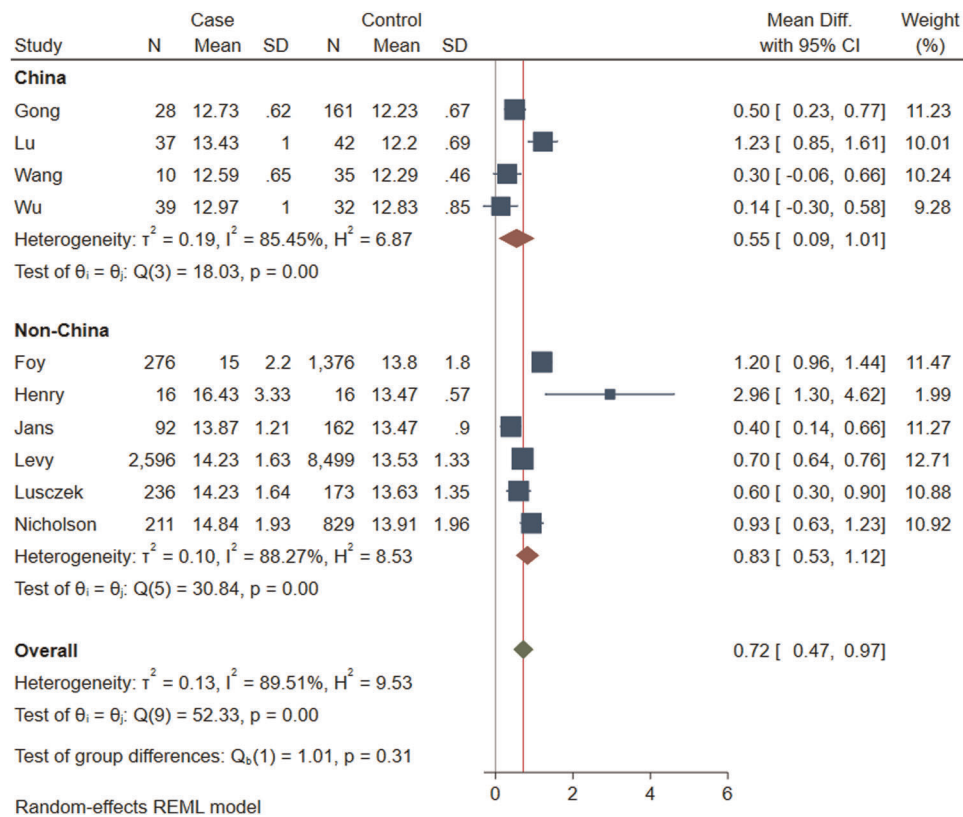


FIGURE 4 Red blood cell distribution width and subgroups of COVID-19 patients with adverse outcomes

direct bilirubin, and lower albumin (area under the receiver operating characteristic [ROC] curve, 0.912; 95% CI: 0.846–0.978], sensitivity: 85.71%, specificity: 87.58%).¹⁸ Of clinical interest, a recent study by Wang et al.²⁸ reported prognostic values of hematological parameters, where an RDW cutoff value of 12.85% demonstrated a sensitivity of 73.9% and specificity of 81.9% with an area under the ROC curve of 0.870 (95% CI: 0.775–0.952) for predicting the prognosis of severe COVID-19 patients. In light of the emergent nature of COVID-19 infection and lack of healthcare resources, a simple and widely available tool, such as RDW, to assist with predicting disease severity and mortality among COVID-19 patients is crucial.

The exact pathophysiology behind the association between increased RDW and adverse outcomes has yet to be elucidated. The findings may be explained by the following potential mechanisms. First, numerous reports have suggested that COVID-19 infection was associated with an increase in the release and production of white blood cell counts and platelets from the bone marrow. The stimulation to the bone marrow may also impact the RBC kinetics, resulting in a wider range of RBC size and subsequently elevated RDW levels.^{17,20} Another possible mechanism is the incompetent bone marrow in producing normal RBCs associated with COVID-19 infection. Prior studies have noted the hyperinflammatory state in certain patients with COVID-19. This overproduction of inflammatory cytokines may influence hematopoiesis by altering the release or response to erythropoietin or affecting the function and structure of RBC, thereby increasing the fragility of RBC and

variability of its size.¹⁸ In addition, systemic inflammatory conditions could have detrimental effects on iron absorption and accessibility, which are required for effective hematopoiesis.¹⁹ Lastly, bone marrow suppression or destruction has also been attributed to immunologic dysregulation following COVID-19 infection. In this scenario, patients typically present with anemia due to decreased production of RBC and develop a compensatory response characterized by the release of immature erythroid progenitor cells into the bloodstream that contributes to an increase in RDW levels.²⁴ On the contrary, RDW may serve as a nonspecific aggregate biomarker of general illness that is not mechanistically associated with the disease progression of COVID-19.

The interaction of age on the association between RDW and mortality was investigated in two studies. In the study by Foy et al.,¹⁷ elevated RDW appeared to have a larger effect on mortality for younger patients (<70 years) than it had for older patients, suggesting a potential effect modification by age. In contrast, the study by Hornick et al.²⁹ showed that the relationship between RDW and mortality was consistent across the age spectrum, and there was no significant interaction between RDW and age. More research is needed to confirm the potential effect modification by age.

Of note, serial measurements of RDW could provide incremental mechanistic insights to the baseline RDW. Foy et al.¹⁷ demonstrated that nonsurvivors had a significantly greater RDW increase during the first week of hospitalization than the survivors. Furthermore, compared to a stable RDW, an increasing RDW during

hospitalization was associated with increased mortality risk among patients with a normal RDW at admission (24% vs. 6%), as well as among those with an elevated RDW at admission (40% vs. 22%).¹⁷ Though elevated on-admission RDW may reflect frailty or poor health at baseline, an increasing RDW during the course of infection may indicate poor hematopoietic regulation, increased RBC destruction, or increased stresses on bone marrow due to increased platelet and white cell production. Future studies should explore the prognostic value of an increasing RDW during hospitalization.

4.1 | Limitations

Several limitations warrant consideration. First, only three studies were available in examining the association between RDW levels and mortality among COVID-19 patients. Second, there were remarkable differences in patient characteristics and study settings between the included studies. Third, the definitions for disease severity of COVID-19 vary across the studies. These variations may have contributed to the heterogeneity in the effect size. However, the consistent associations demonstrated in each study and the pooled results support the utility of RDW in predicting disease progression and mortality among COVID-19 patients. Fourth, as patient-level data from included studies were not available, the current meta-analysis was performed at the study level. Although the association of RDW was robust to geographic regions, further research is warranted to explore whether the effects of RDW would remain consistent across other subgroups such as age, sex, and race. Next, differences in the characteristics and pathology of the study endpoints (i.e., mortality and severity of disease) may have under- or overestimated the results. To assess whether the heterogeneity of study endpoints affected the pooled results, we additionally conducted a subgroup analysis and observed consistent findings that both deceased and severely ill patients had higher levels of RDW. Further, improvement in the study endpoints and reduction of the endpoint heterogeneity could have been reached if additional studies were included by inquiring unpublished RDW values from studies of mortality and severity of COVID-19 patients. Finally, ascertainment bias could occur when more intense surveillance or laboratory tests are arranged for critically ill patients than mildly ill patients. However, the risk of ascertainment bias may be low in the present analysis, as RDW is usually included as a part of the routine CBC test.

5 | CONCLUSION

The meta-analysis demonstrated that elevated RDW levels were associated with adverse outcomes in COVID-19 patients. This finding warrants further research on whether RDW could be utilized as a reliable prognostic tool for predicting COVID-19 severity. As RDW is widely available and included as a routine parameter of CBC, this simple laboratory test can be particularly useful in the context of the COVID-19 pandemic, where identifying high-risk patients and

facilitating timely intervention with limited resources are critical. Future research should also examine whether RDW is mechanistically linked to the pathophysiology of COVID-19.

CONFLICT OF INTERESTS

The work was not funded by industry. Dr. Chi received modest research grant support paid to the Beth Israel Deaconess Medical Center, Harvard Medical School from Bayer, Janssen Scientific Affairs, and CSL Behring. All remaining authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: Gerald Chi and Jane J. Lee. *Acquisition, analysis, or interpretation of data:* Gerald Chi, Jane J. Lee, Jolanta Marszalek, and Michael L. Chuang. *Drafting of the manuscript:* Gerald Chi, Jane J. Lee, Adeel Jamil, and Umer Jamil. *Critical revision of the manuscript for important intellectual content:* Sahar M. Montazerin and Michael L. Chuang. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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