Red blood cell distribution width: A simple parameter with multiple clinical applications

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Abstract
The red blood cell distribution width (RDW) is a simple and inexpensive parameter, which reflects the degree of heterogeneity of erythrocyte volume (conventionally known as anisocytosis), and is traditionally used in laboratory hematology for differential diagnosis of anemias. Nonetheless, recent evidence attests that anisocytosis is commonplace in human disorders such as cardiovascular disease, venous thromboembolism, cancer, diabetes, community-acquired pneumonia, chronic obstructive pulmonary disease, liver and kidney failure, as well as in other acute or chronic conditions. Despite some demographic and analytical issues related to the routine assessment that may impair its clinical usefulness, an increased RDW has a high negative predictive value for diagnosing a variety of disorders, but also conveys important information for short- and long-term prognosis. Even more importantly, the value of RDW is now being regarded as a strong and independent risk factor for death in the general population. Although it has not been definitely established whether an increased value of RDW is a risk factor or should only be considered an epiphenomenon of an underlying biological and metabolic imbalance, it seems reasonable to suggest that the assessment of this parameter should be broadened far beyond the differential diagnosis of anemias. An increased RDW mirrors a profound deregulation of erythrocyte homeostasis involving both impaired erythropoiesis and abnormal red blood cell survival, which may be attributed to a variety of underlying metabolic abnormalities such as shortening of telomere length, oxidative stress, inflammation, poor nutritional status, dyslipidemia, hypertension, erythrocyte fragmentation and alteration of erythropoietin function. As such, the aim of this article is to provide general information about RDW and its routine assessment, to review the most relevant implications in health and disease and give some insights about its potential clinical applications.

Keywords
Hematology, mortality, RDW, red blood cell distribution width, risk factor

Abbreviations:
AC: acute coronary syndrome; AUC: area under the curve; AMI: acute myocardial infarction; BARD: body mass index, aspartate aminotransferase/alanine aminotransferase ratio, diabetes; BNP: B-type natriuretic peptide; CAP: community-acquired pneumonia; CAD: coronary artery disease; CHA2DS2-VASc: congestive heart failure/left ventricle dysfunction, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; CVD: cardiovascular disease; EGFR: estimated glomerular filtration rate; FIB-4: fibrosis 4; HDL: high-density lipoprotein; HER2: epidermal growth factor receptor 2; HIV: human immunodeficiency virus; HR: hazard ratio; ICARIA: Ibermutuamur Cardiovascular Risk Assessment; ICH: International Council for Standardization in Haematology; ICU: intensive care unit; JUPITER: Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL: low density lipoprotein; MACE: major adverse cardiac events; MCV: mean corpuscular volume; MRproADM: mid-regional pro-adrenomedullin; NAFLD: nonalcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis;
Introduction about red blood cell distribution width

Red blood cells (RBC), also conventionally known as erythrocytes, are the most common type of blood cell. The main function of these corpuscular elements in vertebrate organisms is to deliver oxygen through the circulatory system from the lung to the peripheral tissues. In mammals, erythrocytes lack a nucleus and are typically shaped as biconcave disks, flattened and depressed in the center, with a dumbbell-shaped cross section and a torus-shaped rim on the edge of the disk. Erythrocyte volume varies widely across different vertebrate species. In humans, RBCs have a diameter ranging from 6 to 8 μm and a thickness of 2 μm. The overall (physiologic) volume of an erythrocyte is hence typically comprised between 80 and 100 fL, with an overall surface of 136 μm² approximately.

Under particular circumstances, RBCs may be subjected to remarkable increases or decreases in their typical volume. The intrinsic plasticity of the plasma membrane and the relative modest content of intracellular molecules (principally hemoglobin), allows remarkable contraction and expansion of size and volume. Erythrocytes can thus swell up to a 150 fL spherical shape (i.e. macrocytosis), or decrease in size to 60 fL or even lower (i.e. microcytosis) without significant loss of membrane continuity and cell injury. The degree of heterogeneity of RBC volume, which is traditionally known as anisocytosis, is conventionally quantified by means of a simple equation, in which the standard deviation (SD) of RBC volumes is divided by the mean corpuscular volume (MCV) of the erythrocytes, and then further multiplied for 100, to express data as a percentage (i.e. \[ \frac{\text{SD of RBC volumes}}{\text{MCV}} \times 100 \]). The result of this equation is finally known as RBC distribution width (RDW; Figure 1). Since the RDW is mathematically derived from the MCV, its value may be significantly influenced by the average erythrocyte volume (i.e. the MCV). The observation of a RDW value below the conventional reference range is infrequent and clinically meaningless, whereas an increase of the value over an instrument-specific cut-off mirrors the presence of anisocytosis, which may be attributable to the presence of small and large RBCs, or both.

Physiological determinants of RDW

One of the leading technical issues in routine assessment of RDW is that the reference range is highly analyzer-dependent, as will be specifically discussed in the following section. As reported by Ricos et al., the within-subject and between-subject biologic variations are 3.5 and 5.7%, respectively. Besides pathological causes that may enhance RBC size heterogeneity, which will also be specifically reviewed below, the RDW can vary across a discrete number of physiological conditions (Table 1).

The hormone erythropoietin, which regulates bone marrow production, maturation and erythrocyte survival, is indeed one of the major determinants of RDW. It was in fact proven...
that both abnormal erythropoietin production and erythropoietin hyporesponsiveness may induce a gradual increase in RDW values.\textsuperscript{6,7}

A gradual increase of RDW with ageing has been convincingly reported in the scientific literature. Nearly 10 years ago, Cheng et al. originally described that RDW tended to increase in parallel with age in the very large US National Health and Nutrition Examination Survey III (NHANES III), including approximately 25,000 civilian non-institutionalized US citizens, although precise information about this parameter was lacking in the published data.\textsuperscript{8} In a further sub-analysis of the NHANES III including 8175 community-dwelling adults aged 45 and older\textsuperscript{9}, Patel et al. reported that older subjects were more likely to have higher RDW values (highest versus lowest quintile of RDW: 66 versus 58 years; \(p<0.001\)). No significant gender differences in RDW values were observed. The positive correlation between age and RDW was confirmed in two subsequent epidemiological investigations. Chen et al. studied 3226 participants aged 35 years and without cardiovascular disease (CVD) or cancer at baseline\textsuperscript{10}, and found that subjects in the highest RDW quartile were significantly older than those in the lowest quartile (57 versus 52 years; \(p<0.001\)). A marginally but statistically significant increased prevalence of males was also observed when comparing subjects in the highest and lowest quartile of RDW (49% versus 46%; \(p<0.021\)). Bornè et al. measured RDW in 26820 participants in the Malmö Diet and Cancer study aged 45 years and older (62% females) without history of myocardial injury or stroke\textsuperscript{11}. The subjects in the highest RDW quartile were found to be significantly older than those in the lowest (59 versus 57 years; \(p<0.001\)). However, no significant sex differences were appreciated across the four quartiles of RDW. More recently, Qiao et al. measured the RDW value in 1259 healthy subjects (584 males and 675 females), and found a consistent trend towards increased values in the elderly\textsuperscript{12}, with no significant sex differences. In a following investigation in a cohort of 1907 ostensibly healthy blood donors (562 females and 1345 males), Lippi et al. reported that the RDW consistently increased across different age groups, with a median RDW value approximately 11% higher in subjects aged 60 years or older compared to those aged less than 60 years (14.6% versus 13.2%; \(p<0.001\)), and nearly 20% higher in the highest age group (>90 years; RDW, 15.7%) compared to the lowest age group (≤41 years; RDW, 13.1%; \(p<0.001\))\textsuperscript{13}. Interestingly, the median RDW value was also found to be slightly but significantly higher in the female gender compared to males (13.8% versus 13.3%; \(p=0.001\)).

There is only limited information about the potential differences of RDW values among different ethnic cohorts. Saxena and Wong studied 663 whites, 697 blacks, 535 Latin-Americans and 247 Asians, and found that RDW values were significantly higher in blacks that in the other ethnic cohorts\textsuperscript{14}. Similarly, in the NHANES III study, the prevalence of non-Hispanic blacks was also substantially higher in the highest versus the lowest quintile of RDW values (22% versus 4%; \(p<0.001\)), whereas the prevalence of non-Hispanic whites was consequently lower (70% versus 88%; \(p<0.001\))\textsuperscript{9}. In a further sub-analysis of the NHANES III study\textsuperscript{15}, the mean RDW value was found to be significantly higher in Blacks compared to Whites and other ethnicities.

A modest but significant increase in RDW values after physical exercise has been recently reported in three separate investigations, and more specifically after moderate\textsuperscript{16}, long-distance\textsuperscript{17} and exhaustive running\textsuperscript{18}.

With regard to pregnancy, Shehata et al. longitudinally followed 121 pregnant women from 16 weeks gestation to 7 days postpartum\textsuperscript{19}, and reported that the RDW values remained almost unchanged in the period between the 16th and 34th week of gestation, significantly increased between the 34th week of gestation and the onset of labor, but then returned to baseline during the 7 days postpartum. In a separate investigation, Lurie also prospectively followed a group of healthy pregnant women, by assessing RDW between the 12th and the 36th week of gestation and during the latent phase of labor\textsuperscript{20}. In contrast with the previous study, a significant increase of RDW could be observed between the 20th and 32nd weeks, whereas the values thereafter declined towards delivery.

Taken together, the available data suggests that erythropoietin stimulation, ageing, black ethnicity, physical exercise and probably pregnancy should be regarded as determinants of increased RDW values, whereas the relationship between anisocytosis and gender appears contradictory across different epidemiological investigations.

### Laboratory assessment of RDW

The modern automated hematological analyzers generate a broad series of histograms by plotting the signals obtained from each individual cell passing through specific channels. The distribution curve of erythrocyte volumes is an integral part of RBC automated hematology analysis, and is hence supplied by virtually all instruments currently available in the market. Despite this important premise, the methods used for RBC analysis and RDW calculation differ widely among the most commonly used hematological analyzers (Figure 2).

Blood cell enumeration and sizing in instruments manufactured by Beckman Coulter (Beckman Coulter Inc., Brea, CA) are based on the method originally developed by Wallace H. Coulter nearly 60 years ago (i.e. the “Coulter Principle”)\textsuperscript{21}. In brief, a suspension of blood cells is passed through a small orifice along with an electric current. The individual blood element generates an impedance change in the orifice, which is directly proportional to the cell size. The system counts the individual cells and also provides a size distribution. The RDW is then calculated at the 20% height level above the baseline of the RBC histogram. In Abbott hematological analyzers (Abbott Diagnostics, Abbott Park, IL), the RBC volume is also measured by impedance

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**Table 1. Physiological determinants of increased RDW.**

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Description</th>
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<tr>
<td>– Erythropoietin deficiency and hyporesponsiveness</td>
<td></td>
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<tr>
<td>– Ageing</td>
<td></td>
</tr>
<tr>
<td>– Black ethnicity</td>
<td></td>
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<td>– Physical exercise</td>
<td></td>
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<td>– Pregnancy</td>
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technology after isovolumetric sphering, and RDW is then calculated from the RBC histogram at the 50% height level above the baseline of the histogram along with thresholds set at 4% of modal height. In instruments manufactured by Siemens (Siemens Healthcare Diagnostics, Tarrytown, NY), the RBC is analyzed by means of flow cytometry and 2-angle laser light scatter. The erythrocytes are isovolumetrically sphered, so that the optical scatter is no longer dependent upon the cell shape as for impedance-based analyzers. Accordingly, as the cells pass through the laser beam, the final measurement is based on the degree of scatter. The RDW is then calculated from the RBC histogram in a limited window ranging between 60 and 120 fL. In hematological analyzers produced by both Sysmex (Sysmex Corporation, Kobe, Japan) and Mindray (Shenzhen, China), the erythrocyte size is not directly measured, but it is obtained by dividing the hematocrit for the RBC count. In both cases, the RDW is then calculated at a relative height of 20% above the baseline of RBC histogram.

Rather predictably, this broad heterogeneity in both erythrocyte sizing and RDW calculation is reflected in the current laboratory practice by a lack of harmonization across the different analyzers. Buttarello and Plebani assessed the RDW in 220 healthy subjects with five different hematological analyzers and observed a large bias in both the median RDW value and the reference range, with percentage bias ranging from 1% to 24%22. In a following study, Lippi et al., investigated the analytical performance and comparability of RDW obtained with four different hematological analyzers23. Although the imprecision (i.e. coefficient of variation) was found to be excellent and comprised between 0.3 and 1.2%, the percentage bias varied from 2.1% to 6.8%, thus always exceeding the desirable quality specifications for this parameter (i.e. ±1.7%)4. Similar data were also published by Qiao et al., who observed a percentage bias between 3% and 7% by measuring RDW in 1259 blood samples with three different hemocytometers12. In agreement with the technological heterogeneity for erythrocyte sizing and calculating the SD of RBC volumes (Figure 2), the results of these separate investigations demonstrate that RDW values obtained with Sysmex, Mindray and Beckman Coulter hemocytometers are globally comparable but basically higher than those obtained with Siemens instrumentation, whereas values obtained with hematological analyzers manufactured by Abbott appear to be the lowest overall12,22,23.

The predictable conclusion of these studies is that the current lack of harmonization should be regarded as a serious limitation for comparability of RDW values obtained with different hematological analyzers, thus virtually hampering the use of universal reference ranges and univocal decision thresholds across clinical laboratories and epidemiological investigations that use different instrumentation. It is also noteworthy that the International Council for Standardization in Haematology (ICSH) has published, nearly 25 years ago, an official recommendation aimed to promote the standardization of RBC distribution curve analysis24, but this suggestion has been mostly overlooked by the manufacturers, as is clearly noticeable in Figure 2. The widespread adoption of the ICSH recommendations should hence be encouraged to reach a much better degree of harmonization.

RDW in erythrocyte disorders

For many years, RDW has been almost exclusively used for the differential diagnosis of anemias. Although a specific
description of the clinical usefulness of this parameter for troubleshooting erythrocyte disorders has been broadly covered in the past and is hence outside the aim of this article, it seems appropriate to provide a general overview. For practical purposes, the various forms of anemia are classified according to the MCV value, as microcytic (decreased MCV), normocytic (normal MCV) or macrocytic (increased MCV). The combination of MCV and RDW allows a further sub-classification, as reported in Table 2. As a general rule, anemias caused by nutritional deficiencies (such as iron, folate or vitamin B₁₂) tend to be associated with a greater degree of anisocytosis than those caused by genetic defects or primary bone marrow disorders. Although this classification seems helpful to investigate the underlying cause of anemia, potential overlaps exist among the different conditions, particularly with regard to anemia of chronic disease.

### RDW and human disorders

The number of articles investigating the relationship between RDW and human disorders has exponentially increased over the past decades. It is in fact noteworthy that when using “RDW” and “red blood cell distribution width” as keywords in the Scopus database, the number of items retrieved has increased from 5 in the 1970s, to 86 in the 1980s, 206 in the 1990s, up to 418 in the 2000s. Even more pervasively, 461 articles have already been published in the 4 years since 2010, a number that might already be a physiological limit given the exponential increase in the number of related searches. Over the past decades, it has been increasingly recognized that RDW and RDW, not MCV alone, are useful biomarkers to identify patients at increased risk of adverse outcomes in many common disorders, including cardiovascular diseases (CVD), cancer, metabolic disorders, chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes, and others, as evidenced by the large number of articles investigating this relationship, as reported in Table 2.

#### RDW in Cardiovascular Disease

RDW has been investigated in a number of cardiovascular disorders, and has also been recently proposed as a predictive biomarker of adverse outcomes in patients with these conditions. In this section of the article, the most important evidence published to date about the relationship between RDW and coronary artery disease (CAD), coronary artery ectasia, heart failure, atrial fibrillation, stroke and peripheral occlusive artery disease is reviewed.

#### RDW in Myocardial Infarction and Coronary Artery Disease

One of the first studies to assess the role of RDW in CAD was published by Fukuta et al. in 2009. The values of RDW and the plasma levels of B-type natriuretic peptide (BNP) were measured in 226 consecutive patients undergoing cardiac catheterization for CAD. In stepwise multivariate linear regression, the values of RDW were found to be marginally but significantly associated with those of BNP (beta coefficient = 0.477; \( p < 0.01 \)) after adjustment for age, body mass index, renal function, lactate dehydrogenase and hemoglobin. It was hence first hypothesized that the chronic inflammatory state and the neurohumoral activation that are common in patients with CAD may also play a role in increasing the degree of anisocytosis in patients with this condition.

In the same year, Lippi et al. measured RDW in 456 consecutive patients with chest pain and acute coronary syndrome (ACS) who were admitted to the emergency department over a 1-year period. Patients with a final diagnosis of ACS were found to have higher RDW values than those without (15.1% versus 13.5%; \( p < 0.001 \)). The area under the curve (AUC) of RDW for diagnosing ACS was 0.71 (95% CI: 0.69–0.72), with sensitivity of 0.79 and specificity of 0.50 at a cut-off value of 14%.

Nabais et al. also measured RDW in 1796 patients admitted to a coronary care unit with ACS. A higher RDW value was associated with both 6-month overall mortality and 6-month death for ACS. The adjusted odds ratio (OR) and 95% confidence interval (95% CI) for 6-month overall mortality were 1.43 (95% CI: 1.00–2.05) comparing patients in the highest versus the lowest RDW tertile, whereas the adjusted OR for 6-month death for ACS was 1.16 (95% CI: 1.03–1.30) per 1% increase in RDW.

Azab et al. prospectively followed 619 patients with non-ST-segment elevation myocardial infarction (NSTEMI). Patients in the highest RDW tertile had significantly higher risk of both in-patient and 4-year mortality compared to those with lower RDW levels.

### Table 2. Classification of anemias according to values of mean corpuscular volume (MCV) and red blood cell distribution width (RDW).

<table>
<thead>
<tr>
<th>RDW value</th>
<th>Decreased MCV</th>
<th>Normal MCV</th>
<th>Increased MCV</th>
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<tbody>
<tr>
<td>Normal</td>
<td>– Anemia of chronic disease</td>
<td>– Anemia of chronic disease</td>
<td>– Aplastic anemia</td>
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<td></td>
<td>– Heterozygous thalassemia</td>
<td>– Acute blood loss or hemolysis</td>
<td>– Chronic liver disease</td>
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<tr>
<td></td>
<td>– Hemoglobin E trait</td>
<td>– Anemia of renal disease</td>
<td>– Chemo/therapy/antispravals/alcohol</td>
</tr>
<tr>
<td>Increased</td>
<td>– Iron deficiency</td>
<td>– Early Iron deficiency</td>
<td>– Immune hemolytic anemia</td>
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<tr>
<td></td>
<td>– Hemolytic anemia</td>
<td>– Early vitamin B₁₂, folate deficiency</td>
<td>– Vitamin B₁₂, folate deficiency</td>
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<tr>
<td></td>
<td>– HbS/Beta Thalassaemia</td>
<td>– Transfusions</td>
<td>– Hereditary spherocytosis</td>
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<tr>
<td></td>
<td>– Microangiopathic hemolytic anemia</td>
<td>– Chronic hepatobiliary disease</td>
<td>– Sickle cell anemia</td>
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in the lowest tertile. The adjusted hazard ratio (HR) for 4-year all-cause mortality was found to be enhanced by 1.10 (95% CI: 1.004–1.213) for each one unit increase in RDW.

Lappé et al. also studied 1489 patients with CAD, who were followed up for a period of 8.4–15.2 years.33 In stepwise analysis, RDW was found to be a significant predictor of all-cause mortality (HR of highest versus lowest RDW quintile, 1.37; 95% CI: 1.29–1.46).

Cemin et al. measured RDW in 1971 consecutive patients admitted to the emergency room for chest pain of suspected cardiac origin, and although the RDW was not found to be a significant predictor of ACS in men, women with ACS had a higher RDW compared to those without (14.4% versus 13.7%; p = 0.008). It is also noteworthy that in this study RDW was found to be a significant predictor of ACS in the entire study population (AUC: 0.61; 95% CI: 0.54–0.68).

Cavusoglu et al. measured RDW in a cohort of 389 male patients undergoing coronary angiography for suspected ACS, and reported that patients in the highest RDW tertile had a reduced survival compared to those in the lower two tertiles combined (HR: 2.69; 95% CI: 1.50–4.84).

Dabbah et al. investigated the baseline values and the relative change in RDW during hospital course in 1709 patients with acute myocardial infarction (AMI), who were followed up for a median period of 27 months.36 Compared to patients in the lowest quintile of RDW, those in the highest quintile displayed an adjusted HR for death of 2.8 (95% CI: 1.6–4.7). A RDW increase during hospital course was also found to be significantly associated with death (HR for 1-SD increase in RDW, 1.13; 95% CI: 1.02–1.25).

Uyarel et al. retrospectively studied 2506 consecutive ST elevation myocardial infarction (STEMI) patients who underwent primary percutaneous coronary intervention (PCI), and were followed for a mean period of 1.8 ± 1.3 years. A higher mortality rate and a worse long-term cardiovascular prognosis were both observed in patients with elevated RDW at admission. In particular, elevated admission RDW exhibited a HR of 1.83 (95% CI: 1.03–3.24) for predicting cardiovascular mortality.

Wang et al. measured RDW on admission in 1654 consecutive patients diagnosed with ACS. Higher RDW values were associated with increased 1-month heart failure and recurrent infarction (OR: 2.13; 95% CI: 1.60–2.84), as well as with 1-month cardiac mortality (OR: 2.12; 95% CI: 1.43–3.14).

Gul et al. performed a prospective study including 310 patients with NSTEMI, who were followed up for 3 years, and observed that an increased RDW value at admission (i.e., >14%), which was significantly associated with cardiovascular mortality (HR: 3.2; 95% CI: 1.3–7.78).

Uysal et al. investigated the association between RDW and STEMI by studying 198 young AMI patients (41 ± 4 years), 172 elderly AMI patients (64 ± 10 years) and 91 young and 65 elderly control individuals. Higher RDW values were found in young AMI patients compared to young controls (14.1% versus 13.4%, p < 0.01), whereas the RDW value was slightly but not significantly higher in elderly AMI patients than in elderly controls (13.7% versus 13.5%; p = 0.10). In multivariable logistic regression analysis, elevated RDW levels were independent predictors of STEMI in young patients (OR: 3.37; 95% CI: 2.98–5.58).

Çetin et al. performed a cross-sectional and observational study, including 296 consecutive patients undergoing coronary angiography for suspected CAD. The RDW values were found to be significantly increased in patients with a final diagnosis of CAD than in those without, and were also significantly higher in patients with more severe CAD (i.e., ≥50% stenosis). The sensitivity and specificity of RDW for detecting CAD were 0.68 and 0.52, respectively.

Vayá et al. measured RDW before hospital discharge in 119 consecutive AMI patients, who were followed for a mean period of 21 months. An increased RDW value (i.e., >14%) was significantly associated with the risk of recurrent cardiovascular events (OR: 6.19; 95% CI: 2.1–18.5).

In an observational, cross-sectional study including 503 adult patients undergoing coronary angiography, et al. reported that increased RDW values on admission (i.e., >16.3%) were significantly associated with higher recourse to coronary artery bypass graft compared to non-surgical strategy (OR: 2.39; 95% CI: 1.04–5.50).

Isik et al. prospectively followed 100 consecutive patients with STEMI, who underwent PCI. The values of RDW were found to be higher in patients with no-reflow (n = 30) than in those with normal reflow (OR: 2.9; 95% CI: 1.4–6.0). An increased RDW value (i.e., >14%) was also associated with higher 6-month mortality (OR: 5.9; 95% CI: 1.6–21.2).

Karabulut et al. retrospectively analyzed the RDW values of 556 patients with STEMI. An elevated RDW value (i.e., >14.8%) was associated with a post-interventional thrombolysis in myocardial infarction (TIMI) flow lower than 3 in multivariate regression analysis (OR: 2.20; 95% CI: 1.01–4.57).

Akin et al. studied 580 consecutive patients with CAD undergoing coronary angiography, and found an increased RDW value in CAD patients with Syntax scores >32 (15.1% versus 14.1%; p < 0.001). The RDW value was also found to be a significant predictor of CAD severity (OR: 1.16; 95% CI: 1.02–1.32) in multiple logistic regression analysis.

Osadnik et al. measured RDW in 2550 consecutive patients with stable CAD undergoing PCI, and who were followed up for a mean period of 2.5 years. The RDW value was found to be significantly associated with mortality in the entire cohort of patients (adjusted HR: 1.23; 95% CI: 1.13–1.35).

Ma et al. studied 677 consecutive subjects who underwent coronary angiography for angina-like chest pain and/or positive treadmill exercise test. Patients with evidence of CAD had significantly higher RDW values compared to controls (13.0% versus 12.7%; p = 0.001). The RDW value and the Gensini score were also positively correlated (r = 0.37, p < 0.001). The RDW was finally found to be an independent predictor of both angiographic CAD (OR: 1.34; 95% CI: 1.02–1.77) and higher Gensini score (OR: 2.23; 95% CI: 1.62–3.08).

Lee et al. studied 1596 consecutive patients with AMI, who were followed up for 12 months. The RDW value was found to be higher in patients with 12-month major adverse cardiac events (MACEs; 13.8% versus 13.3%; p < 0.001), displaying an adjusted HR of 6.18 (95% CI: 2.10–18.21) comparing patients in the highest quartile of RDW to those in the lowest quartile.
In a retrospective cohort study, Ephrem analyzed RDW values in 503 subjects with unstable angina or NSTEMI, who were followed up for a median period of 3.8 years. Patients with elevated RDW values (≥16.3%) had an increased risk of readmission compared to those with normal RDW (HR: 1.35; 95% CI: 1.02–1.79).

Fatemi et al. studied 6689 patients subjected to PCI, and observed that baseline RDW values were significantly higher in patients with major bleeding, vascular complications and in those who needed blood transfusions. In multivariate logistic regression analysis, an increased RDW significantly predicted the risk of major post-procedural bleeding (OR: 1.12; 95% CI: 1.06–1.19).

Demirkol et al. performed a cross-sectional study including 81 patients with CAD and 85 controls, and reported that the RDW values of patients with CAD were significantly higher than in controls (14.0% versus 13.4%; p < 0.01).

Ren et al. studied 1442 patients with stable angina pectoris, who were followed up for 1 year after hospital discharge. The RDW values were found to be significantly associated with clinical outcomes. More specifically, the OR of the highest versus the lowest RDW quartile was 1.54 (95% CI: 1.06–3.22) for cardiac mortality and 1.87 (95% CI: 1.23–3.49) for all-cause mortality.

More recently, Borné et al. studied 26,820 subjects without history of AMI or stroke, who were followed up for 4 years. After adjustment for multiple risk factors, the baseline RDW value was significantly associated with the incidence of fatal coronary events (HR 1.82; 95% CI: 1.35–2.44).

Kurt et al. investigated 251 patients with history of coronary stenting who underwent control coronary angiography (128 with in-stent restenosis and 123 without). Patients with in-stent restenosis had significantly higher RDW values compared to those without (14.5% versus 13.6%; p < 0.001). In multivariate analysis, increased RDW values were independently associated with the risk of in-stent restenosis (OR: 2.12; 95% CI: 1.71–3.15).

Arbel et al. investigated the association of RDW with coronary artery ectasia in 3222 patients undergoing coronary angiography. In multivariable Cox’s proportional hazard analysis, RDW was found to be a significant and independent predictor of 3-year MACE (HR for each 1% increase in RDW, 1.12; 95% CI: 1.07–1.18).

Finally, Yao et al. measured RDW in 2169 patients with CAD, who were subjected to successful PCI and had at least one drug-eluting stent placed. In multivariate Cox regression analysis, increased RDW value was found to be an independent predictor of all-cause mortality (HR: 1.37; 95% CI: 1.15–1.62) or major adverse cardiovascular and cerebrovascular events (HR: 1.21; 95% CI: 1.04–1.39).

**RDW and coronary artery ectasia**

Dogdu et al. measured RDW in 54 patients with coronary artery ectasia without significant stenosis and 40 matched control individuals. Higher RDW values were found in patients than in controls (14.8% versus 13.1%; p = 0.001).

The association between increased RDW and coronary artery ectasia was also investigated by Isik et al. in a retrospective study including 75 patients with isolated coronary artery ectasia and 96 controls with normal coronaries. The value of RDW independently predicted both the presence (OR: 4.91; 95% CI: 2.27–10.64) and severity (OR: 4.92; 95% CI: 1.41–17.13) of isolated coronary artery ectasia.

Guo et al. studied 84 patients with isolated coronary artery ectasia and 60 angiographically normal controls, and found that the RDW values were significantly higher in patients than in controls (12.9% versus 12.5%; p = 0.021). Finally, Li et al. also measured RDW in 113 patients with coronary artery ectasia, 144 patients with CAD and 157 angiographically normal controls. Patients with coronary artery ectasia (RDW value, 13.0%) or CAD (RDW value, 12.9%) displayed higher values compared to controls (RDW value, 12.3%; both p = 0.020). No significant differences were found, however, between patients with coronary artery ectasia or CAD.

**RDW and heart failure**

The association between RDW and heart failure has been thoughtfully reviewed in a previous article published in this journal, so discussion about this topic will be limited to a brief overview. Interestingly, all the studies that have assessed RDW for its capacity to predict the onset of heart failure, as well as the short- and long-term prognosis (i.e. worsening of cardiac function, hospitalization, cardiovascular and non-cardiovascular death) of patients with cardiac dysfunctions have been globally in agreement to attribute a significant diagnostic and prognostic role to this parameter, either alone or in combination with other validated biomarkers such as the natriuretic peptides.

**RDW in atrial fibrillation and stroke**

A limited number of studies have also investigated the relationship between RDW, atrial fibrillation and stroke. Ertaş et al. retrospectively analyzed RDW values and incidence of post-operative atrial fibrillation in 132 patients undergoing coronary artery bypass grafting, and reported that preoperative RDW levels were significantly higher in patients who developed atrial fibrillation on follow up compared to those who did not (13.9% versus 13.3%; p = 0.03).

Ramírez-Moreno et al. performed a cross-sectional study including 224 patients suffering from first-ever ischemic stroke confirmed by magnetic resonance imaging and 224 randomly selected patients free of cerebrovascular disease, and found that RDW (highest versus lowest quartile) was independently associated with the presence of atrial fibrillation (r = 0.148; p = 0.009) and stroke (OR, 5.9; 95% CI, 3.1–11.4).

Kurt et al. studied 320 patients with atrial fibrillation, and found that RDW values were significantly correlated with the stroke risk assessment in non-valvular atrial fibrillation according to the CHA2DS2-VASc score (congestive heart failure/left ventricle dysfunction, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category) score (r = 0.383; p < 0.001). In multiple logistic regression analysis, an increased RDW value (i.e. ≥14%) was a significant predictor of high (≥2) CHA2DS2-VASc score (OR: 1.25; 95% CI: 1.11–1.42).

The association between RDW and post-operative atrial fibrillation was also investigated in 117 patients with...
non-valvular atrial fibrillation\textsuperscript{82}. In comparison with 60 healthy controls, increased RDW values were observed in patients with atrial fibrillation (13.4\% versus 12.6\%; \( p = 0.01 \)). In multivariate logistic regression, a RDW value >12.9\% was found to be an independent predictor of non-valvular atrial fibrillation (OR: 4.18; 95\% CI: 2.15–8.15).

Adamsson et al. studied 27,124 subjects with no previous history of CVD, who were followed up for a mean period of 13.6 years\textsuperscript{83}. Patients with RDW values in the highest versus those in the lowest quartile of RDW had a significantly increased risk for incident atrial fibrillation on follow up (HR: 1.30; 95\% CI: 1.13–1.51) after adjustment for incident AMI or hospitalizations due to heart failure.

**RDW in peripheral artery occlusive disease**

Ye et al. studied 13,039 outpatients with peripheral artery occlusive disease identified by means of non-invasive lower-extremity arterial testing, who were followed-up for a median period of 5.5 years\textsuperscript{84}. Patients in the highest quartile of RDW had a 66\% higher risk of mortality compared to those in the lowest quartile (HR: 1.66; 95\% CI: 1.49–1.85) after adjustment for age, gender, cardiovascular risk factors and co-morbidities. Each 1\% increase in RDW value was associated with a 1.10 (95\% CI: 1.08–1.12) increased HR of death.

In a further cross-sectional study, Zalawadiya et al. investigated 6,950 participants of the NHANES 1999–2004 study\textsuperscript{85}. The rate of subjects with peripheral artery occlusive disease increased significantly across quartiles of RDW, displaying an OR of 1.19 (95\% CI: 1.06–1.34) for having peripheral artery occlusive disease for each unit increase in RDW after adjustment for age, sex, race, body mass index, hypertension, hyperlipidemia, diabetes, smoking, renal function, C reactive protein (CRP), hemoglobin, MCV and nutritional factors.

**RDW in venous thromboembolism**

Zorlu et al. prospectively assessed 136 consecutive patients with acute pulmonary embolism\textsuperscript{86,87}, and found that an increased RDW above 14.6\% at emergency unit admission was independently associated with increased risk for early mortality from acute pulmonary embolism in a fully adjusted multivariate analysis (HR: 15.5; 95\% CI: 1.8–132.1).

Cay et al. measured RDW in 216 patients with deep vein thrombosis and 215 controls\textsuperscript{87}, and reported that the mean RDW value was significantly higher in the former group of patients compared to the latter (OR for deep vein thrombosis, 1.37; 95\% CI: 1.21–1.55).

Rezende et al. also performed a cross-sectional study including 2473 patients with venous thrombosis and 2935 controls\textsuperscript{88}, and found a strong, independent association between RDW and the risk of this condition, with an OR of 3.1 (95\% CI: 2.0–4.8) after adjustment for age, sex, malignancy and co-morbidities.

Similar findings were reported by Zöller et al.\textsuperscript{89}, who measured RDW in 27,042 subjects without previous history of venous thrombosis or cancer enrolled in the Malmö Diet and Cancer study. During a mean follow-up period of 13.8 years, the HR for venous thrombosis in subjects in the fourth quartile of RDW values was 1.74 (95\% CI: 1.38–2.21) compared to those in the bottom quartile.

In another retrospective cohort study including 203 consecutive patients with acute pulmonary embolism, Abul et al. reported that RDW values were significantly higher in patients who developed chronic thromboembolic pulmonary hypertension than in those who did not (HR: 1.58; 95\% CI: 1.09–2.30)\textsuperscript{90}.

Sen et al. measured RDW in 208 consecutive patients hospitalized with a diagnosis of acute pulmonary embolism\textsuperscript{91}, and reported that the RDW was independently associated with a 4.1-fold (95\% CI: 1.2–13.3) increased risk of mortality.

Finally, Wang et al. measured RDW in 56 patients with chronic thromboembolic pulmonary hypertension and 56 sex- and age-matched healthy controls\textsuperscript{92}, and found that an increased RDW value was significantly associated with the presence of chronic thromboembolic pulmonary hypertension (OR: 6.3; 95\% CI: 2.9–13.7).

**RDW in cancer**

In a retrospective case–control study, Spell and co-workers evaluated the RDW changes in 494 patients who had a negative flexible sigmoidoscopy performed over a 5-year period, 225 of whom (46\%) were finally diagnosed with colorectal cancer\textsuperscript{93}. The mean value of the RDW was significantly increased in patients with colorectal cancer compared to those without. Moreover, a remarkable number of patients with both right-sided (84\%) and left-sided (50\%) colorectal cancer were found to have an elevated RDW value. Accordingly, the RDW exhibited sensitivity (0.69) and specificity (0.88) for identifying patients with malignancy.

Ozkalemkas et al. investigated 19 consecutive patients with non-hematologic cancers (5 stomach, 3 gastrointestinal tract, 3 prostate, 2 lung, 1 muscle and 5 of unknown origin)\textsuperscript{94}, and reported that the RDW value was increased above the upper limit of the local reference range in all cases.

Baicus et al. studied 253 consecutive patients with involuntary weight loss admitted in a secondary care university hospital, 61 of whom (24\%) were finally diagnosed with malignancies\textsuperscript{95}. The mean RDW was found to be significantly higher in cancer patients (14.6\% versus 15.1\%; \( p = 0.022 \)), and the AUC of this parameter for diagnosing of cancer was 0.59 (95\% CI: 0.52–0.67).

Seretis et al. carried out a retrospective study to investigate whether RDW was correlated with presence and histopathological features of breast cancer in 14 women with fibroadenomas and 35 with breast cancer\textsuperscript{96}. The mean RDW value was found to be significantly higher in cancer patients (14.6\% versus 15.1\%; \( p = 0.022 \)), and the AUC of this parameter for diagnosing of cancer was 0.59 (95\% CI: 0.52–0.67).

Koma and colleagues retrospectively analyzed data from 332 patients diagnosed with lung cancer\textsuperscript{97}. High RDW values were associated with cancer stage irrespective of comorbidity. An increased RDW value was also associated with worse prognosis. The survival rate of stage I and II patients with increased RDW (\( n = 19 \)) was also lower than that of patients...
with normal RDW. In the multivariate Cox proportional hazard model, increased RDW (i.e. >15%) was a significant and independent predictor of death (HR: 2.15; 95% CI: 1.04–4.46).

Lee et al. studied 146 symptomatic multiple myeloma patients. RDW was correlated to multiple myeloma stage ($p < 0.001$). The complete response rate to therapy was found to be significantly better in patients with normal RDW (i.e. <14.5%) than in those with high RDW (36.6% versus 13.5%; $p = 0.005$). After a median follow up of 47 months, patients with normal RDW had a better progression-free survival than those with increased RDW (24.2 versus 17.0 months; $p = 0.029$). An increased RDW exhibited a HR of 1.69 (95% CI: 1.05–2.75) for predicting poor progression-free survival and a HR of 3.04 (95% CI: 1.16–8.01) for predicting death.

**RDW in diabetes**

Several studies have directly or indirectly investigated whether RDW may be significantly associated with diabetes and its complications. In regards to the epidemiological investigation which directly assessed RDW in relationship with this condition, Veeranna et al. performed a cross-sectional study including 15,343 non-diabetic adults, free of CVD enrolled in the NHANES 1999–2008. A significant association was appreciated between RDW and glycated hemoglobin ($r = 0.27$; $p < 0.001$). The RDW value was also found to be higher in subjects with glycated hemoglobin >5.8% compared to those with glycated hemoglobin $\leq 4.8$% (12.9% versus 12.6%; $p < 0.001$). In multivariable regression analysis, RDW was found to be positively and independently associated with glycated hemoglobin ($\beta$-coefficient, 0.034; $p < 0.001$).

Engström et al. assessed RDW in 26,709 non-diabetic participants aged 45 years and older from the Malmö Diet and Cancer cohort study, who were followed up for a mean period of 14.3 years. The values of glycated hemoglobin consistently increased across quartiles of RDW (from 4.6% to 4.9%, $p < 0.001$) and a 1-SD increment in RDW (i.e. 3.6 fL) was associated with an increase in glycated hemoglobin of 0.10% after adjustment for age, sex, MCV, glucose, waist circumference, body mass index and smoking. In contrast with previous data, the incidence of diabetes was significantly lower in subjects with high RDW at baseline. In particular, subjects in the highest compared to those in the lowest quartile of RDW had a 52% lower risk of developing diabetes after adjustment for age, sex, waist circumference, body mass index, smoking, leukocyte count, MCV and alcohol intake. It could hence be concluded that high RDW was associated with a reduced incidence of diabetes, independent of other risk factors.

In another retrospective study including 2515 community-dwelling adults aged 65 and older, a significant, positive and independent association was found between values of glycated hemoglobin and RDW ($r = 0.11$; $p < 0.001$) after adjustment for age and sex. The glycated hemoglobin values were also found to be significantly higher in patients with increased RDW (i.e. >14.0%) than in those with RDW values below such threshold. Similarly, the rate of patients with glycated hemoglobin $>53$ mmol/mol was significantly higher in patients with increased RDW than in those with RDW $<14.0$.

Useful information about the relationship between RDW and diabetes also indirectly emerges from population cohort trials. In the NHANES III study, subjects in the highest quintile of RDW had a higher prevalence of diabetes compared to those in the lowest quintile. This association remained significant in the entire study population (11.0% versus 7.0%; OR, 1.55; 95% CI, 1.30–1.85), as well as in patients aged 45 years and older (13.6% versus 7.7%; OR, 1.88; 95% CI, 1.50–2.37).

In agreement with these findings, Arbel et al. showed that subjects with RDW values $>17$% had a higher prevalence of diabetes compared to those with RDW $<13$% (12.3% versus 10.1%; OR: 1.25; 95% CI: 1.09–1.42).

Nevertheless, opposite results were found in a Taiwanese population by Chen et al., since subjects in the highest quintile of RDW had a lower prevalence of diabetes compared to those in the highest quintile (9.7% versus 16.6%).

Increased RDW values have also been associated with diabetes-associated complications. Malandrino et al. performed a cross-sectional study in 2497 diabetic participants of the NHANES III aged 20 years and older. After stratification of the study population in quartiles of RDW, subjects in the highest quartile were more likely than individuals in the lowest quartile to have at least one diabetic complication (OR: 2.06; 95% CI: 1.11–3.83). When RDW was entered in a logistic regression model as a continuous variable, the OR of each 1% increment in RDW for predicting the presence of at least one diabetic complication was 1.21 (95% CI: 1.01–1.45) after adjustment for age, sex, race/ethnicity, education, smoking, body mass index, hypertension, total cholesterol, CRP, glycated hemoglobin, duration of diabetes, haemoglobin, albumin, MCV, iron, B12 and folate deficiency. In specific sub-analyses according to the type of diabetic complications, subjects in the highest quartile of RDW were more likely than individuals in the lowest quartile to have AMI (OR: 2.45; 95% CI: 1.13–5.28), heart failure (OR: 4.40; 95% CI: 1.99–9.72), stroke (OR: 2.56; 95% CI: 1.21–5.42) and nephropathy (OR: 2.33; 95% CI: 1.42–3.82), but not retinopathy (OR: 1.06; 95% CI: 0.37–3.03).

Liu et al. performed a small cross-sectional study including 48 patients with diabetes, 26 patients with diabetic ketoacidosis and 30 age- and gender-matched controls. Patients with diabetic ketoacidosis had higher values of RDW compared to the other patient populations. Interestingly, the RDW/MCV ratio was independently associated with the presence of diabetic ketoacidosis in logistic regression analysis (OR: 1.55; 95% CI: 1.03–2.33). Magri and Fava studied 196 diabetics who were screened for the presence of diabetic nephropathy, diabetic neuropathy and peripheral arterial disease. In univariate analysis, no association was found between RDW and diabetic nephropathy ($p = 0.09$) or peripheral arterial disease ($p = 0.49$). An increased RDW value was however found to be associated with diabetic nephropathy in multivariate analysis (OR: 1.64; 95% CI: 1.15–2.35).

Regarding the metabolic syndrome, Sánchez-Chaparro et al. investigated 215767 workers of the Ibermutuamur Cardiovascular Risk Assessment (ICARIA) study who underwent a routine medical check-up. In multivariate logistic regression analysis, subjects in the highest quartile of RDW had a 14% higher risk (95% CI: 7–21) of metabolic syndrome compared to those in the lowest quartile after
adjustment for age, sex, smoking, alcohol consumption, body mass index, white blood cell count, hemoglobin level, MCV, previous diagnosis of diabetes or CVD.

Due to the controversial data that has emerged from published studies, it seems hence challenging to draw a definitive conclusion about the relationship between RDW and diabetes so far. Indeed, the indirect evidence emerged from the three larger population studies as well as that provided by two out of three trials that have specifically assessed the correlation of this parameter with diabetes or its surrogate markers (i.e. glycated hemoglobin), suggests that the impairment of hyperglycaemia may exert some effects on erythropoiesis and RBC survival, a relationship that seems to be magnified in patients with diabetic complications. On the other hand, other studies failed to find a significant association.

RDW in kidney disease

The clinical usefulness of RDW in kidney disease has been investigated in a limited number of studies. Lippi et al. performed a retrospective, cross-sectional study including 8585 adult unselected outpatients, 912 of whom (11%) had impaired renal function as defined by an estimated glomerular filtration rate (EGFR) lower than 60 mL/min/1.73 m². A strong, graded and independent association was found between RDW and EGFR values. In particular the OR for risk of reduced renal function was 1.98 (95% CI: 1.54–2.53) by comparing the lowest versus the highest quartile of RDW, independent of age, gender, MCV and hemoglobin values.

In a following study, Oh et al. performed a retrospective analysis on 470 patients with acute kidney failure who were treated with continuous renal replacement therapy, and reported that RDW was an independent predictor of 28-day all-cause mortality (HR: 1.06; 95% CI: 1.01–1.17) in multivariate Cox proportional hazard analysis after adjustment for age, gender, low mean arterial pressure, hemoglobin, albumin, total cholesterol, CRP and Sequential Organ Failure Assessment (SOFA) score.

Ujczaszi et al. assessed both RDW and EGFR in 723 prevalent kidney transplanted recipients, and found a significant and inverse association between these variables (r = –0.38; p < 0.001), which remained highly significant after multivariate adjustments for comorbidity, iron deficiency, inflammation and nutritional status. In particular, an increased RDW value (>14.0%) was associated with an OR of 1.27 (95% CI: 1.13–2.71) for each 10 mL/min decrease in EGFR.

More recently, Solak et al. measured RDW in 367 patients with chronic kidney disease stages from 1 to 5, and reported that RDW values significantly increased from stages 1 to 5, also exhibiting a significant and inverse correlation between EGFR values (r = –0.58; p < 0.001). Interestingly, RDW was also found to be an independent predictor of endothelial dysfunction assessed with flow-mediated dilatation (beta coefficient, –0.190; p < 0.001) in stepwise linear regression analysis after adjustment for smoking status, diabetes mellitus, parathyroid hormone, albumin and CRP.

Finally, Mucsi et al. measured RDW in 723 prevalent kidney transplant recipients, who were followed up for 3 years. In a fully adjusted Cox regression analysis, a 1% increase in RDW value was associated with a significantly increased risk of 3-year mortality (HR: 1.60; 95% CI: 1.27–2.02). Accordingly, the inclusion of RDW in all-cause mortality prediction models produced a net reclassification improvement (0.189; p < 0.001).

RDW in liver disease

In a retrospective study, Beyazit et al. studied 194 consecutive patients with obstructive jaundice (101 malignant and 93 benign), and showed that RDW values were increased over the local cut-off (i.e. >14.8%) in twice as many cases of patients with malignancies compared to those with benign obstructive jaundice (68% versus 31%).

Lou et al. performed a cross-sectional study including 16 patients with acute hepatitis B, 61 with chronic hepatitis B, 46 with chronic severe hepatitis B and 48 healthy controls, and found that RDW was an independent prognostic parameter of 3-month mortality in patients with liver diseases (OR: 1.97; 95% CI: 1.29–2.17). It was also observed that patients with hepatitis B had significantly higher RDW values compared with healthy subjects, and those with chronic severe hepatitis B had the highest RDW values among all patients with liver diseases.

In a following investigation, Cengiz et al. performed a retrospective investigation including 62 patients with non-alcoholic steatohepatitis (NASH), 32 with simple steatosis and 30 healthy controls. It was hence reported that the RDW values in patients with NASH were significantly higher compared to those of patients with simple steatosis or those of the healthy control group. The value of RDW was found to be an independent predicting factor of NASH, displaying an OR of 1.75 (95% CI: 1.13–2.71). Patients with biotic evidence of advanced fibrosis had also higher RDW values than those with mild fibrosis, and the RDW was significantly correlated with fibrotic scores.

Chen et al. studied 458 eligible patients with chronic hepatitis B cirrhosis (310 in estimation group and 148 in validation). In multivariate regression analysis, RDW values were significantly associated with both fibrosis (OR: 1.80; 95% CI: 1.20–2.69) and cirrhosis (OR: 2.06; 95% CI: 1.21–3.51). The severity of liver fibrosis was also significantly correlated with increasing values of RDW.

Hu et al. showed that RDW was positively associated with well-established prognostic factors such as serum bilirubin and creatinine levels, prothrombin time, and negatively correlated with platelet counts and serum albumin concentration in patients with several liver diseases including non-cirrhotic chronic hepatitis, liver cirrhosis after hepatitis B virus infection, primary hepatocellular carcinoma, alcoholic liver cirrhosis and primary biliary cirrhosis. They also showed that an increased RDW value (i.e. >15.5%) was independently associated with poor hospitalization outcome (OR: 13.3; 95% CI: 1.7–105.7) after adjustment for age, bilirubin, albumin, platelet count and prothrombin time. Interestingly, it was also concluded that RDW might reflect liver disease status for a longer period compared with other well-established parameters, since erythrocyte survival is approximately 3–4 months compared to the much shorter survival of platelets (7–10 days), and the shorter half-life of bilirubin (around 12 h) and albumin (15–20 days).
Kim et al.\(^{118}\) retroactively investigated RDW in 24,547 patients who were diagnosed with non-alcoholic fatty liver disease (NAFLD) according to abdominal ultrasonography and surveys about alcohol consumption. Both the Fibrosis 4 (FIB-4; platelets, aspartate aminotransferase, alanine aminotransferase and age) and BARD (body mass index, aspartate aminotransferase/alanine aminotransferase and diabetes) scores were found to increase in parallel across quartiles of RDW values. Accordingly, the overall risk (i.e., the OR) of having advanced fibrosis comparing the highest versus the lowest quartiles of RDW was 1.76 (95% CI: 1.55–2.00) using the BARD score and 1.69 (95% CI: 1.52–1.98) with FIB-4 score.

In a follow-up investigation, Yang et al.\(^{119}\) also measured RDW in 619 patients with NAFLD and 1637 healthy controls, and described that RDW was significantly increased in NAFLD patients. In binary logistic regression analysis, the RDW values were found to be significantly associated with NAFLD.

Huang et al.\(^{120}\) enrolled 130 patients (69 with chronic hepatitis B and 61 with hepatitis B-related liver cirrhosis), and showed that RDW values were significantly higher in patients with hepatitis B-related liver cirrhosis compared to the chronic hepatitis B patients and healthy controls (OR for the presence of hepatitis B virus-related liver cirrhosis, 6.52; 95% CI: 1.26–33.83). A significant association was also found between RDW value and Child-Pugh score.

**RDW in chronic obstructive pulmonary disease and community-acquired pneumonia**

Chronic obstructive pulmonary disease (COPD), an obstructive lung disorder characterized by chronically poor airflow, is mainly caused by tobacco smoke, air pollution and occupational exposure to workplace dusts, chemicals or fumes. Patients with COPD have a high risk of developing community-acquired pneumonia (CAP), and may thus experience worse clinical outcomes.

Braun et al.\(^{121}\) retrospectively analyzed the data of 637 consecutive patients aged 60 years old or younger, who were diagnosed with CAP, and reported that a RDW value >14.5% was significantly associated with complicated hospitalization in multivariate analysis. Interestingly, patients with increased RDW were more likely to have both complicated hospitalization (OR: 4.1; 95% CI: 2.6–6.5) and increased 90-day mortality (OR: 4.8; 95% CI: 1.5–15.3), irrespective of their hemoglobin level.

In a subsequent study Lee et al.\(^{122}\) carried out a retrospective investigation of 744 patients with CAP. After stratifying the study population in quartiles of RDW, the values of several prognostic scales were found to gradually increase from the lowest to the highest RDW quartiles. Patients with a RDW value in the highest quintile also had a significantly higher 30-day mortality compared to those in the lowest quintile (OR: 2.37; 95% CI: 1.04–5.42).

Seyhan et al.\(^{123}\) performed a retrospective analysis of 270 patients with stable COPD who underwent hospitalization, and reported that the RDW value was positively correlated with the presence of right ventricular dysfunction \(r = 0.25\); \(p < 0.001\) and pulmonary arterial hypertension \(r = 0.14\); \(p = 0.03\). In multivariate analysis, RDW levels were significant predictors of mortality (OR: 1.12; 95% CI: 1.01–1.24).

Braun et al.\(^{124}\) also carried out a retrospective analysis of 3815 patients aged 18 years or older who were diagnosed with CAP, and found that a RDW value >15% was a significant predictor of both complicated admission (OR: 2.10; 95% CI: 1.81–2.44) and 90-day mortality (OR: 3.04; 95% CI: 2.61–3.54).

Finally, Balta et al.\(^{125}\) studied 39 consecutive patients with not less than 10-year history of COPD, along with 39 age- and sex-matched controls. Patients with COPD had significantly higher values of RDW compared to controls (16.1 ± 2.5% versus 13.6 ± 1.3%; \(p < 0.001\). In multivariable logistic regression, an increased RDW value was the only predictor of right ventricular failure in patients with COPD (OR: 2.10; 95% CI: 1.14–3.86). Accordingly, a RDW value >17.7% predicted the presence of right ventricular failure with sensitivity of 0.70 and specificity of 0.93, respectively.

**RDW in other human disorders**

The clinical usefulness of RDW has also been established in several studies in critically ill patients\(^{128}\). Kim et al. measured RDW in 409 out-of-hospital cardiac arrest victims, 219 of which with return to spontaneous circulation\(^{129}\), and reported that the highest RDW quartile was associated with an increased risk of death during a 30-day post-resuscitation period (HR: 1.95; 95% CI: 1.05–3.60). Hunziker et al.\(^{130}\) performed an observational cohort study including 17,922 intensive care unit (ICU) patients with available RDW values, and reported that RDW was significantly associated with inhospital mortality (OR per 1% increase in RDW, 1.14; 95% CI: 1.08–1.19). ICU mortality (OR: 1.10; 95% CI: 1.06–1.15) and 1-year mortality (HR: 1.20; 95% CI: 1.14–1.26). Meynaar et al.\(^{131}\) studied 2915 consecutive patients admitted to an ICU, 387 of whom (13.3%) did not survive to hospital discharge, and reported that RDW was an independent risk factor for mortality (OR for each fL of SD-RDW increase, 1.04; 95% CI: 1.02–1.06). In another study, Kim et al.\(^{132}\) prospectively studied 329 patients admitted to the emergency department (ED) for severe sepsis or septic shock, and reported that patients with increased RDW displayed the highest risk of both 28-day (HR: 10.0; 95% CI: 2.0–49.9) and 90-day (HR, 13.7; 95% CI: 2.9–64.10) mortality. Similar results were published by Sadaka et al.\(^{133}\), who also measured RDW in 279 patients with septic shock and found an OR of 12.3 (95% CI: 2.1–73.3) for mortality by comparing patients in the highest with those in the lowest quintile of RDW. Zhang et al.\(^{134}\) performed a retrospective study in a ICU of a tertiary hospital including 1539 patients (1084 survivors and 455 non-survivors), and reported that RDW was significantly and independently associated with mortality (OR for RDW >14.8%, 1.1; 95% CI: 1.03–1.16). Paulus et al.\(^{135}\) measured RDW in 3994 trauma patients admitted at a first level trauma center, and found that an increased RDW (highest versus lowest quintile) independently predicted the need for massive transfusion (OR 3.5: 95% CI: 2.70–5.83). It is also noteworthy that in a small epidemiological study including 46 consecutive patients admitted to the emergency department with acute infections\(^{136}\), RDW was found to be significantly and...
Table 3. Clinical usefulness of red blood cell distribution width (RDW) in human disorders.

- Cardiovascular and thrombotic disorders
  - Cardiovascular disease
  - Coronary artery ectasia
  - Heart failure
  - Atrial fibrillation
  - Peripheral occlusive artery disease
  - Acute mesenteric ischemia
  - Venous thrombosis
- Metabolic disorders
  - Diabetes
  - Kidney disease
  - Liver disease
  - Subclinical hypothyroidism
- Acute conditions
  - Acute poisoning
  - Acute pancreatitis
  - Preeclampsia
  - Critically ill patients
  - Trauma
  - Hip fracture
- Chronic conditions
  - Cancer
  - Inflammatory bowel disease
  - Chronic obstructive pulmonary disease (COPD)
  - Community-acquired pneumonia (CAP)
  - Migraine
- Overall mortality in the general population

RDW and mortality in the general population

Along with the clinically important associations found between anisocytosis and the human disorders described in the previous sections of this article, several lines of evidence now suggest that RDW may support the risk stratification of mortality in general populations with or without CVD, heart failure, cancer and other frequent comorbidities, alone or in combination with other biomarkers (Table 3).

The very first epidemiological investigation on this topic was published by Perlstein et al. The study was based on 15,852 community-dwelling adults aged 20 years and older enrolled in NHANES III. The primary outcome over a mean period of 8.7 years of follow up was all-cause mortality, whereas secondary outcomes included death due to CVD, cancer and chronic lower respiratory disease. A 1-SD increment in RDW was associated with 23% increased risk of all-cause mortality, 22% increased risk of cardiovascular mortality, 28% increased risk of cancer mortality and 32% increased risk of chronic lower respiratory disease mortality after multiple adjustment for age, sex, race/ethnicity, physical activity level, achieved education level, smoking status, pack-years of smoking, body mass index, systolic blood pressure, hypertension, glycated hemoglobin, diabetes mellitus, hypercholesterolemia, chronic kidney disease and estimated glomerular filtration.

During the same year, a sub-analysis of the NHANES III study including 8,175 community-dwelling adults aged 45 and older. The primary outcome over a mean period of 7.9 years of follow up was all-cause mortality, whereas secondary outcomes included death due to CVD, cancer and chronic lower respiratory disease. After stratification of the study population according to quintiles of RDW, subjects in the highest quintile of RDW had a 2.0-fold higher risk of all-cause mortality, 2.1-fold higher risk of cardiovascular mortality, 1.7-fold higher risk of cancer mortality and 2.0-fold higher risk of mortality for other causes compared to those in the lowest quintile after multiple adjustment for age, sex, ethnicity, education, body mass index, smoking status, cancer, congestive heart failure, diabetes, heart attack, pulmonary disease, stroke, overnight hospitalization, EGFR, hemoglobin, MCV and CRP.

In another separate publication from the NHANES III study including 15,460 subjects aged 20 years and older free of CVD or diabetes, the RDW was found to be a significant predictor of mortality (highest versus lowest quartile) in both women (HR for all-cause mortality: 1.22 and 95% CI: 1.14–1.31; HR for CAD death: 1.17 and 95% CI: 1.07–1.28) and in men (HR for all-cause mortality: 1.29 and 95% CI: 1.20–1.38; HR for CAD death: 1.25 and 95% CI 1.13–1.39; HR for cardiovascular death: 1.18; 95% CI: 1.03–1.35) and in men (HR for all-cause mortality: 1.29 and 95% CI: 1.20–1.38; HR for CAD death: 1.25 and 95% CI 1.13–1.39; HR for cardiovascular death: 1.27 and 95% CI: 1.17–1.37).

One year thereafter, Chen et al. measured RDW in 3226 adults aged 35 years and older residing in a suburban township north of Taipei City, Taiwan, who were followed up for a mean period of 15.9 years. The primary outcome was all-cause mortality, whereas secondary outcomes included death due to CVD or to other causes. After stratification of the study population according to quintiles of RDW, subjects in the highest compared to those in the lowest quintile of RDW had a 46% higher risk of all-cause mortality, 45% higher risk of cardiovascular mortality and 46% higher risk of non-cardiovascular mortality after multiple adjustment for age, sex, body mass index, smoking, history of diabetes, hypertension, total cholesterol, triglycerides, albumin, EGFR, RBC count, hemoglobin and MCV. Interestingly, these associations remained significant in both anemic and non-anemic individuals.

Lappe et al. studied a population of 449 subjects free from CAD for a period of 8.4–15.2 years, and found that subjects...
in the highest quintile had a significantly higher risk of all-cause mortality compared to those in the lowest quintile (HR: 1.33; 95% CI: 1.15–1.55).

Lam et al.149 performed a longitudinal study on 36,226 elderly US citizens (65 years and older) observed at an outpatient clinic. The RDW was measured within 3 months of the initial visit and the maximum period of follow-up was 10 years. Patients with RDW >16.6% had an age, hemoglobin and gender-adjusted 2.3-fold higher risk of all-cause mortality than those with RDW values ≤16.6%. Interestingly, the risk was found to be higher in non-anemic than in anemic subjects (HR: 3.7 versus 1.9).

In a following study, Arbel et al. reviewed RDW values of a community based healthcare maintenance organization in Israel, including 225,006 patients aged 40 and older, to assess the relationship of this parameter with risk of cardiovascular morbidity and all-cause mortality over a period of 5 years103. After stratification of the study population according to different RDW thresholds, subjects with RDW values >17% had a substantially higher risk of all-cause mortality (4.6-fold in males and 3.3-fold in females) compared to those with RDW values <13% after multiple adjustment for age, hemoglobin, blood glucose, high-density lipoprotein (HDL), non-HDL-cholesterol, triglycerides, body mass index, diabetes, hypertension, smoking status and chronic obstructive pulmonary disease. The trend was found to be similar in both anemic and non-anemic subjects.

More recently, Horne et al.150 investigated the predictive role of RDW for all-cause mortality among 17,197 CVD-free subjects enrolled for up to 5 years in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), and who were followed up for a mean period of 1.9 years. In multivariable analysis adjusted for age, sex, low density lipoprotein (LDL)-cholesterol, HDL-cholesterol, CRP, family history of CVD, smoking, race, creatinine, glucose and trial drug assignment, the RDW was found to be significantly associated with a 46% higher risk of all-cause mortality, but not of cardiovascular mortality.
RDW and human pathology: cause or effect?

Although reliable evidence has been provided about the clinical significance of RDW in health and disease, an open question remains: is anisocytosis a risk factor or a simple epiphenomenon (e.g. a ‘marker’) of an underlying biological or metabolic imbalance? Although a simple and unequivocal answer to this question cannot be given so far, some considerations can be made.

RDW as a biomarker of human disorders

It is rather unquestionable that several biological and metabolic abnormalities associated with human disorders may also exert a considerable influence on erythropoiesis (Table 5). In general, shortening of telomeres (i.e. the DNA-protein structures located at the ends of chromosomes) length is a hallmark of cellular aging and is associated with several age-associated human disorders such as heart disease, diabetes, cancer and infections, along with overall mortality. Kozlitina and human disorders such as heart disease, diabetes, cancer and of cellular aging and is associated with several age-associated general, shortening of telomeres (i.e. the DNA-protein struc-

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Table 5. Leading biological and metabolic imbalances contributing to increase anisocytosis in human disorders.
surrogate biomarker of underlying metabolic abnormalities that are known to predict the clinical outcome\textsuperscript{168}.

In regards to diabetes, several structural and functional properties of RBCs are remarkably altered in the presence of hyperglycemia. These substantially include an increased glycosylation of cell surface proteins, decreased plasma membrane fluidity and reduced erythrocyte deformability, which would impair the dynamic proprieties of RBCs, complicate their flow through the microcirculation and ultimately increase their vulnerability to injuries\textsuperscript{170,171}. Diabetic nephropathy is also associated with erythrocyte fragmentation, which is a well-established cause of anisocytosis\textsuperscript{172}.

In chronic kidney disease, the gradual decline of erythropoietin synthesis, especially when accompanied by erythropoietin hyporesponsiveness, not only causes a reduced production of RBCs, but is also responsible for the generation of erythrocytes with different sizes, thus ultimately increasing the degree of anisocytosis\textsuperscript{6}. Additional factors that would contribute to increase the RDW values in patients with both kidney and liver diseases include increased erythrocyte fragmentation, inflammation, poor nutritional status\textsuperscript{173}, along with increased oxidative stress\textsuperscript{174}.

Several conditions that impair erythrocyte production and survival may be present in patients with liver disease. These basically include down-regulation of erythropoietin receptor expression, nutritional deficiencies (e.g. iron, vitamin B\textsubscript{12}, folic acid) along with chronic inflammation and increased red cell destruction\textsuperscript{115}. Of particular interest is the evidence that the expanded plasma volume associated with portal hypertension in cirrhotic patients may ultimately lead to reduced RBC survival\textsuperscript{175}, since an enlarged spleen efficiently sequesters and destroys RBC cells.

**RDW as a cause of human disorders**

The role of RBC biology in the pathogenesis of some non-hematological disorders has also been recently reevaluated, thus opening some intriguing scenarios, where anisocytosis may behave as an active player.

Specifically concerning cardiovascular disorders (Figure 3), Tziakas et al.\textsuperscript{176} recently showed that a strong and direct relationship exists between the degree of anisocytosis (i.e. the RDW value) and the cholesterol content of erythrocytes membranes ($r = 0.320; p < 0.001$), and that the cholesterol content of erythrocytes membranes is positively and independently associated with clinical instability in patients with cardiovascular disorders\textsuperscript{177}. Recent evidence also suggests that the total amount of free cholesterol contained within the necrotic core of advanced atherosclerotic plaques appears to be much greater than that expected from apoptotic death of inflammatory cells. It is hence conceivable that the free cholesterol in excess within the primary atherosclerotic lesion may originate from other cellular sources, including RBCs\textsuperscript{178}, and that anisocytosis may directly participate in the pathogenesis of CVD through a variety of mechanisms. The erythrocytes may be entrapped within the atherosclerotic plaque by either injury of the fibrous cap and consequent thrombus formation or due to plaque hemorrhage after injury of intraplaque microvessels. Once entrapped within the atherosclerotic plaque core, RBCs can then contribute to accelerate atherogenesis by a multi-step process. First, the accumulation of free and crystallized cholesterol driving from the erythrocyte membrane, which is reportedly higher in subjects with increased RDW values\textsuperscript{176}, promotes the expansion of the lipid core (i.e. 50\textmu L of RBC...
are capable to generate a ≥0.2-mm³ necrotic core) and the ulceration of the fibrous cap. The iron contained in the hemoglobin molecules released after erythrocyte injury within the atherosclerotic plaque is also effective to trigger a foreign-body reaction, free oxygen radicals generation, tissue injury, and activation of several pro-inflammatory cytokines pathways. Erythrophagocytosis mediated by interaction of RBCs with scavenger receptors on macrophage and other phagocytes may also amplify the formation of foam cells and promote the growth of the atherosclerotic plaque. The neutralization of nitric oxide by cell-free hemoglobin released upon injury of erythrocytes within the necrotic core of the atherosclerotic plaque may also contribute to inhibit endothelium-dependent nitric oxide-mediated vasodilation. Another potential mechanism supporting the pathogenetic role of anisocytosis in CVD is related to the physical properties of RBCs in patients with high degree of anisocytosis. Patel et al. recently showed that an increased RDW is significantly and positively associated with decreased erythrocyte deformability (p = 0.003). It is hence plausible that a greater variation of erythrocyte volumes would increase blood viscosity and concomitantly impair blood flow through the microcirculation, thus triggering or amplifying the adverse consequences of a pre-existing vascular occlusion in both CVD and venous thrombosis.

The potential causal association of anisocytosis and other non-cardiovascular disorders has been scarcely investigated and seems overall less clear at this point in time. It seems hence reasonable to conclude that increased anisocytosis may be regarded more as a cause rather than an effect in these conditions so far.

Conclusions

After being used for the differential diagnosis of anemia for decades, the RDW has undergone a notable renaissance in recent years. Increasing and convincing evidence shows that anisocytosis is associated with a variety of human disorders, with their complications and, even more importantly, with overall mortality in the general population (Table 3). Whether the RDW plays an active role in health and disease or simply behaves as a biomarker, it is increasingly clear that its clinical usefulness should be now broadened beyond its conventional application for troubleshooting anemia. An increased RDW mirrors a profound deregulation of erythrocyte homeostasis involving both impaired erythropoiesis and abnormal erythrocyte metabolism and survival, which may be caused by a variety of abnormalities, namely, shortening of telomeres length, oxidative stress, inflammation, erythrocyte fragmentation, poor nutritional status, hypertension, dyslipidemia and abnormality of erythropoietin function. All these conditions are important prognostic factors for severe morbidity and death. It seems hence conceivable that this simple and inexpensive parameter may provide valuable information about the general health status, the presence of subclinical and clinical diseases, as well as for predicting the prognosis of patients with a variety of frequent acute or chronic conditions. Regardless of the underlying disorder, patients with increased RDW values should hence be more closely and intensively managed to improve their clinical outcomes.

Another important implication that can be inferred from the current scientific literature is that the treatment of anisocytosis itself may be a potential target of future therapies. Despite the lack of interventional studies aimed to investigate the effect of reducing anisocytosis for preventing disease onset and progression, or even for reducing all-cause mortality, it is undeniable that an increased value would still mirror an impairment of one or more important metabolic pathways. Thus, regardless of whether RDW may be regarded as a cause or an effect of human disease, ample interventional studies should be planned to clarify the potential therapeutic implications of lowering RDW in patients with a variety of acute or chronic disorders.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

Clinical applications of red blood cell distribution width


