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# Red blood cell distribution width and ischaemic stroke

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## ABSTRACT

The red blood cell distribution width (RDW) is a measure of red blood cell (RBC) size heterogeneity, which is easily calculated by dividing the SD of erythrocyte volumes for the mean corpuscular volume. Recent reporter suggested that, besides haematological diseases and anaemia, many human disorders may be closely associated with the elevated RDW. A literature review has revealed the RDW may be closely related to the development of ischaemic stroke, carotid artery atherosclerosis and cerebral embolism. Higher RDW could independently predict adverse outcomes in patients in these conditions.

## INTRODUCTION

The red blood cell distribution width (RDW) is a parameter that reflects the heterogeneity of the red blood cell volume. It is indicated that the variation coefficient of the red blood cell volume is more objective and accurate than that of the red blood cell on the blood smear. RDW is in about 11.0%–16.0% in normal population. RDW will rise under some physiological and pathological conditions.[1 2]

RDW has at least five clinical significant meanings:

1. To diagnose and guide the treatment of iron deficiency anaemia. Traditionally, anaemia deficiency from iron can be differentiated from folate deficiency according to the size of RDW. RDW would increase because of the release of immature red blood cells into the blood stream in certain haematological diseases.[3–5] RDW increases in iron deficiency anaemia, and such increase would appear earlier than the decline of mean corpuscular volume (MCV), which can be an early indication of iron deficiency. When MCV is low, RDW would increase more significantly. When iron therapy is given, RDW would elevate first and then gradually reduce at the normal level.
2. To diagnose small cell and low pigment anaemia.
3. To classify anaemia.
4. Previously, many research suggested that RDW was closely related to the mortality and cardiovascular events, such as acute coronary syndrome, ischaemic cerebrovascular disease, peripheral artery disease, heart failure (HF), atrial fibrillation (AF) and hypertension.[4 6–10]
5. RDW can be made as a predictor of mortality in patients with cancer, chronic lung disease or acute renal failure.[4 11]

Stroke is the result of cerebral vascular occlusion or haemorrhage, and it is the leading cause of death in the world.[12–14] At present, clinical diagnosis relies on history, neurological examinations and neuro-imaging. Several scoring systems are used to quantify the degree of severity of stroke: the Glasgow Coma Scale, Canadian Neurological Scale, Scandinavian Stroke Scale and National Institutes of Health Stroke Scale (NIHSS).[15] However, there is no biological surrogate marker to diagnose stroke. RDW by flow cytometry could be an option for this purpose and predict the occurrence of stroke.[1 16–18]

## METHODS

In this meta-analysis, we analysed the current scientific literature on the putative role and the potential epidemiological association between RDW and ischaemic stroke (including carotid artery atherosclerosis). Keywords used include the RDW, ischaemic stroke and the outcomes of ischaemic stroke. Data base used include CNKI and PubMed. Fifty-seven manuscripts were identified, and 40 of them were included.

## RESULTS

Overall, considerable and convincing evidence has been demonstrated that an increased RDW value is likely associated with ischaemic cerebrovascular disease, carotid artery atherosclerosis and cerebral embolism. Higher RDW could independently predict adverse outcomes in patients in these conditions.[19 20]

## RDW IN ISCHAEMIC STROKE

Cerebral infarction (CI) is a general term of ischaemic stroke, including cerebral

thrombosis, lacunar infarction and cerebral embolism. Ischaemic stroke accounted for about 70% of all strokes, which is caused by brain–blood supply disorder of brain lesions.

Current study confirms that RDW is closely related to the occurrence of ischaemic stroke. Jia *et al* studied 392 patients with a primary diagnosis of ischaemic stroke with MRI, then performed carotid ultrasound and laboratory examination. They have found that the levels of RDW in these patients was higher than those with no strokes.[21] This study confirmed that RDW played an important role in the progression of an ischaemic stroke. Similarly, Söderholm *et al* found that high levels of RDW could increase the risk of stroke or CI in a population-based cohort study in 2015.[22] However, Lappegård *et al* have found that elevated RDW levels did not predict any increased risk of death after stroke.[23]

Clinically, the severity of stroke is evaluated by several bedside scoring systems or imaging studies. Kara *et al* studied the RDW in 128 patients with acute ischaemic stroke (AIS; symptoms <24 hours) and compared their scoring systems to the levels of RDW. They have found that significantly higher levels of RDW could predict increased risk of total stroke occurrence with the bedside scoring systems.[15] Therefore, it is likely that RDW could predict the severity and functional outcomes in patients with stroke. Kim *et al* reported that the greater the magnitude of RDW, the higher the mortality rate and worsening of functional outcome in acute stroke. These studies seemed to indicate that RDW can be used as a biomarker for assessing the severity of stroke and prognosis of patients with AIS.[24]

## RDW IN CEREBRAL EMBOLISM

Cerebral embolism can be generated from several sources. It can be cardiogenic or arterial to arterial embolisation. One of the sources is the internal carotid artery. At present, RDW cannot be used to predict the mechanism of a stroke, such as in cerebral embolism. Through CHS computerised database, Saliba *et al* conducted a prospective study of 77 297 patients and found that RDW change was directly related to a stroke. However, it also showed correlation of stroke to AF. Adamsson *et al* selected 27 124 middle-aged subjects (45 years old–73 years old, female 62%) with AF, HF, myocardial infarction or stroke and followed up for 13.6 years. They found that RDW levels correlated well to the incidence of stroke caused by AF in Sweden.[25] The results showed that RDW may be related to the risk of cerebral embolism.

## RDW IN CAROTID ARTERY ATHEROSCLEROSIS (CAS) AND HYPERTENSION

A large number of studies have confirmed that CAS was a risk factor for ischaemic stroke.[26–29] This was supported by a large number of epidemiological studies on cardiovascular diseases. Similarly, Furer *et al* studied 522 patients with high RDW and carotid Intima-medial thickness (IMT) by using carotid artery ultrasound. They have found that elevated RDW was related to preclinical and clinical CAS and suggested that RDW was an independent risk factor for severe atherosclerosis.[30] Martin *et al* have come to the same conclusion based on a cohort study of Swedish population.[31]

Wen studied IMT by ultrasound in 156 hypertensive patients (60–85 years old). They have found that RDW level was an independent predictor of IMT and plaque-related incidences.[32] And a large number of studies have confirmed that elevated RDW levels may have result in the hardening of the arteries.

## DISCUSSION

The exact biological mechanism between RDW and ischaemic stroke remains unclear. Inflammation and oxidative stress (OS) may play an important role in RDW in ischaemic stroke.[15 24] Inflammation can reduce the survival rate of red blood cells, inhibit the production of red blood cells or erythropoietin and finally lead to red cell damage.[33 34] Some studies have suggested that RDW was similar to tumour necrosis factor receptor or C-reactive protein (CRP), which were also markers for inflammation.[35] Ferrucci *et al* thought a variety of inflammatory cytokines can be used as a parameter, suggesting that higher levels of inflammation and high concentrations of RDW in non-anaemic elderly was closely related to the production of erythropoietin, while it was negatively associated with anaemia.[36] High CRP and erythrocyte sedimentation rate in elevated RDW was independent of other confounding factors.

OS was the imbalance between in vivo oxidation and antioxidation, resulting in neutrophil infiltration, increased protease secretion and accumulation of a large number of oxidation intermediates.[36] OS was a result of negative effect produced by free radicals in the body and an important factor leading to ageing and disease. The imbalance between antioxidant and oxidant will cause oxidative damage to nucleic acids, proteins and lipids, thus affecting the survival of red blood cells.[37] This may lead to the damage of red blood cell membrane, increased red blood cell fragility, reduced red blood cell maturation and red blood cell longevity and elevation of RDW.[38]

In addition, studies have suggested that oxidative damage and antioxidant levels were associated with cerebral ischaemia and reperfusion injury. Toxic protections from oxidative damage would affect functional outcome and mortality in stroke.[39 40] Semba *et al* followed 786 women with moderate to severe disability for 24 months in Baltimore. Their serum levels of oxidants increased with RDW.[37]

Recent studies have shown that antioxidants can improve the body's antioxidant capacity, reduce blood lipids and oxidative damage from ischaemic stroke.[39] In other words, RDW values was related to the levels of oxidation and antioxidants, which were related to the severity of ischaemic stroke (including carotid sclerosis).

Although a lot of studies considered that RDW might be a biomarker or predictor of outcome and mortality in ischaemic stroke, and RDW was associated with IMT and the incidence of carotid plaque, few trials suggested that RDW could predict severity of stroke and functional outcome in patients with early AIS.

## CONCLUSION

Although the biological mechanisms of higher RDW remains uncertain, RDW is a strong predictor for mortality and risk of ischaemic stroke (including CAS). More studies are required to evaluate and validate this correlation.

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