

REVIEW

The Clinical Value of Red Blood Cell Distribution Width as a Prognosis Factor and Severity Marker in Sepsis and Septic Shock

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Nothing to declare

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Abstract

Red blood cell distribution width (RDW) is a hematological parameter usually measured with every complete blood count. Its place in daily practice is mainly in the differential diagnosis of anemia, but nowadays, researchers are focused on different approaches for the erythrocyte's changes in function and morphology.

Sepsis and its most advanced form, septic shock, induces profound disturbances into organ system's function and morphology. The red blood cells physiology and structure are directly and indirectly altered by these im-

balances produced in sepsis. RDW was studied in many diseases, like acute heart failure, acute stroke, inflammatory bowel diseases, chronic lung diseases and cancer, but also in sepsis. Its changes are seen to be mainly associated with prognosis. Higher values of RDW are correlated with mortality and severity of illness in septic and all-cause critically ill patients. RDW was studied also as an independent variable in different predictive scores and some studies suggest it should be introduced in the scores use on a daily basis in critical care settings and emergency departments.

In this review we will focus on how RDW was associated with mortality and severity of illness in the recent literature, as an independent

prognosis factor and as a component part in different predictive and severity scores.

Introduction

Red blood cell distribution width (RDW) represents a hematological parameter measured with every complete blood count. RDW evaluates the red blood cells (RBCs) grade of anisocytosis, which means the variability in erythrocyte's size. RDW is used by clinicians mostly for the differential diagnosis of anemia. In this review we will focus on the changes of RDW in sepsis and septic shock. This easy to obtain tool has become the area of interest for researchers in many disorders [1-3], in terms of mortality, most authors considering it an independent prognosis factor [4,5] or as a part of possible scoring systems [6-8], progression to more severe conditions [9, 10] and therapeutic response [11,12].

Possible pathophysiological mechanisms explaining RDW changes in septic patients

Red blood cells rheological changes can alter RDW in septic patients [13]. Mechanisms of changes in shape (sphericity), volume and deformability are still not completely understood [13], but several have been proposed in septic patients: phosphatidylserine redistribution on the outer red blood cell membrane leaflet [14,15], alterations of RBC sialic acid membrane content [16,17], band 3 protein phosphorylation [18], redox imbalances [19-21], calcium [22], 2,3-diphosphoglycerate [23] and adenosine triphosphate [24] homeostasis alterations and nitric oxide pathway modulation [25,26]. Also, inflammatory response indirectly modulates hematopoiesis through abnormal iron metabolism, increased hemolysis and decreased erythrocyte life span which will lead, in turn, to an increased release of the immature forms into the bloodstream [19].

RDW and prognosis in septic patients

Most of the studies focusing on RDW and prognosis were conducted on all cause critically ill patients [27, 28], including septic patients too. Only several studies have focused on how RDW can predict mortality in septic patients [4-7]. Some authors studied in-hospital mortality [4, 29] while others aimed for the short- [5,30] and long-term prognosis [31].

A retrospective study [4] including 279 patients with septic shock described „RDW as a

strong predictor of hospital mortality”. Subjects were categorized into quintiles based on RDW value on day 1 of septic shock (<13.5%, 13.5% to 15.5%, 15.6% to 17.5%, 17.5% to 19.4%, and >19.4%). RDW significantly correlated with mortality across RDW ranges with odds ratio [OR] = 4.6 (95% confidence interval [CI], 1.0-23.4; p = 0.06), OR = 8.0 (95% CI, 1.5-41.6; p<0.01), OR = 25.3 (95% CI, 4.3-149.2; p<0.001), OR = 12.3 (95% CI, 2.1-73.3; p<0.006), for RDW given intervals: 13.5% to 15.5%, RDW 15.6% to 17.5%, RDW 17.6% to 19.4% and RDW > 19.4%, respectively. Mortality across these intervals was studied relative to subjects with RDW < 13.5%. RDW values at ICU admission and its relationship with mortality in the intensive care unit (ICU) was studied in patients with community-acquired intra-abdominal sepsis also [32]. In these patients, RDW had very good discriminatory capacity in predicting ICU mortality with an area under the curve (AUC) estimated by the receiver operating characteristics (ROC) analysis of 0.867 (95% CI, 0.791–0.942).

Furthermore, some authors focused on geriatric patients with sepsis and septic shock [29,33]. Both studies found a significant correlation between increased RDW and ICU mortality [29] and 30-day mortality [33], respectively, in elderly patients. *Wang et al* [29] reported a mean age of 81.5 ± 8.3 , and *Kim et al* [33] a median age of 78. The potential problems regarding these studies are related firstly by their type – retrospective, but secondly and most importantly, the studied population. Is it the geriatric population more prone to RDW changes irrespective of sepsis and septic shock? As we discussed above, there are many conditions and disorders that can alter RDW and geriatric population should be taken into account, because elderly patients frequently present not one, but many conditions, and most of them are probably in an advanced stage. Thus, this concept of frailty should be added to any alterations in RDW [34]. Hopefully, RDW changes in geriatric septic patients will significantly correlate with mortality after multivariate analysis will take into account all of these risk factors and RDW will still be correlated with ICU mortality. *Wang et al* [29], after multivariable adjustment, found that RDW was significantly correlated with ICU mortality (hazard ratio [HR]=1.18; 95% CI, 1.03-1.35; p=0.019).

Jo et al [30] retrospectively studied a cohort of 566 patients with severe sepsis and septic shock (as defined by the old definitions for sepsis). RDW values were classified into tertiles (< 14%, 14.1% to 15.7%, > 15.8%) and mortality was studied range by range. The authors found

that RDW was increased in non-survivors and was significantly correlated with 28-day mortality. COX regression analysis revealed that RDW was an independent determinant for 28-day mortality: 44.9% for patients with a RDW > 15.8% (HR=2.57; 95% CI, 1.53-4.34; p<0.001), while patients with a RDW of less than 14% had a mortality of 13.1%. Also, mean corpuscular volume (MCV) was higher in non-survivors with a mean value of 96.1 femtoliters (fL) (92.5-100.4), p<0.001.

Lorente et al [5] conducted a prospective, observational, multicenter study including 297 patients with severe sepsis. The authors found increased RDW values of 15.6, 16.0 and 16.6 at days 1, 4 and 8 respectively in non-survivors compared with RDW values of 14.7, 15.2 and 16.0 at days 1, 4 and 8 in survivors, respectively. Higher RDW values at day 1, 4 and 8 were significantly correlated with 30 day-mortality (p = 0.001, p = 0.001, p = 0.002). Malondialdehyde (MDA) as an indicator of redox imbalance and tumor necrosis factor-alpha (TNF-α) as a marker of the inflammatory response had the same timing of measuring. RDW was correlated with serum MDA levels at day 1 (p<0.001) and day 4 (p = 0.009) and serum TNF-α levels at day 4 (p =0.002) and day 8 (p = 0.007), respectively. These results sug-

gest even further that a relation between redox species, inflammatory molecules and RDW exists in sepsis. Kaplan-Meier analysis estimated a 70% higher risk of mortality for patients with a RDW > 15.5%.

28-day and 90-day mortality was studied by Kim et al [35]. RDW values were collected at the admission time and their dynamics in the next 72 hours (ΔRDW72hr-adm). Patients with increased baseline RDW value and those with an increase of >0.2% in the first 72 hours (ΔRDW72hr-adm >0.2%) presented the highest risk for 28-day and 90-day mortality.

Finally, long-term prognosis was just recently studied by Han et al [31]. This retrospective observational study used a large critical care database (Medical Information Mart for Intensive Care Medicine III), with a total number of 4264 septic patients being included and their 4-year mortality studied in relationship with baseline RDW values. RDW was independently associated with all-cause mortality in multivariable COX analysis and also, presented moderate discriminatory capacity with an AUC estimated by the ROC analysis of 0.64 (95% CI, 0.63–0.66). In Table 1 are summarized the main studies of how RDW is changed in septic patients.

Table 1, RDW as an independent prognosis factor and an indicator of illness severity

| Author, year and country | Study design | Setting and patients | Results | Endpoints | Main conclusions |
|---------------------------------|---------------|---|---|--|--|
| Braun et al [36] 2011, Israel | Retrospective | 637 patients aged ≤60 years with community-acquired pneumonia | RDW > 14.5% associated with complicated hospitalization RDW>14% and WBC <4 or >12 × 10 ⁹ /L OR = 5.62 (3.34-9.45) p<0.0001 for complicated hospitalization | 90-day mortality RDW>14.5%, OR=3.81 (95%CI, 1.979-7.324) p<0.0001, univariate analysis RDW>14% and WBC <4 or >12 × 10 ⁹ /L OR = 8.6 (95%CI, 2.9-26.1) p<0.0001 | Higher RDW levels are associated with higher mortality rates and severe morbidity. RDW was significant as a prognostic factor irrespective of hemoglobin levels |
| Jo et al [30] 2013, South Korea | Retrospective | 566 patients with severe sepsis and septic shock admitted to the ED | RDW categorized into tertiles <14%, 14.1% to 15.7%, >15.8% or greater Overall mortality 29% Mortality for RDW ranges: 13.1% for RDW<14% 30.1%for RDW = 14,1-15.7% 44.9% for RDW > 15.8% | 28-day mortality RDW 14.1% to 15.7% (HR, 1.66; 95% CI, 1.00-2.76) RDW>15.8% (HR, 2.57; 95% CI, 1.53-4.34) AUC RDW = 0.68 (95% CI, 0.63-0.72) | RDW at day 1 can be considered a prognosis factor and is associated with 28-day mortality and severity of illness in patients with severe sepsis and septic shock. |

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|--|----------------------|--|--|--|---|
| <p>Sadaka et al [4] 2012, USA</p> | <p>Retrospective</p> | <p>279 patients with septic shock admitted in the ICU RDW on day 1 of septic shock</p> | <p>Quintiles based on RDW: <13.5%, 13.5% to 15.5%, 15.6% to 17.5%, 17.5% to 19.4%, >19.4% ICU mortality RDW day 1 = 17.6, Nonsurvivors: 94, p<0.0001 RDW day 3 = 18.2, Nonsurvivors: 63, p<0.0001 RDW day 7 = 18.7, Nonsurvivor = 31, p<0.0001</p> | <p>Hospital mortality: 13.5% to 15.5% (OR, 4.6; 95%CI, 1.0-23.4; p<0.06); RDW 15.6% to 17.5% (OR, 8.0; 95% CI, 1.5-41.6; p<0.01); RDW 17.6% to 19.4% (OR, 25.3; 95%CI, 4.3-149.2; p<0.001); RDW >19.4% (OR, 12.3; 95% CI, 2.1-73.3; p<0.006)</p> | <p>Increased RDW at admission is significantly associated with ICU and hospital mortality Increased RDW is associated with increased oxidative stress and proinflammatory cytokines The sum of RDW and APACHE predicted mortality better</p> |
| <p>Ku et al [37] 2012, South Korea</p> | <p>Retrospective</p> | <p>161 patients with Gram-negative bacteremia, tertiary-care teaching hospital</p> | <p>RDW ranged from 11.7% to 27.4% mean, 14.9% ± 2.3%), 70 patients with RDW>14.6% Escherichia coli 50.3% Klebsiella pneumoniae 20.5%</p> | <p>28-day mortality RDW at the onset of bacteremia (per 1% increase; HR, 1.1794 [1.011-1.365, p = 0.036) RDW at 72 h higher in nonsurvivors p = 0.001</p> | <p>RDW at diagnosis of bacteremia is an independent prognosis factor RDW at 72 hours is a predictor of all cause mortality</p> |
| <p>Kim et al [35] 2013, South Korea</p> | <p>Prospective</p> | <p>329 patients with severe sepsis and septic shock admitted in the Emergency Department</p> | <p>Group 1: normal RDW at baseline and ΔRDW72hr-adm ≤0.2%, Group 2: increased RDW at baseline and ΔRDW72hr-adm ≤0.2%, Group 3: normal RDW at baseline and ΔRDW72hr-adm >0.2% Group 4 was made up of patients with increased RDW at baseline and ΔRDW72hr-adm >0.2%</p> | <p>Primary end-point: 28-day mortality: 10% Group 4 after multivariable adjustment (HR, 7.85; 95% CI, 1.63 to 37.76; p = 0.010) Second end-point: 90-day mortality: 14.6% Group 4 after multivariable adjustment (HR, 13.74; 95% CI, 2.95 to 64.10; p = 0.001)</p> | <p>An increase in 72 hours of RDW from baseline is associated with poor prognosis A combination between increased baseline and 72 hours RDW values can be an independent prognosis factor</p> |
| <p>Lee et al [38] 2013, South Korea</p> | <p>Retrospective</p> | <p>744 patients with community-acquired pneumonia admitted in the ED</p> | <p>Quartile RDW <13.3 (n = 196) RDW 13.3-14.1 (n = 172) RDW 14.1-15.2 (n = 190) RDW ≥15.2 (n = 186)</p> | <p>30-day mortality RDW ≥15.2, OR=2.37, 1.04-5.42, p<0.040</p> | <p>Admission RDW values are associated with 30-day mortality, length of hospital stay, and the use of vasopressors in patients with CAP RDW added to PSI or CURB-65 severity scales performed better as prognosis markers</p> |

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| Lorente et al [5] 2014, Spain | Prospective, observational, multicenter | 297 patients with severe sepsis from six Spanish Intensive Care Units | RDW day 1 = 15.7, Nonsurvivors: 104, p=0.001 RDW day 4 = 16.0, Nonsurvivors: 77, p=0.001 RDW day 8 = 16.6, Nonsurvivor = 60, p=0.002 | 30-day mortality RDW at day 1: OR=1.13, 95%CI 1.05–1.22, p=0.001 RDW at day 4: OR=1.11, 95%CI, 1.03–1.21, p=0.01 RDW at day 8: OR=1.10, 95%CI, 1.01-1.21, p=0.04 | RDW during the first week is correlated with sepsis severity and mortality and also with MDA and TNF- α levels |
| Ozdogan et al [32] 2015, Turkey | Retrospective | 103 patients with community-acquired intra-abdominal sepsis admitted in the ICU | Overall mortality= 50.5% RDW at day 1 higher in non-survivors | ICU mortality AUC RDW at day 1 = 0.867 (95% CI, 0.791–0.942) | Increased RDW is an independent prognosis factor in patients with C-IAS |
| Kim et al [33] 2015, South Korea | Retrospective | 458 elderly patients aged > 65 years with severe sepsis or septic shock from a single tertiary emergency department | For each 1% increase in RDW, the 30-day mortality risk increased by 15% | 30-day mortality Independent predictor (HR, 1.10; 95%CI, 1.0-1.17; p<0.001) | Higher RDW values are associated with 30-day mortality in elderly patients with severe sepsis and septic shock |
| Wang et al [29] 2017, Taiwan | Retrospective | 117 elderly patients aged \geq 65 years with severe sepsis and/or septic shock admitted in ICU | Subgroup analysis Mortality of patients with qSOFA<2: non-survivors had higher RDW levels than survivors (17.0 \pm 3.3% versus 15.3 \pm 1.4%, p = 0.044) | ICU mortality RDW was an independent variable for mortality: HR, 1.18 [1.03–1.35] for each 1% increase in RDW, p=0.019 after multivariable adjustment | RDW predicted independently in-hospital mortality in elderly patients with sepsis. In patients with qSOFA scores < 2, an increased RDW value was associated with poor prognosis. |
| Han et al [31] 2018, China & Italy | Retrospective | Based on a large critical care database; 4264 subjects with severe sepsis admitted in the ICU | Group 1: RDW \leq 13.9, Mortality = 31.20% Group 2: RDW between 14.0 and 15.5 Mortality = 45.94% Group 3: RDW \geq 15.6 Mortality = 60.60% | 4-years mortality HR of RDW between 1.13 and 1.16, independently of all severity scores (p < 0.01 for all) after multivariable adjustment | Increased RDW in patients with severe sepsis is associated with poor long-term prognosis RDW improved predictive accuracy of conventional severity scores |

APACHE = Acute Physiology and Chronic Health Evaluation, C-IAS = community-acquired intraabdominal sepsis, CAP = community-acquired pneumonia, CI = confidence interval, CURB-65 = Confusion, Urea, Respiratory rate, Blood pressure, Age \geq 65, ED = emergency department, HR = hazard ratio, ICU = intensive care unit, MDA = malondialdehyde, OR = odds ratio, PSI = pneumonia severity index, qSOFA = quick Sequential Organ Failure Assessment, RDW = red blood cell distribution width, TNF- α = tumor necrosis factor-alpha, WBC = white blood cells, Δ RDW72hr = red blood cell distribution width value variation in the first 72 hours

Further research should focus on introducing RDW as an independent variable in predictive scores used for septic patients

Predictive scores such as Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS II) and others, are routinely used in the critical care settings. These scores are correlated not only with the prognosis, but also with the severity of illness in ICU patients. Until now, RDW was described mostly in terms of mortality as an independent prognosis factor. Added to these scores, RDW had proof to increase not only their predictive value [4,30], but sepsis severity also [39].

RDW as an independent variable in different proposed severity scores for septic patients

A predictive score in patients with suspected sepsis based on a PIRO concept (Pre-disposition, Infection, Response and Organ dysfunction) was developed by *Chen et al* [6]. The study included 7011 patients in the derivation cohort and 12,110 in the validation cohort. This score was named CHARM, each letter corresponding to the independent predictors for mortality identified: Chills, Hypothermia, Anemia, RDW and history of Malignancy. RDW was an independent predictor for mortality with an OR = 3.27 (95% CI, 2.63–4.05; $p < 0.001$). This score has good discriminatory capacity with an AUC = 0.77 (95% CI, 0.75–0.79; $p = 0.05$). Sensitivity and negative predictive value for this score were almost perfect with values of 99.4% and 99.7% respectively. Furthermore, CHARM score had better predictive capacity than other scores such as Mortality in Emergency Department Sepsis (MEDS), PIRO, CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, Age ≥ 65), Systemic Inflammatory Syndrome (SIRS) and biomarkers like C-reactive protein, lactate and procalcitonin.

Recently, *Kim et al* [7] used only hematological parameters and described a predictive score for patients with severe sepsis and septic shock in a retrospective study including 730 patients. Three models have been developed, including RDW value, platelet count and the delta neutrophil index (DNI). In the first model, 1 point was given if RDW $> 14.5\%$, or DNI $> 5\%$, or platelet count $< 150,000/\text{mm}^3$. A maximum value of 3 was significantly correlated with

mortality (HR=20.6; 95% CI, 7.2296-58.871; $p < 0.001$), while a score equal with 1 was not ($p = 0.128$). In the second model, DNI and platelet count were subdivided in different value ranges and points were assigned according to these intervals. A score ≥ 2 was significantly associated with 28-day mortality (HR=5.166; 95% CI, 1.7372-15.362; $p = 0.0003$), with a maximum value of 7 points (HR=43.783; 95% CI, 9.7906-195.797; $p < 0.0001$). This score presented good discriminatory power with a ROC curve (AUC) of 0.785 (95% CI, 0.736-0.833; $p < 0.001$) and performed better than lactate (AUC = 0.724; 95% CI: 0.666-0.782; $p < 0.001$) and SOFA score (AUC = 0.738; 95% CI, 0.683-0.794; $p < 0.001$).

Yeh et al [8] described a new predictive score for patients with bacteremia admitted in the emergency department derived from a PIRO model. RDW was included as an independent variable and 2 points were assigned for a RDW value higher than 15%. The AUC of this new score was 0.88 (95% CI, 0.848-0.913), having better discriminatory power than Pitt bacteremia score (AUC 0.750; 95% CI, 0.699-0.800; $p < 0.001$).

RDW relation with ICU and ED scoring systems

In several studies, the relation between RDW value of septic patients and their predictive scores was studied. In one study, RDW had better discriminative power than APACHE and SOFA (AUCRDW=0.74 versus AUCAPACHE=0.69 versus AUCSOFA=0.69), but when RDW was added to APACHE, the discriminative power was better than these variables taken alone (AUCRDW+APACHE=0.77) [4]. APACHE II and SOFA were observed to increase with increasing values of RDW [30]. Moreover, *DeBari et al* [39] found a correlation between RDW value and APACHE II value. Henceforth, a RDW ≥ 16 significantly correlated with an APACHE II ≥ 15 , authors concluding that septic patients with RDW ≥ 16 possibly have higher severity of illness. Also, dynamic changes of RDW in the first 72 hours performed better in predicting death than SOFA score (AUC 0.802; (95% CI, 0.703-0.901; $p < 0.001$) versus 0.703 (95% CI, 0.552-0.855; $p = 0.008$) [35].

In patients with community-acquired pneumonia, RDW added to CURB-65 and Pneumonia Severity Index (PSI) scores increased AUC marginally: AUCCURB-65 = 0.74 (95% CI, 0.69-0.79) versus AUCCURB-65+RDW = 0.79 (95% CI, 0.75-0.84) and AUCPSI = 0.74 (95% CI, 0.70-0.79) versus AUCPSI+RDW = 0.79 (95% CI, 0.75-0.83) [38]. In another study, RDW

discriminative power was useful in patients with a qSOFA < 2 in terms of prognosis [29]. Added to SAPS II, RDW increased the predictive capacity for long-term prognosis in septic patients [31].

Conclusions

Red blood cell distribution width value in sepsis and septic shock can be a very good independent prognosis factor and also a measurement we should take into consideration in terms of illness severity. Future studies are needed in order to find the right place for RDW in the ICU and ED scoring systems, but the past research gives us many perspectives on how we should look at this simple paraclinical tool. The dysregulated response induced by the host in sepsis is generalized and part of the homeostasis imbalances are reflected by erythrocyte's abnormal function and morphology. Maybe it is the time we should start seeing red blood cells as more than just anucleated cells responsible for oxygen transport, but as a more complex system.

Abbreviations

APACHE = Acute Physiology and Chronic Health Evaluation, AUC = area under the curve, C-IAS = community-acquired intra-abdominal sepsis, CAP = community-acquired pneumonia, CI = confidence interval, CURB-65 = Confusion, Urea, Respiratory rate, Blood pressure, Age \geq 65, DNI = delta neutrophil index, ED = emergency department, HR = hazard ratio, ICU = intensive care unit, MCV = mean corpuscular volume, MDA = malondialdehyde, Mortality in Emergency Department Sepsis = MEDS, OR = odds ratio, PIRO = Predisposition, Infection, Response and Organ dysfunction, PSI = pneumonia severity index, qSOFA = quick Sequential Organ Failure Assessment, RBC = red blood cell, RDW = red blood cell distribution width, ROC = receiver operating characteristics, SAPS II = Simplified Acute Physiology Score II, SIRS = Systemic Inflammatory Response Syndrome, SOFA = Sequential Organ Failure Assessment, TNF- α = tumor necrosis factor-alpha, WBC = white blood cells, Δ RDW72hr = red blood cell distribution width value variation in the first 72 hours

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