

Red blood cell distribution width and ischaemic stroke

Gang-Hua Feng,¹ Hai-Peng Li,¹ Qiu-Li Li,¹ Ying Fu,² Ren-Bin Huang¹

To cite: Feng G-H, Li H-P, Li Q-L, et al. Red blood cell distribution width and ischaemic stroke. *Stroke and Vascular Neurology* 2017;2:e000071. doi:10.1136/svn-2017-000071

Received 19 January 2017
Revised 28 April 2017
Accepted 7 May 2017
Published Online First
23 June 2017

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



CrossMark

¹Department of Neurology, The First People's Hospital of Chenzhou, University of South China, Chenzhou, China

²Thyroid Medicine Department/ Radionuclide Therapy Department (Ward 31), Hunan Provincial Tumor Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China

Correspondence to

Professor Ren-Bin Huang;
470165013@qq.com

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.

Contributors FF and RH conceived this study. HL provided technical supports. QL conducted statistical analysis and interpreted the data. FF drafted this manuscript and JB and ZL made critical revisions. HL supervised this study.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional unpublished data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Lippi G, Plebani M. Red blood cell distribution width (RDW) and human pathology. One size fits all. *Clin Chem Lab Med* 2014;52:1247–9.
- Salvagno GL, Sanchis-Gomar F, Picanza A, et al. Red blood cell distribution width: a simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci* 2015;52:86–105.
- Sousa R, Gonçalves C, Guerra IC, et al. Increased red cell distribution width in fanconi Anemia: a novel marker of stress erythropoiesis. *Orphanet J Rare Dis* 2016;11:102.
- Förhécz Z, Gombos T, Borgulya G, et al. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. *Am Heart J* 2009;158:659–66.
- Akkermans MD, Vreugdenhil M, Hendriks DM, et al. Iron Deficiency in inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2016;1.
- Gul M, Uyarel H, Ergelen M, et al. The relationship between red blood cell distribution width and the clinical outcomes in non-ST elevation myocardial infarction and unstable angina pectoris: a 3-year follow-up. *Coron Artery Dis* 2012;23:330–6.
- Rodríguez-Carrio J, Alperi-López M, López P, et al. Red cell distribution width is associated with cardiovascular risk and disease parameters in rheumatoid arthritis. *Rheumatology* 2015;54:641–6.
- Adamsson Eryd S, Borné Y, Melander O, et al. Red blood cell distribution width is associated with incidence of atrial fibrillation. *J Intern Med* 2014;275:84–92.
- Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular diseases. *J Thorac Dis* 2015;7:E402–11.
- Kaya A, Isik T, Kaya Y, et al. Relationship between red cell distribution width and stroke in patients with stable chronic Heart failure. *Clinical and Applied Thrombosis/Hemostasis* 2015;21:160–5.
- Grant BJ, Kudalkar DP, Muti P, et al. Relation between lung function and RBC distribution width in a population-based study. *Chest* 2003;124:494–500.
- O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016;388:761–75.
- Harris R, Nelson LA, Muller C, et al. Stroke in American Indians and Alaska Natives: a systematic review. *Am J Public Health* 2015;105:e16–e26.
- Patra J, Taylor B, Irving H, et al. Alcohol consumption and the risk of morbidity and mortality for different stroke types—a systematic review and meta-analysis. *BMC Public Health* 2010;10:258.
- Kara H, Degirmenci S, Bayir A, et al. Red cell distribution width and neurological scoring systems in acute stroke patients. *Neuropsychiatr Dis Treat* 2015;11:733.
- Patel KV, Ferrucci L, Ershler WB, et al. Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med* 2009;169:515–23.
- Vayá A, Hernández V, Rivera L, et al. Red blood cell distribution width in patients with cryptogenic stroke. *Clin Appl Thromb Hemost* 2015;21:241–5.
- Patel HH, Patel HR, Higgins JM. Modulation of red blood cell population dynamics is a fundamental homeostatic response to disease. *Am J Hematol* 2015;90:422–8.
- Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. *J Neurol Sci* 2009;277(1-2):103–8.
- Lee HB, Kim J, Oh SH, et al. Red blood cell distribution width is associated with severity of Leukoaraiosis. *PLoS One* 2016;11:e150308.
- Jia H, Li H, Zhang Y, et al. Association between red blood cell distribution width (RDW) and carotid artery atherosclerosis (CAS) in patients with primary ischemic stroke. *Arch Gerontol Geriatr* 2015;61:72–5.
- Söderholm M, Borné Y, Hedblad B, et al. Red cell distribution width in relation to incidence of Stroke and Carotid Atherosclerosis: a Population-Based Cohort Study. *PLoS One* 2015;10:e124957.
- Lappegård J, Ellingsen TS, Skjelbakken T, et al. Red cell distribution width is associated with future risk of incident stroke. The Tromsø Study. *Thromb Haemost* 2016;115:126–34.
- Kim J, Kim YD, Song TJ, et al. Red blood cell distribution width is associated with poor clinical outcome in acute cerebral infarction. *Thromb Haemost* 2012;108:349–56.
- Saliba W, Barnett-Griness O, Elias M, et al. The association between red cell distribution width and stroke in patients with atrial fibrillation. *Am J Med* 2015;128:192.e11–192.e18.
- Selwaness M, Hameeteman R, Van 't Klooster R, et al. Determinants of carotid atherosclerotic plaque burden in a stroke-free population. *Atherosclerosis* 2016;255:186–92.
- Imahori T, Hosoda K, Fujita A, et al. Long-Term outcomes of carotid endarterectomy and carotid artery stenting for carotid artery Stenosis: real-world status in Japan. *J Stroke Cerebrovasc Dis* 2016;25:360–7.
- Wilson D, Charidimou A, Ambler G, et al. Recurrent stroke risk and cerebral microbleed burden in ischemic stroke and TIA: a meta-analysis. *Neurology* 2016;87:1501–10.
- Doig D, Turner EL, Dobson J, et al. Predictors of Stroke, myocardial infarction or death within 30 days of carotid artery stenting: results from the International carotid stenting study. *Eur J Vasc Endovasc Surg* 2016;51:327–34.
- Furer A, Finkelstein A, Halkin A, et al. High red blood cell distribution width and preclinical carotid atherosclerosis. *Biomarkers* 2015;20(6-7):376–81.
- Söderholm M, Borné Y, Hedblad B, et al. Red cell distribution width in relation to incidence of stroke and carotid atherosclerosis: a population-based cohort study. *PLoS One* 2015;10:e124957.
- Wen Y. High red blood cell distribution width is closely associated with risk of carotid artery atherosclerosis in patients with hypertension. *Exp Clin Cardiol* 2010;15:37–40.
- Fu Y, Mao Y, Chen S, et al. A novel inflammation- and Nutrition-Based Prognostic System for patients with laryngeal squamous cell carcinoma: combination of Red Blood cell distribution width and body Mass Index (COR-BMI). *PLoS One* 2016;11:e163282.
- Giuseppe Lippi M, Giovanni Targher M, Martina Montagnana M, Gian Luca Salvagno M, Giacomo Zoppini M, Gian Cesare Guidi M. Relation between Red Blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med* 2009;2009:628–32.
- MacDougall IC, Cooper A. The inflammatory response and epoetin sensitivity. *Nephrol Dial Transplant* 2002;17(Suppl 1):48–52.
- Ferrucci L, Guralnik JM, Woodman RC, et al. Proinflammatory state and circulating erythropoietin in persons with and without Anemia. *Am J Med* 2005;118:1288.e11–1288.e19.
- Semba RD, Patel KV, Ferrucci L, et al. Serum antioxidants and inflammation predict red cell distribution width in older

- women: the Women's Health and Aging Study I. *Clin Nutr* 2010;29:600–4.
38. Kiefer CR, Snyder LM. Oxidation and erythrocyte senescence. *Curr Opin Hematol* 2000;7:113–6.
39. Cherubini A, Polidori MC, Bregnocchi M, *et al.* Antioxidant profile and early outcome in stroke patients. *Stroke* 2000;31:2295–300.
40. Ullegaddi R, Powers HJ, Gariballa SE. Antioxidant supplementation enhances antioxidant capacity and mitigates oxidative damage following acute ischaemic stroke. *Eur J Clin Nutr* 2005;59:1367–73.