Systematic Review and Meta-Analysis

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Association between red cell distribution width level and risk of stroke

A systematic review and meta-analysis of prospective studies

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Abstract

Background: Red cell distribution width level may have relations with the incidence and prognosis of cerebrovascular diseases. Recent researches have reported that red cell distribution width level was linked to the occurrence of stroke. However, the predicted effect of red cell distribution width in stroke is still disputed. We sought to assess the relationship between red cell distribution width and risk of stroke in this meta-analysis.

Methods: Relevant studies were picked out from the databases of Embase, PubMed, and Cochrane Library. Hazard ratio with 95% confidence interval was chosen to analyze each trial, which was extracted from results of the highest and lowest red cell distribution width group. Funnel plots, Begg and Egger test were used to assess publication bias in the meta-analysis. Stata(12.0) was utilized to perform statistic analysis in the process.

Results: A total of 6 studies with 5783 patients were included in this meta-analysis. The results showed that red cell distribution width level in patients with stroke was significantly higher than it in those without stroke (HR = 1.34, 95%CI:1.23–1.47, $P < .001$), in particular ischemic stroke(HR = 1.34,95% confidence interval:1.1–1.54, $P < .001$). There was no evidence of heterogeneity across the studies ($P = .355$, $I^2 = 5.53\%$).

Conclusions: The higher red cell distribution width level was associated with an increased risk of stroke, especially ischemic infarction.

Abbreviations: BMI = body mass index, CHF = congestive heart failure, CI = confidence interval, DM = diabetes mellitus, HDL = high density lipoprotein cholesterol, HR = hazard ratio, IS = ischemic stroke, LDL = low density lipoprotein cholesterol, MCV = mean corpuscular volume, NOS = Newcastle-Ottawa scale, RDW = red cell distribution width level.

Keywords: meta-analysis, red cell distribution width level, risk, Stroke

1. Introduction

It is well known that stroke is a multifactorial disease, which has a bad affect on our fitness and quality of life. The incidence rate of stroke has increased in recent years. The stroke risk rate among men was 41.1% and 36.7% among women in China. The stroke risk rate from the age of 25 years globally has risen from 22.8% to 24.9% between 1990 and 2016.[1] Early treatment especially optimization of time management can give patients a favorable prognosis.[2] Therefore, we need more effective biomarkers which can be used for early prediction and diagnosis of stroke. However, there are still no highly sensitive biomarkers so far.[3]

The red cell distribution width (RDW) is a biochemical parameter representing the variability in size of circulating red blood cells. Elevated RDW may be involved in the incidence and prognosis in many cadiocerebrovascular diseases.[4] However, previous studies about the relation between RDW and stroke were incompatible. Several studies had reported that high RDW was a risk factor of stroke in aspects of incidence and prognosis, while 1 study came to the insignificant conclusion.[5–7] So more studies to deliberate the correlation between RDW and stroke are needed.

The purpose of this meta-analysis was to verify the association between RDW and risk of stroke.

2. Materials and methods

2.1. Search methods

This meta-analysis was conducted with a detailed protocol following the Preferred Reporting Items for Systematic reviews and Meta-Analyses(PRISMA).[8] Three databases were used including PubMed, EMBASE, and Cochrane Library from inception to April 29, 2019. Keywords including red cell distribution width, stroke, and cerebral infarction. Languages

Editor: Massimo Tusconi.

The authors have no conflicts of interest to disclose.

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

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How to cite this article: Li B, Liu S, Liu X, Fang J, Zhuang W. Association between red cell distribution width level and risk of stroke: a systematic review and meta-analysis of prospective studies. Medicine 2020;99:16(e19691).

Received: 6 November 2019 / Received in final form: 15 February 2020 / Accepted: 2 March 2020

http://dx.doi.org/10.1097/MD.0000000000019691

were restricted to English for inclusion. We conducted this meta-analysis by using rest of articles after removing duplicated and unrelated articles.

2.2. Inclusions/exclusions

The following inclusion criteria included:

1. Prospective studies researching the RDW in participants with stroke;
2. Stroke was diagnosed by cranial computed tomography or magnetic resonance imaging;
3. Providing RDW as continuous data;
4. Follow-up period of studies was at least 1 year;
5. The hazard ratio (HR) and 95% confidence interval (CI) could be used in studies after adjusting for multiple factors; and
6. Outcomes regarding incidence of stroke.

Exclusion criteria were as follows:

1. The articles were not in English;
2. Lack of related data.

This meta-analysis was approved by the ethics committee of the first affiliated hospital of Shantou University Medical College.

2.3. Data extraction and quality assessment

Two authors independently reviewed the included studies. Titles and abstracts were reviewed to identify potentially eligible studies. The full text were evaluated if meeting potential articles, with disagreement resolved by discussion until a consensus was reached. Variables included first author information, publication year, region, sample size, age, follow-up durations, RDW, HR, and 95%CI (adjusted most factors) were extracted. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of include studies by 2 authors independently. The NOS scores were considered poor (0–4), moderate (5–6), and good (7–9).[9]

2.4. Statistical analysis

The incidence of stroke were represented as dichotomous data. We chose the HR with 95% CI to analyze and a P value $<.05$ was defined as statistically significant. We calculated the Cochrane I^2 test to evaluate the heterogeneity of included studies in the article.[10] I^2 values of less than 50%, 50% to less than 75%, and more than 75% were indicated as evidence of low, moderate, and high levels of heterogeneity, respectively. If the studies had no heterogeneity, a fixed effect model was utilized to pool relative effect estimates. Otherwise, a sensitivity analysis was performed to achieve homogeneity. If there was still heterogeneity among included studies, a random effect model was used. Funnel plots with Begg and Egger test were used to evaluate publication bias. We used stata(12.0) to analyze the collected data.

3. Results

3.1. Study selection and characteristic

The literature selection procedure were shown in the flow diagram in Figure 1. Our electronic search identified 208 articles. After removing 38 duplicated studies, 170 articles were remained. Then we excluded 155 studies based on the abstracts. Then full-text studies were retrieved for detailed evaluation. Of the remained 15 articles, 9 articles were not prospective studies. Finally, 6 studies were pooled in our meta-analysis to further analyze relation between RDW and risk of stroke.[5,6,11–14] Study characteristics and quality assessment were presented in Table 1. Among the 6 trials, there were 5783 patients in total. Study sample sizes ranged from 806 to 10179, deriving from different countries and regions in Europe and Asia. In the included studies, the median age among each study was similar, mainly in the middle and old age, ranging from 35 to 74.5 years old. The interval of RDW in each study was different. Four studies were divided into 4 intervals, 1 study was divided into 5 intervals, and another study was divided into 7 intervals. All studies evaluated by the NOS showed high quality with a score of ≥7 points.

3.2. Outcomes and meta-analysis

According to the selection criteria, 6 selected articles were meta-analyzed. The heterogeneity test showed that there was no heterogeneity in the midst of the studies ($P=.355$, $I^2=5.53\%$). Therefore, the fixed effect model was used to evaluate in our study. Pooled analysis demonstrated that higher RDW level had an increased risk of stroke (HR = 1.34,95%CI:1.23–1.47, $P<.001$)(Fig. 2). Meanwhile, the pooled HR of the cerebral infarction was 1.34 (95%CI:1.1–1.54, $P<.001$) with low heterogeneity ($I^2=49.08\%$)(Fig. 3).

3.3. Subgroup analysis

For purpose of reducing the impact of heterogeneity, we conducted a subgroup analysis of the area, follow-up time, study quality and number of stroke (Fig. 4). In the subgroup analysis, the heterogeneity of each subgroup was not significantly decreased, but the combined value of subgroup effect was statistically significant. This suggested that none of the above subgroups is the source of heterogeneity.

3.4. Publication bias

The funnel plot(Fig. 5)was performed to evaluate the publication bias. The P value for Egger and Begg test were .107 and .133. These results suggested that there was no significant publication bias in this study. However, the results of the funnel plot, Egger and Begg test may be influenced by a type II error, which rely on the performance of the test.

4. Discussion

This study was, to the best of our knowledge, the first meta-analysis to research the relationship between RDW and risk of stroke. The results showed that RDW was the index to predict the risk of stroke particularly ischemic infarction. Our meta analysis including 6 studies concluded that higher RDW could increase the risk of stroke. Three of them reported the risk of ischemic infarction and it increased the risk as well. Otherwise, only 2 studies reported the risk of cerebral hemorrhage, which could not have enough data to analysis.

RDW was a new routine parameter representing the variability in size of circulating erythrocytes, which could early identify iron deficiency before other test. Therefore, it could point out the earliest morphologic changes in anemia caused by deficiency of folic acid, iron, and vitamin B12.[15] At the same time, it also happened in some autoimmune diseases, hemolytic anemia, sickle cell disease, and blood transfusion.[16] Previous data had reported

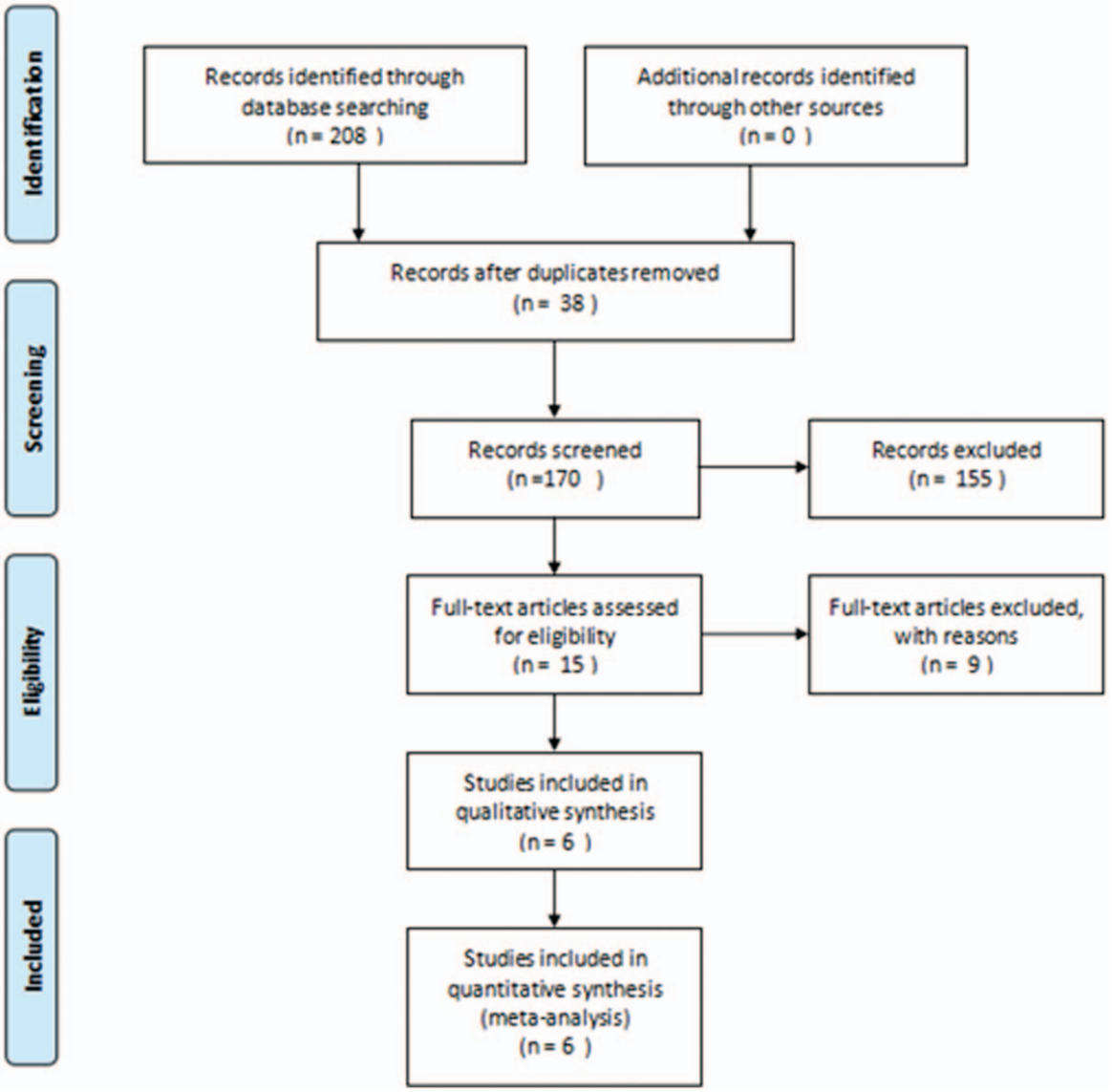

Figure 1. PRISMA flow diagram. The flow diagram of procedure to select studies.

Table 1

Characteristics of studies.

Auther	Region	Year	Follow-up time(year)	Age (median year)	Case/total	RDW(cutoff)	HR/95%CI	NOS score	Adjustment factors
Saliba et al (Walid)	israel	2014	1	74.5±13.1	1962/10179	15%,14.1%, 13.4%	1.30(1.13–1.49)	7	CHF, age hypertension, DM, previous stroke, sex, vascular disease
Soderholm et al (Martin)	Sweden	2015	15.2±3.9	58.0±7.6	576/6758	Men:42.4fL, 40.1fL,38.2fL, Women:42.7fL, 40.6fL,38.6fL	1.31, 1.11–1.54)	8	blood pressure, medication, smoking, DM, alcohol, waist circumference, low physical activity, white blood count, atrial fibrillation, CHF, MCV hemoglobin
Lappegard et al (Jostern)	Norway	2016	15.8	With stroke: 64.0±12.7; Without stroke: 45.7±14.4	362/4466	13.5%,13.0%,12.7%, 12.4%,12.3%	1.37 (1.11–1.69)	7	Age, sex, BMI, smoking, hemoglobin, white blood cell count, thrombocytes, cholesterol, triglycerides, DM, red blood cell count
Chen et al (Pen-Chun)	taiwan	2009	15.9	≥35	55/806	13.7%,13.1%,12.7%	1.20 (0.80–1.81)	8	RDW, age, sex, BMI, smoking, DM, hypertension, cholesterol, LDL, HDL, triglycerides, albumin, glomerular filtration rate, hematocrit, MCV
Mo et al (Liyi)	China	2017	4.17	60.4±14.3	62/442	17.0%,16%, 15%	2.99(1.37–6.52)	7	RDW, age, hypertension, albumin, Charlson Comorbidity Score, C-reactive protein
Pilling et al (Luke C)	UK	2018	≤9	55.05±8.1	—/6050	15%,14.5%, 14.0%, 13.5%,13.0%,12.5%	1.57 (1.13–2.19)	7	age, sex, smoking, educational attainment, hemoglobin MCV

BMI = Body Mass Index, CHF = congestive heart failure; DM = diabetes mellitus, HDL = high density lipoprotein cholesterol, HR = hazard ratio, LDL = low density lipoprotein cholesterol, MCV = mean corpuscular volume, NOS = Newcastle-Ottawa scale, RDW = red cell distribution width.

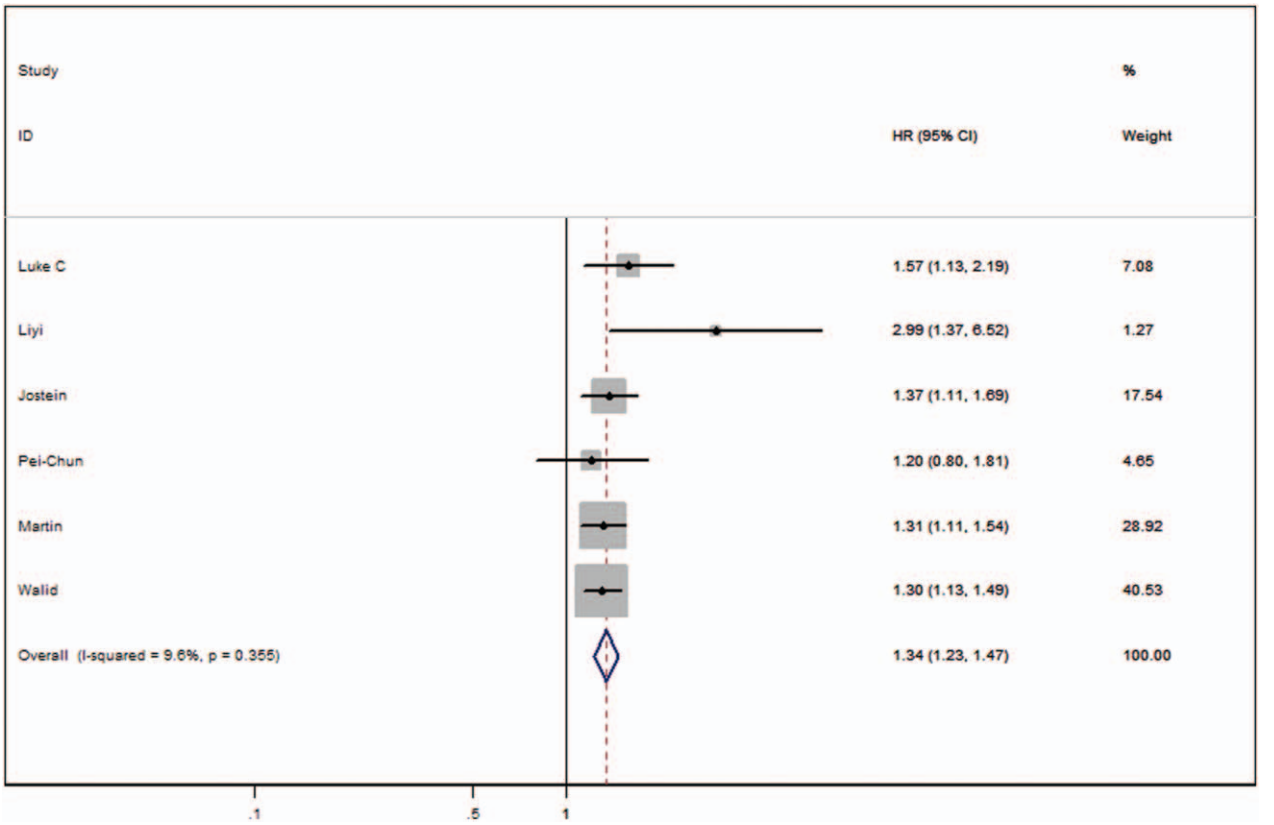

Figure 2. Forest plot for the relation between red cell distribution width level and risk of stroke.

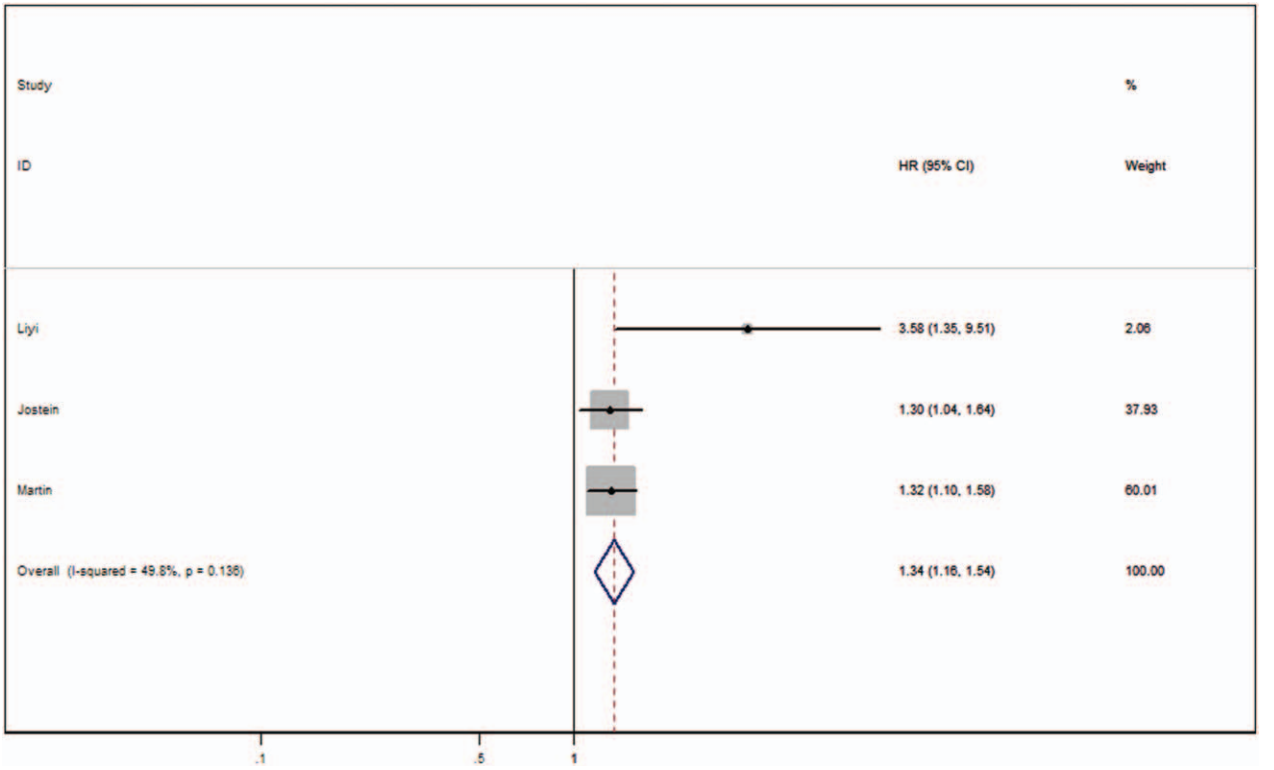

Figure 3. Forest plot for the relation between red cell distribution width level and risk of cerebral infarction.

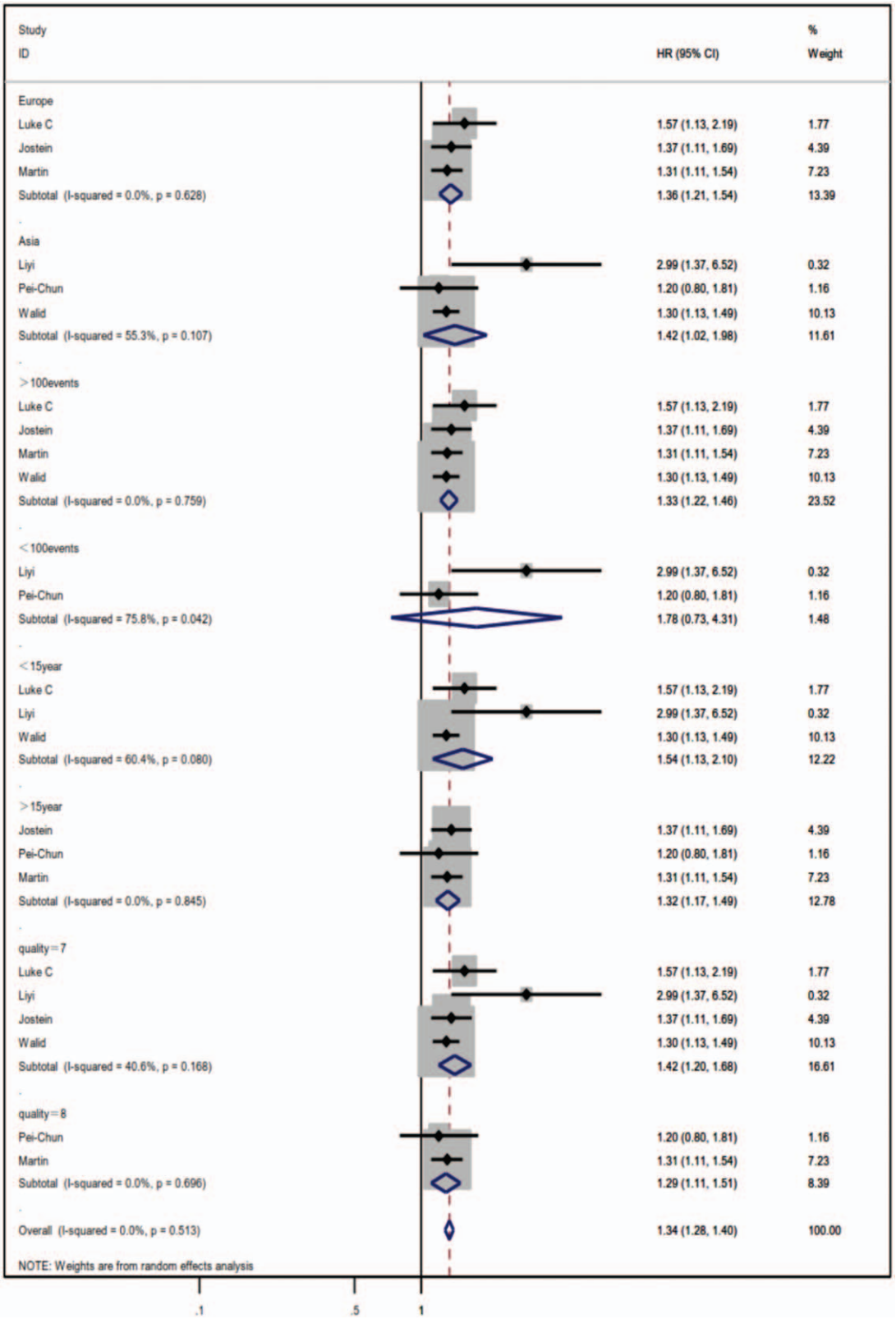

Figure 4. Forest plot for RDW and stroke risk subgroup analysis.

that higher RDW levels could be an independent predictor of increased stroke incidence, and even in those with atrial fibrillation and heart failure.[13,17] Besides, it was also related to carotid atherosclerosis and hypertension, which could cause some small vascular stroke.[18,19] RDW also may be used as a biomarker to predict the functional outcomes and mortality in

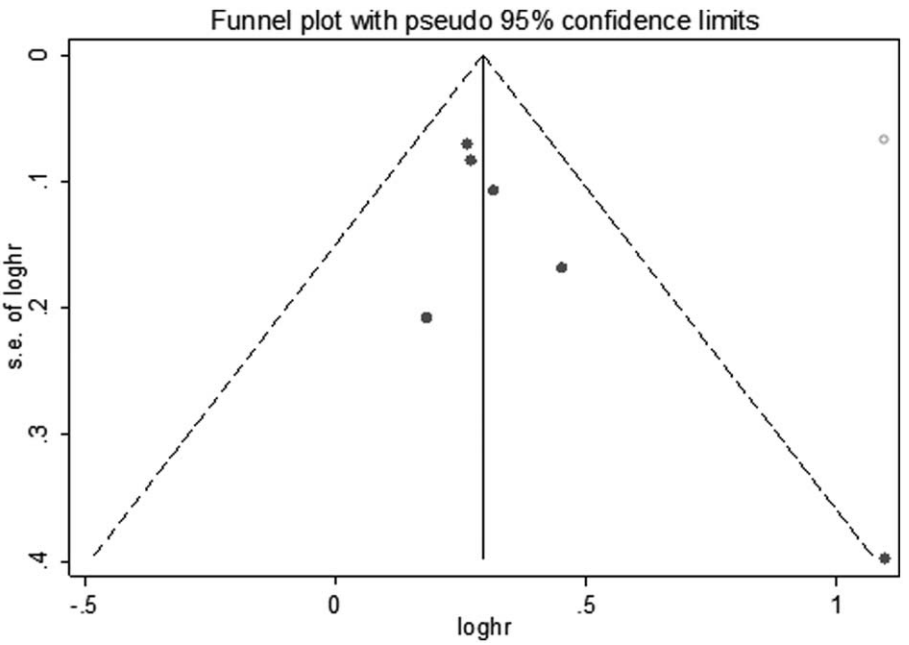

Figure 5. The funnel plot.

patients with cerebral infarction.[20–22]With regard to cryptogenic stroke, some studies had confirmed that RDW > 14% was an independent predictor to forecast risk of cryptogenic stroke, which could increase 2.5 times in patients with RDW > 14%.[23] However, there were still few studies about RDW and stroke, particularly lacking of TIA and hemorrhagic stroke research, all of which needed quite more studies to prove.

The mechanisms between elevated RDW levels and stroke had not yet been fully understood. Inflammatory factors and oxidative stress were considered as 2 different important mechanisms causing cerebral infarction. More evidence about increased inflammatory responses may play an important role and have detrimental effects in the pathophysiology of stroke, both of ischemic and hemorrhagic type. Previous study suggested elevation of CRP in intracerebral hemorrhage during acute-phase is associated with the outcomes such as death and vascular complications.[24] Neutrophils induce and activate inflammatory responses, while lymphocytes have anti-inflammatory and endothelial protective functions. So this imbalance between them is the basis of inflammatory responses. In general, the elevated NLR (neutrophil to lymphocyte ratio) suggests a strong inflammatory response. Lots of studies have shown that it can be used to predict prognosis of patients with ischemic and hemorrhagic stroke, which is closely related to worse functional prognosis and increased nosocomial mortality.[25–27] RDW may reflect the inflammation state, which leads to impair erythrocyte maturation and shorten erythrocyte survival.[14] Some researches indicated that inflammatory mediators such as IL-6, TNF-α, CRP, and ESR was associated with RDW independent of multiple confounding factors, as a part of inflammatory process.[28,29] High oxidative stress and low antioxidant levels may be related with high RDW.[28,30] It can damage erythrocyte membrane and increase the fragility of RBCs. It also reduces the rate of erythroid maturation and RBCs life span. Besides, higher RDW reflect the agglutination state of RBCs, playing an important role in haemostasis and the fibrinolytic process and leading to vascular occlusion considering as one of independent factors.[31]

A systematic review about this aspect was still lacking, not only few RCTs, but also prospective, case-control and cross-sectional studies. In consequence, this is the first meta-analysis to discuss about RDW and stroke. Only 6 prospective studies were included in this article. Although proper statistic methods were used and no heterogeneity was detected in our meta-analysis, there were some certain limitations. First, there were only 6 studies that can be extracted in the article, and the data of 3 studies were incomplete, which could not be further analyzed. Second, the interval division of RDW was different in each study, 4 studies were divided into 4 intervals, 1 study was divided into 5 intervals, and 1 study was divided into 7 intervals. Third, other risk factors of stroke such as hypertension and coronary heart disease were not further analyzed, which could have an influence on the outcome. Not only high blood pressure, but also blood pressure variability is a recognized risk factor of cerebrovascular disease and contribute to brain damage. Higher systolic blood pressure variability (SBPV) may be associated with poor outcome in patients with intracerebral hemorrhage (ICH) and be a significant determinant of brain alterations.[32,33] Besides, The adjusted factors were different among the studies, and the follow-up time was also various, ranging from 1 to 15.9 years. Also, the search strategy was lack of the terms about cerebral hemorrhage and might have biased the results reducing the likelihood to find out studies about hemorrhagic stroke.[31] Finally, prospective studies may well identify the relationship between the 2 variables, but the causal relationship was still uncertain. Although this study had obtained positive results, it needed more studies especially RCTs to prove the result and confirm the importance of RDW in stroke in the future. Considering the cheap, fast and regular indicators, RDW may be a useful biochemical index to predict the risk of stroke, allowing us to prevent and detect early.

5. Conclusion

Our meta-analysis revealed that RDW was associated with risk of stroke. Based on the evidence, which was cheap, fast, and regular, may be a predictor for the risk of stroke, in particular ischemic stroke.

Author contributions

Conceptualization: Xiaoqiang Liu, Jingnian Fang, Weiduan Zhuang.
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Project administration: Bingxian Li.
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Visualization: Bingxian Li, Jingnian Fang.
Writing – original draft: Bingxian Li, Xiaoqiang Liu.
Writing – review & editing: Bingxian Li, Shuo Liu.

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