Red blood cell distribution width (RDW) and human pathology. One size fits all

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Red blood cell distribution width (RDW), an index of variation of erythrocyte volume (i.e., anysocytosis), is conventionally included in a standard complete blood count (CBC). In brief, this parameter is automatically calculated by dividing the standard deviation (SD) of erythrocyte volume from the mean corpuscular volume (MCV). The result of this straightforward equation is then multiplied by 100 to express results in percentage (%). According to the “Holy Bible” of laboratory medicine (i.e., Henry’s Clinical Diagnosis and Management by Laboratory Methods) [1], the conventional reference range of RDW is roughly comprised between 12% and 15%.

The RDW has been historically used to help classify anemia because it reflects the degree of variation in erythrocyte size. In fact, the value of this parameter increases in parallel with anysocytosis, so that when an elevated RDW is reported on the CBC, a marked anysocytosis is also expected after revision of the peripheral blood smear (Figure 1). The RDW is thus conventionally increased in patients with anemia attributable to iron deficiency, deficit of folic acid and/or vitamin B12, as well as in patients with autoimmune disorders, myelodysplastic syndrome, hemolytic anemia, liver impairment, sickle cell disease and blood transfusions [2]. Recently, however, RDW has found some new, intriguing and appealing applications in human pathology.

The first ever report that RDW could be used in clinics beyond the differential diagnosis of anemia was published by Felker et al. in 2007 [3]. This study was divided into two parts. In the former, 2679 symptomatic chronic heart failure patients from the North American Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program were tested for a broad range of laboratory measures, thus obtaining Cox’s proportional hazards model between routine blood tests and outcomes. The findings were thus replicated in a cohort of 2140 patients with symptomatic heart failure from the Duke Databank. In the first cohort of patients RDW was found to be significantly associated with cardiovascular death or hospitalization for heart failure (HR 1.17; 95% CI 1.10–1.25). Identical results were then obtained in the replication cohort, in which RDW was also significantly and independently associated with all-cause mortality (HR 1.29; 95% CI 1.16–1.43). Another milestone was published by Tonelli et al. in 2008 [4]. RDW was assessed in 4111 subjects with hyperlipidemia and a history of prior myocardial infarction, selected from the Cholesterol and Recurrent Events study. By using Cox’s proportional hazards models, RDW was found to be independently associated with adjusted risk of all-cause mortality (HR per percent increase in RDW 1.14; 95% CI 1.05–1.24). Even more importantly, this parameter was significantly associated with a number of secondary endpoints, including fatal coronary disease or non-fatal myocardial infarction (HR 1.08; 95% CI 1.00–1.17), stroke (HR 1.20; 95% CI 1.05–1.37) and symptomatic heart failure (HR 1.15; 95% CI 1.05–1.26). A third important paper was published in the following year by Lippi et al. [5], who first demonstrated the existence of a strong, graded and independent association between RDW and subclinical inflammation, thus providing a convincing pathophysiological basis to the clinical evidence previously published by Felker and Tonelli [3, 4]. In the same year, two independent and very large population studies showed that higher RDW is associated with increased overall mortality also in the general population [6, 7].

There is an ongoing, virtually spasmodic search for simple and inexpensive biomarkers that may provide clinically useful (and usable) information on future risk of mortality and morbidity [8]. It is hence noteworthy that, after the publication of the first study by Felker et al. in 2007 [3], the number of papers about RDW as predictor of morbidity and mortality in health and disease has exponentially increased, with a mean raise of 27% per year (Figure 2). More recently, this journal has also published some original research that have further expanded the
boundaries of potential clinical applications of RDW, for prediction of survival in patients with liver disease [9] and Eisenmenger syndrome [10], as well as for prognostication of chronic pulmonary hypertension in patients with acute pulmonary embolism [11]. A recent study published in this issue of the journal has also convincingly demonstrated that both gender and age are important determinants of RDW, and hence the reference ranges along with the diagnostic/decisional thresholds should be revised accordingly [12]. Another important aspect that should be clearly acknowledged is that RDW may vary widely according to the analytical technique used for measuring the erythrocyte volume, the different algorithms used for partitioning the distribution and the position in the red blood cell histogram that is chosen for calculating the SD of erythrocyte volumes, so that reference ranges may span from 10.7%–13.8% up to 11.9%–15.3% using different routine hemocytometers [13, 14].

In everyday life, as well as in laboratory diagnostics, there is a false assumption that more complicated and expensive tools work better than others. However, this does not always hold true. RDW is a simple equation which is automatically generated by all routine hemocytometers, and does not require additional costs, specific activities or complex interpretation. Although it has not been definitely established whether anysocytosis is directly involved in the pathogenesis, or merely behaves as a biomarker of underlying human disorders, such as inflammation, oxidative damage, impaired liver or kidney function and malnutrition [15], it seems now undeniable that the clinical applications of this straightforward and inexpensive parameter should be broadened far beyond the differential diagnosis.
of anemia. It is also noteworthy, however, that the association between this parameter and outcome measures or clinical endpoints in cohort studies cannot be thoughtfully applied to diagnosis and prognostication of single individuals. As in other field of diagnostics [16], the clinical judgment will remain essential, since RDW cannot be regarded as the “panacea” of the new century.

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References


*Corresponding author: Giuseppe Lippi, U.O. Diagnostica Ematochimica, Azienda Ospedaliero-Universitaria di Parma, Via Gramsci, 14, 43126 Parma, Italy, Phone: +39 0521 703050/ -39 0521 703791, E-mail: gilippi@ao.pr.it; ulippi@tin.it, http://orcid.org/0000-0001-9523-9054 and Laboratory of Clinical Chemistry and Hematology, Academic Hospital of Parma, Parma, Italy and Associate Editor of Clinical Chemistry and Laboratory Medicine

Mario Plebani: Department of Laboratory Medicine, University Hospital of Padua, Padua, Italy and Editor in Chief of Clinical Chemistry and Laboratory Medicine