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Review Article

Red Blood Cell Distribution Width (RDW): Relation with Veterinary Diseases

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Abstract

RDW is a parameter that reveals the degree of heterogeneity of erythrocyte volume (anisocytosis) and has been used for differentiation of anaemias. Recently it has been shown that RDW has other uses, being the degree of anisocytosis common in disorders such as cardiovascular disease, venous thromboembolism, diabetes, community-acquired pneumonia, chronic obstructive pulmonary disease, liver and kidney failure, as well as in certain types of cancer, such as colon, prostate and breast. This parameter also allows us to establish a short and long term prognosis of patients with any of these disorders.

Keywords: Red Blood Cell Distribution Width; Mean Corpuscular Volume; Cardiovascular Disease; Cancer

Introduction

Red blood cell distribution width (RDW) is a calculated, simple and cheap parameter that reflects the degree of heterogeneity of the volume of RBCs (Red blood cells), known as anisocytosis, contained in a sample, and is traditionally used in haematology for the differential diagnosis of anaemias [1].

The RDW concept is based on the existence of different size RBCs. It is normal for there to be some slight variation between the different volumes of circulating red blood cells. When representing this variation in an axis of coordinates, being the axis of the abscissae the volumes and the axis of the ordinate ones, the quantity of RBCs of that size would be represented by a Gauss curve in which the central part would correspond to the average size of the majority of the existing volumes and the left and the right, the smallest and the largest, respectively. The existing area below the Gauss curve is that is known as RDW (Figure 1). This parameter indirectly reflects the degree of anisocytosis of a sample.

Mathematically, the RDW value is obtained from the following equation: (SD of RBCs volume/VCM) x100, in which SD is the standard deviation and MCV the mean corpuscular volume or size of the RBCs, expressed in fL. This formula can be related to the coefficient of variation (CV) or to the DS, responding to the acronyms RDW_SD or RDW_CV [2]. The difference between the two expressions is given by the units (Table 1).

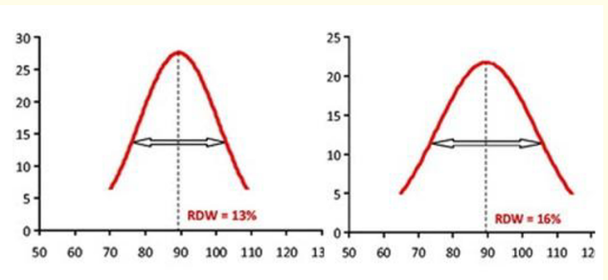

Figure 1: Coordinate-axis representation of the RBCs volumes of a sample.

	Units	Normal values in dog
RDW_SD	fL (10^{-15}L)	39-46
RDW_CV	%	11,5-14,5

Table 1: Units and normal values in RDW dog.

The value of RDW is being considered as an indicator of mortality in the population. Although it has not been definitively established whether an increase in the value of RDW is a risk factor or should only be considered a phenomenon linked to an underlying biological and metabolic imbalance, it is reasonable to suggest that the evaluation of this parameter should be extended beyond the differential diagnosis of anaemias. For example, an increase in this parameter has a high predictive value for the evolution of a wide variety of disorders, but also provides relevant information for the short and long-term prognosis. Thus, in cases of non-regenerating anaemia in which the bone marrow is being stimulated, an increase in the RDW value would be an indication that spinal cord activity has begun although it may not be intense enough to consider regenerative anaemia.

RDW: Early or late dialer?

Is anisocytosis a risk factor or a simple reflection of an underlying biological or metabolic imbalance? Although a simple and unequivocal answer to this question cannot yet be given, some considerations can be made.

RDW as a biomarker of disorders

Shortening of the length of telomeres (i.e., DNA-protein structures located at the ends of chromosomes) is a hallmark of cellular aging and is associated with several age-related disorders such as heart disease, diabetes, cancer, and infections, in addition to overall mortality [3].

Oxidative stress is a condition characterized by the deterioration of the balance between oxidant and antioxidant defenses, and it is associated with the formation of oxygen free radicals and consequent damage to nucleic acids, proteins and lipids. This condition is common in most chronic disorders, including cancer, diabetes, cardiovascular disease (CVD), inflammatory disorders, liver failure, and chronic kidney disease [4]. In addition, oxidative stress has a profound influence on erythrocyte homeostasis and survival. Therefore, this condition may be another underlying biological mechanism that may lead to an increase in RDW, probably through an alteration in erythrocyte metabolism, thus contributing to the association between anisocytosis and pathology [4].

Inflammation is common in most disorders and it's also the primary mechanism responsible for the presence of anisocytosis in CVD patients, as several pro-inflammatory cytokines inhibit the synthesis or activity of erythropoietin [3].

Atherosclerosis is a pathological process that occurs as a result of multiple metabolic disorders, including dyslipidaemia, inflammation, and thrombosis [5]. Because of the existence of a strong, positive and independent association between RDW and inflammatory biomarkers, increased anisocytosis may be a consequence of common inflammation in patients with this disease [6]. Inflammation could, in fact, promote anisocytosis through deterioration of iron metabolism and consequently of haemoglobin necessary for erythrocyte maturation, resulting in medullary release of smaller RBCs.

The relation between RDW and venous thromboembolism is probably multicausal. Several nutritional deficiencies occur in patients with chronic immobilization and impaired renal function, both of which are common in patients with deep vein thrombosis and/or pulmonary embolism. Hypoxia secondary to obstruction of the pulmonary arteries may also cause hyperactivation of both the neurohormonal and adrenergic pathways, eventually triggering the release of pro-inflammatory cytokines [7]. In patients with venous thromboembolism RDW may therefore be increased as a result of the interaction of these underlying conditions.

There are also some logical explanations that would justify increased RDW values in cancer patients, and these include inflammation and poor nutritional status (e.g., iron, folic acid and vitamin B12 deficiency). Increased RBC schistocytosis is also common in malignancy, especially in patients with metastatic cancer and those undergoing chemotherapy [8].

In chronic renal disease, the gradual reduction of erythropoietin synthesis, especially when accompanied by hypoactivity of the same, not only causes a lower synthesis of red blood cells, but is also responsible for the generation of erythrocytes of different sizes, thus increasing the degree of anisocytosis [9].

In diabetes, several functional and structural properties of red blood cells are altered in the presence of hyperglycaemia. These include increased glycation of cell surface proteins, decreased plasma membrane fluidity, and reduced erythrocyte deformability, which

would damage the dynamic properties of red blood cells, hinder their flow through microcirculation, and ultimately increase their vulnerability to injury [1]. Diabetic nephropathy is also associated with erythrocyte fragmentation, which is a cause of anisocytosis.

RDW: Its application in the characterization of anaemia's

Several studies have shown that anaemias can be classified by taking into account MCV, RDW and size distribution histograms obtained using haematological autoanalysers [10] (Table 2).

Low MCV **Normal RDW** **(homogeneus microcytic)**	**Low MCV** **High RDW** **(heterogeneus microcytic)**	**Normal CVM** **Normal RDW** **(homogeneus normocytic)**	**Normal CVM** **High RDW** **(heterogeneus normocytic)**	**High MCV** **Normal RDW** **(homogeneus macrocytic)**	**High MCV** **High RDW** **(heterogeneus macrocytic)**
B-Heterozygous thalassemia Chronic disease	Iron deficiency S **β**-Thalassemia Haemoglobin H Schistocytosis	Normal Chronic liver disease Nonanemic haemoglobinopathy Transfusion Chemoterapy Chronic lymphocytic leukemia (CLL) Chronic Myeloid Leukemia (CML) Hereditary spherocytosis	Mixed deficiency Early iron or folate deficiency Anaemic haemoglobinopathy Myelofibrosis Sideroblastic anaemia	Aplasic anaemia	Folate deficiency Vitamin B12 deficiency Immune haemolytic anaemia

Table 2: Classification of Anemias based on MCV and RDW.

RDW and non-cancer diseases

RDW in cardiovascular disease

In cases of myocardial infarction and coronary artery disease, the inflammatory state and neurohormonal activation that occur play a role in increasing the degree of anisocytosis. Several studies have confirmed that RDW is a significant predictor of cardiovascular mortality. In addition, an increase in RDW value is significantly associated with the risk of recurrent cardiovascular events [11].

There is an association between RDW and coronary artery ectasia. Higher-than-normal RDW values predict the presence and severity of coronary ectasia [12]

All studies have evaluated RDW for its ability to predict the onset of heart failure, as well as short and long-term prognosis (i.e. worsening heart function, hospitalization, cardiovascular and non-cardiovascular death) of patients with cardiac dysfunction coincided by attributing a significant diagnostic and prognostic role to this parameter, alone or in combination with other validated biomarkers such as natriuretic peptides (atrial natriuretic peptide -ANP- and cerebral natriuretic peptide -BNP-) [13].

The progressive increase in RDW is associated with disease progression in patients with chronic heart failure. It is also associated with physical inactivity and heart failure, regardless of established risk factors, inflammation, or iron metabolism. This parameter predicts short- and long-term outcomes of acute congestive heart failure more effectively than haemoglobin.

The ability of RDW to predict mortality in patients with peripheral artery occlusive disease has been evaluated, concluding that patients with higher values of RDW have a higher risk of mortality from this cause than patients with lower values [14].

Increased RDW is associated with deep vein thrombosis. RDW values are significantly higher in patients who develop chronic pulmonary thromboembolic hypertension than in those who do not [15].

RDW in renal disease

It has been shown that there is an association between the values of RDW and the estimated glomerular filtration index (EGFI). RDW is an independent predictor of mortality in patients with acute renal injury treated with continuous renal replacement therapy.

It has been shown that there is an association between the values of RDW and the (EGFI). RDW is an independent predictor of mortality in patients with acute renal injury treated with continuous renal replacement therapy.

In addition, RDW is independently related to endothelial dysfunction in patients with chronic kidney disease. Studies have been conducted based on the measurement of RDW in patients with stages of chronic kidney disease from 1 to 4, concluding that RDW values increase significantly from stages 1 to 4, also showing a significant and inverse correlation between EGFR values [9].

RDW in liver disease

Patients with malignant obstructive jaundice have higher values of RDW than those with benign obstructive jaundice. Patients with chronic hepatitis have higher RDW values than healthy patients, and those with severe chronic hepatitis have higher RDW levels among all patients with liver disease [16].

RDW in chronic obstructive pulmonary disease and community-acquired pneumonia

Patients with COPD (Chronic Obstructive Pulmonary Disease) have a high risk of developing community-acquired pneumonia (CAP) and may experience worse clinical outcomes. These patients tend to have higher values of RDW, which in this case is a predictor of disease complication and mortality from this cause. In addition, several studies have shown that a higher RDW value is a predictor of right ventricular failure in COPD patients [17].

RDW and diabetes

Studies have been carried out to evaluate the relationship between RDW and diabetic neuropathy, peripheral arterial disease and diabetic nephropathy, with no relationship being found between RDW and the first two. However, an increased RDW value associated with diabetic nephropathy was found [18].

As for metabolic syndrome, there is a relationship between it and RDW; in patients with higher values of RDW they are at greater risk of suffering metabolic syndrome associated with diabetes [19]. Diabetes mellitus and related metabolic syndrome are associated with chronic inflammation. Inflammation can influence erythropoiesis, the circulatory half-life of erythrocytes, and erythrocyte deformability, promoting anisocytosis and thus increasing RDW values.

RDW and cancer

In cancerous processes, both inflammation and poor nutritional status are known risk factors [20].

Since cancer is accompanied by a prolonged inflammatory response and inflammatory processes influence RDW, the previous design of these studies precludes determining whether increased RDW is the cause of cancer development. In addition, there may be a correlation between elevated RDW, stage of cancer (more advanced cancers) and worse prognosis [8].

RDW and colon cancer

It has been investigated if RDW can be a biomarker that can be used in the early detection of colon cancer. In a study of 110 human patients with colon polyp and 30 patients with colon cancer, it was concluded that RDW increased significantly in cancer patients compared to polyp patients (Figure 2). In addition to RDW, MCV, platelets, and haemoglobin were also measured, and no difference was observed between the two groups.

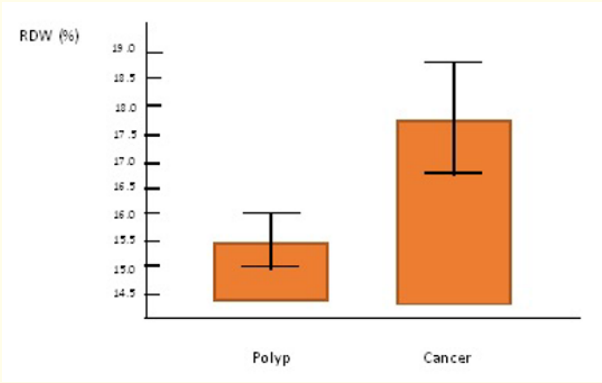

Figure 2: Comparison of groups in terms of RDW values.

Colorectal cancers have a tendency to bleed more than normal which reduces iron storage leading to iron deficiency anaemia. RDW is used as an early indicator of increased oxidative stress, impaired iron mobilization, and iron-deficiency anaemia as noted above.

Because the variability in red blood cell size increases before anaemia clinically manifests, a high RDW at a normal blood count may be a sensitive indicator of iron deficiency.

Low serum ferritin and low serum iron levels are already considered markers of chronic blood loss through the gastrointestinal tract. Low serum ferritin may be more sensitive than an elevated RDW for the detection of occult blood in stool in colon cancer, as depletion of iron stores occurs prior to the development of anisocytosis. A high RDW is probably more useful than a low level of serum iron, because serum iron varies diurnally, limiting valid specimens to early morning; RDW has no diurnal variation [21].

RDW and breast cancer

Inflammation in the tumor microenvironment promotes tumor growth, invasion, angiogenesis, and eventually metastasis. Elevated inflammatory markers, such as C-reactive protein (CRP), neutrophil-lymphocyte (N/L) ratio, and interleukin 6 have been associated with decreased survival among breast cancer patients. In addition, inflammation could bring changes in the maturation of red blood cells by disturbance of the membrane of these, resulting in an increase in RDW [22].

Several studies have shown that elevated RDW could be useful in the differential diagnosis of the nature of a benign or malignant breast tumor, being significantly higher in the group of breast cancer patients (Figure 3). However, RDW cannot be considered as a specific malignancy detector.

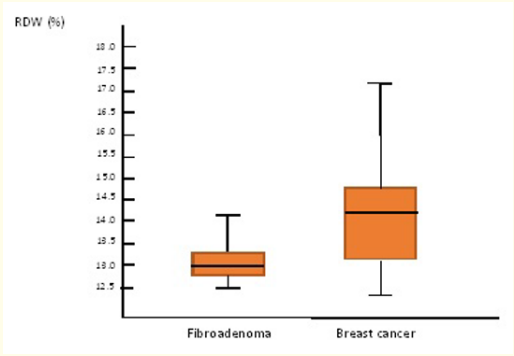

Figure 3: Comparative distribution of RDW in patients with fibroadenoma and breast cancer.

RDW and prostate cancer

Inflammation increases the incidence of prostate cancer, similarly to other types of cancer [23]. Inflammatory cells release a series of oxidative molecules, which can lead to genomic and cellular damage. These factors increase the risk of prostate cancer. Similarly, molecular studies have suggested that inflammation increases the risk of prostate cancer.

Sixty-two patients diagnosed with prostate cancer and 62 healthy patients were studied. The current study showed that the RDW values of prostate cancer patients were significantly higher than those of the healthy control group. A higher RDW was associated with a higher risk of progression, while a lower RDW value was associated with a lower risk of progression.

The correlation between prostate cancer rate and RDW values suggested that higher values of RDW could be used along with other parameters to predict prostate cancer. therefore, prognostic markers are urgently needed that can identify aggressive prostate cancer in its early stages and help select appropriate therapy to ultimately reduce mortality [24].

The fact that RDW, an indicator of inflammation, correlated with other predictive parameters of prostate cancer progression and aggressiveness suggests the potential association of inflammatory cascade with cancer aggressiveness and progression.

Conclusion

As a conclusion and in response to the objective of finding out whether the assessment of RDW as an early marker of different pathologies, we can affirm that it is an important parameter to take into account in the assessment of the treatment, prognosis and evolution of diseases. Because of RDW values can be routinely examined using an hemogram, RDW could be a new and convenient marker to understand the patient's general condition and to predict the risk of mortality of a patient within a stage of the disease.

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