EDITORIAL COMMENT

José Paulo Andrade
Department of Biomedicine, Unit of Anatomy,
Faculdade de Medicina da Universidade do Porto

The prognostic value of some neglected hematological parameters in carotid artery disease

In 1988, when I was a young resident in the first year of the Clinical Pathology residency in the Emergency Laboratory, we had to perform parts of the complete blood count (CBC) manually. It took approximately 1 minute to have the blood ready to be introduced in a first-generation CBC automated analyzer. The analyzer would give us the basic CBC and hemoglobin values, and the white blood differential was performed in certain selected cases by identifying and counting the cells in a blood smear under a microscope. The values were expressed as relative percentages, and the morphology of the red blood cells and platelets was qualitatively reported. Fortunately, new CBC analyzers were introduced that same year in the Hematology and Emergency Laboratories. The new analyzers presented a series of new parameters, the RDW (red blood cell distribution width) and PDW (platelet distribution width). The word "width" in the RDW and PDW tests does not mean the size of individual red blood cells or platelets. Instead, it refers to the difference in size from the largest to the smallest cells. Most of the CBC counters calculate RDW as a coefficient of variation (CV), and it is expressed as a percentage (12-15%), thus reflecting the distribution curve of the corpuscular volume. I noticed that no one was looking at those still new parameters. At that time I designed some small studies about RDW and presented them in Internal Medicine meetings. One was called "The value of RDW in ferropenic anemias," presenting the classification of anemias based on the RDW and the mean corpuscular volume (MCV). Another was called "RDW is not related to reticulocyte count", where the reticulocyte count was performed manually. At that time, RDW was already seen as a strong marker of iron deficiency, as it often rises before the mean corpuscular volume falls, acting as an early diagnostic clue.

Fast forward to the 21st century. RDW is still a little neglected, but now, evidence has accumulated showing that there is a strong link between RDW and inflammation, and it may have prognostic value in nonhematological pathologies.[1] This is particularly prominent in cardiovascular disorders, and RDW-CV was associated with the incidence of myocardial infarction and stroke.[1] It was also described as a good predictor of mortality in coronary artery disease in patients undergoing percutaneous coronary intervention and ischemic stroke.[2,3] Concerning RDW-CV and carotid atherosclerosis, an association between RDW-CV and carotid intimal thickness was found.[4] and the Tromsø Study found that increased RDW was a predictor of carotid plaque development and progression.[5] It was advanced that the high values of RDW may reflect deficiencies of the integrity of the cell membrane by inducing adhesion between RBCs and endothelium with effects on multiple organ systems and, consequently, associated with adverse outcomes.[1] With these data in mind, Duarte-Gamas et al. in a paper I also co-authored,[6] hypothesized that if there is a high prognostic value of RDW-CV in the aforementioned clinical situations, it could be used to predict long-term outcomes after carotid endarterectomy (CEA). It was found that RDW-CV was associated with MACE (major adverse cardiovascular events defined as a composite outcome of non-fatal myocardial infarction, acute heart failure, and all-cause mortality), myocardial infarction, and all-cause mortality in patients submitted to CEA. The associations were maintained for long-term all-cause mortality and MACE even after adjustment for hemoglobin levels, a potential confounding factor.

The role of inflammation and oxidative stress as culprits of atherosclerosis led Pereira-Neves *et al.*[7,8] to write a narrative review of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) concerning their prognostic ability in patients with carotid artery disease. The review of these easily obtained hematological ratios included 18 papers with a total of 5339 patients. It was known that NLR was linked to prolonged low-grade inflammation presenting a positive correlation with high-sensitivity C-reactive protein,[9] and PLR was associated with cardiovascular diseases.[10] Both neutrophils and platelets have been implicated in pro-inflammatory status and repair, and there are suggestions of an active role in atherogenesis

due to activation of the complement cascade and cytokine production.[10,11]

As inflammation markers, it was not surprising to find that these hematological ratios revealed an ability to predict outcomes in patients presenting carotid artery disease. In detail, NLR and PLR may predict sub-clinical atherosclerosis and atherosclerosis progression in carotid artery disease. Moreover, they also predict the propensity for carotid stenosis to become symptomatic and morbidity after CEA and carotid stenting. More importantly, these hematological ratios may potentially identify patients with increased susceptibility to becoming symptomatic and with a higher likelihood of postoperative morbidity.

An important caveat: each clinical laboratory should estimate their own reference values as they are not only instrument-dependent but also population-dependent. The advantages of these hematological biomarkers (RDW, NLR, PLR) is that their quantification is fast, easy, inexpensive, and almost universally present and available in all automatic CBC counters. They can not provide definitive prognostic information, but they can supplement clinical decision-making to manage carotid artery disease when understood and used correctly. The information they can deliver is clinically valuable, and these markers can help assess patients who can benefit from CEA.

REFERENCES

1. Tonelli M, Wiebe N, James MT, Naugler C, Manns BJ, Klarenbach SW, et al. Red cell distribution width associations with clinical outcomes: A population-based cohort study. PLoS One. 2019;14(3):e0212374.
2. Poludasu S, Marmur JD, Weedon J, Khan W, Cavusoglu E. Red cell distribution width (RDW) as a predictor of long-term mortality in patients undergoing percutaneous coronary intervention. Thromb Haemost. 2009;102(3):581-7.
3. Ye WY, Li J, Li X, Yang XZ, Weng YY, Xiang WW, et al. Predicting the One-Year Prognosis and Mortality of Patients with Acute Ischemic Stroke Using Red Blood Cell Distribution Width Before Intravenous Thrombolysis. Clin Interv Aging. 2020;15:255-63.
4. Ren D, Wang J, Li H, Li Y, Li Z. Red blood cell distribution width and carotid intima-media thickness in patients with metabolic syndrome. BMC Cardiovasc Disord. 2017;17(1):44.
5. Lappegard J, Ellingsen TS, Vik A, Skjelbakken T, Brox J, Mathiesen EB, et al. Red cell distribution width and carotid atherosclerosis progression. The Tromso Study. Thromb Haemost. 2015;113(3):649-54.
6. Duarte-Gamas L, Pereira-Neves A, Jacome F, Fragao-Marques M, Vaz RP, Andrade JP, et al. Red Blood Cell Distribution Width as a 5-Year Prognostic Marker in Patients Submitted to Carotid Endarterectomy. Cerebrovasc Dis Extra. 2020;10(3):181-92
7. Pereira-Neves A, Fragão-Marques M., Rocha-Neves J., Gamas L., Oliveira-Pinto J., Cerqueira A., Andrade J.P., Fernando--Teixeira J. The Impact of Neutrophil-to-Lymphocyte Ratio and Platelet-To-Lympocyte Ratio in arotid Artery Disease. SPCCTV. 2021.28(1)
8. Pereira-Neves A, Rocha-Neves J, Fragao-Marques M, Duarte--Gamas L, Jacome F, Coelho A, et al. Red blood cell distribution width is associated with hypoperfusion in carotid endarterectomy under regional anesthesia. Surgery. 2021.
9. Akpek M, Kaya MG, Lam YY, Sahin O, Elcik D, Celik T, et al. Relation of neutrophil/lymphocyte ratio to coronary flow to in-hospital major adverse cardiac events in patients with ST--elevated myocardial infarction undergoing primary coronary intervention. Am J Cardiol. 2012;110(5):621-7.
10. Kim H, Conway EM. Platelets and Complement Cross-Talk in Early Atherogenesis. Front Cardiovasc Med. 2019;6:131.
11. Rosinska J, Ambrosius W, Maciejewska J, Narozny R, Kozubski W, Lukasik M. Association of platelet-derived microvesicles and their phenotypes with carotid atherosclerosis and recurrent vascular events in patients after ischemic stroke. Thromb Res. 2019;176:18-26.