Original Article

The Role of Red Cell Distribution Width as a Predictor of Mortality for Critically Ill Patients in an Inner-city Hospital

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Abstract

Background: Red cell distribution width (RDW) is a measure of the variation in the red blood cell volume that is usually recorded as a part of the standard complete blood cell count. Recent studies have demonstrated the prognostic value of RDW in many different clinical settings. The objective of this research study is to investigate the independent association of RDW with 30-day mortality in Intensive Care Unit (ICU) patients. **Methods:** One hundred and fifty-six patients admitted to the ICU of our hospital between July 2009 and June 2011 were included in our study. Out of 156 patients, 124 survived the hospital stay. The data on patient's demographics, interventions done in ICU, and their comorbidities were collected. Baseline variables and the RDW value were compared between survivors and nonsurvivors. The cutoff point for RDW used for the comparison was 15.75. Both univariable and multivariable analyses were done. $P < 0.05$ was considered statistically significant. **Results:** In the univariable analysis of the study between survivors and nonsurvivors, the median RDW was 17.20 for nonsurvivors, implying statistical significance ($P = 0.007$). In multivariable analysis, RDW remained significantly associated with inpatient mortality. The receiver operating characteristic is 0.656 ($P = 0.007$), with an optimal cutoff of 15.75 for RDW. At the cutoff of RDW, i.e., 15.75, the sensitivity and specificity for inpatient mortality was 71% and 89%, respectively. **Conclusion:** In critically ill ICU patients, RDW is an independent predictor of 30-day mortality. Taking into consideration the fact that RDW is routinely measured in complete blood count with no additional cost, this can serve as an "inexpensive prognostic marker" in critically ill patients.

Keywords: Critical care, inner city, mortality, red cell distribution width

Introduction

Red cell distribution width (RDW) is a parameter for measuring variability in red blood cell size and the normal value ranges from 11.5 to 15.5.[1-5] Various studies have identified RDW as a prognostic marker in community-acquired pneumonia, septic shock, acute kidney injury, pulmonary hypertension, pulmonary embolism, peripheral artery disease, and in patients with clinically significant cardiovascular disease.[1-3] The exact pathophysiologic explanation for why RDW can serve to be an effective indicator of mortality is not completely understood. It has been hypothesized that an increased oxidative state attributed to the release of inflammatory cytokines leads to iron immobilization which may play a pivotal role in increasing the RDW.[1-5] RDW thereby serves as a widely available, "inexpensive prognostic marker" which if increased in a clinical setting is suggestive of an underlying complex hyperinflammatory pathologic process.[3-6] Considering the fact that the RDW is routinely included in the automated complete blood count (CBC) analyses and has no additional cost, this makes our study of RDW as a prognostic marker efficacious and interesting. Intensive Care Unit (ICU) has a very heterogeneous patient population with an extended spectrum of illness. At the time of admission, it is important to risk-stratify patients based on the prognosis since this will ultimately result in the proper utilization of limited resources in ICU. This can be potentially accomplished by measuring an inexpensive serologic marker, i.e., RDW, to aid in making, especially prognosticating, clinical decisions. The goal of this

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research study is to investigate the prognostic value of RDW as an individual factor in assessing "30-day mortality" in ICU patients.

Methods

The study was conducted in the single combined medical and surgical adult ICU of St. Michael's Medical Center in Newark, New Jersey. Approval for the study was granted by the Institutional Review Board of our medical center which happens to be a 365-bed teaching hospital covering all specialties including cardiac surgery. The closed format ICU has approximately ten beds, and an intensivist who runs it is accessible 24/7. All consecutive ICU patients admitted between July 1, 2009, and June 30, 2011, for whom a CBC with RDW was available in the laboratory database, were included in the study. Exclusion criteria were Age 18 years, pregnancy, lactation, white blood cell count 1000 cells/ml, solid or hematological tumor or immunosuppressive, and outpatient steroid or radiation therapy.

The primary end point of the study was patient mortality during the same hospitalization, analyzed as a binary variable. Univariable analysis was done to determine the association between patient factors and patient mortality. D'Agostino and Pearson omnibus normality test was used to test for normality of distribution of continuous data. Chi-square test was done for categorical variables, whereas independent samples *t*-test or Mann–Whitney U-test was used to analyze interval data as appropriate. After evaluating them individually, multivariable logistic regression analysis was done on patient factors that had a significant association with patient mortality. Those with $P = 0.10$ or less on univariable analysis was included. A probe of multicollinearity between patient factors was done using Pearson R to avoid including very closely related variables into the final analysis. Two-tailed significance tests were done with $P < 0.05$ was considered statistically significant. Odds ratios (ORs) were also computed with 95% confidence intervals for categorical variables. Receiver operating characteristic (ROC) curve analysis was done for the optimal RDW cutoff and its association with hospital mortality. OR was also computed for RDW using the optimal cutoff to construct nominal data. Data were analyzed using SPSS software version 19.0 and GraphPad software version 5.0 (IBM Analytics in Texas, USA).

Results

A prospective study was done on 156 patients admitted in the ICU of the inner-city hospital from July 2009 to June 2011. Patients were divided into two groups: the alive group and the deceased group. One hundred and twenty-four patients were alive during hospitalization and 32 died during inpatient admission. The mean age of the patients was 63.2 ± 15.5 years. The prognostic value of RDW as an indicator of mortality within 30-day mortality was investigated for both the groups. The primary end point of this study is to analyze the significant association of RDW with 30-day mortality as an individual factor. The RDW values of the patients were measured at the time of admission in our laboratory, and the reference range is 11.5–15.5. The RDW value of 15.75 was used as a cutoff in our study. A set of variables that might confound the RDW association with the mortality was analyzed in this study. This includes demographic information (age cutoff - 67.5), glomerular filtration rate (GFR), presence of gastroesophageal reflux disease (GERD), and other comorbidities. Wide analyses were done on the patient intervention which included the use of steroids, broad-spectrum antibiotics, nebulizers, highly active antiretroviral therapy, anticonvulsants, oral hypoglycemics, diuretics, sedatives, and calcium channel blockers. Table 1 provides the description of patient demographics and comorbidities in both alive and deceased groups. Table 2 highlights the primary diagnoses of the patients admitted to the ICU. They were predominantly medical diagnoses, and majority of the patients had septic shock. Table 3 shows the patient intervention with univariable analysis. Univariable analysis showed a significant association between inpatient mortality and age ($P = 0.009$), GFR ($P = 0.006$), RDW ($P = 0.007$), presence of GERD (OR: 13.29 [1.33–132.60], $P = 0.025$), and use of broad-spectrum antibiotics (OR: 0.20 [0.08–0.47], $P = 0.002$). Table 4 highlights the multivariable analysis, age (cutoff - 67.5), GFR (cutoff - 57.2 ml/min), GERD, use of nebulizers, and broad-spectrum antibiotics were included. Use of broad-spectrum antibiotics remained significantly associated with inpatient mortality (OR: 0.27 [0.11–0.68], $P = 0.004$). There was also a trend toward RDW being associated with mortality, with $P = 0.05$ (OR: 0.40 [0.15–1.004]). Figure 1 shows the ROC curve analysis for RDW. The area under the curve-ROC is 0.656 ($P = 0.007$), with an optimal cutoff of 15.75. At the cutoff of RDW, i.e., 15.75, the sensitivity and specificity for inpatient mortality is 71% and 89%, respectively.

Discussion

There has been a peak interest in the recent years in discovering novel prognostic markers in critically ill patients in the ICU. The belief is that early and efficient prognostication helps ameliorate crucial decisions with regard to timely patient discharges and management and treatment decisions. In this prospective research study of ICU patients, RDW strongly and independently predicted the 30-day mortality. Our study confirmed the findings in the previous study by Zhang *et al*. that concluded that RDW is associated with increased risk of hospital mortality in unselected critically ill patients.[1] We studied the patients admitted to our inner-city hospital in the USA, and hence our results and findings, the first of its kind, in a prospective study demonstrating an association between admission RDW and mortality in critically ill patients admitted to an inner-city hospital are more applicable to the urban population. Previous research studies have demonstrated results in accordance with our findings that RDW is associated with increased long-term mortality in cardiovascular diseases, chronic heart failure, in older adults, and also in acute kidney

Table 1: Patient demographics and characteristics between the two groups with univariable analysis

Patient characteristics	Alive	Deceased	OR with 95% CI	*P*
	Group (*n*=125), *n* (%)	Group (*n*=31), *n* (%)		
Mean age in years	61.8	69.8	N/A	0.009
Median GFR (mL/min)	73.0	46.7	N/A	0.006
Hypertension, *n* (%)	68 (54)	21 (68)	1.76 (0.77-4.04)	0.225
Diabetes mellitus, *n* (%)	13 (42)	35 (28)	1.86 (0.8233-4.189)	0.191
HIV infection, *n* (%)	15 (12)	4 (13)	1.09 (0.33-3.54)	1.000
COPD, *n* (%)	24 (19)	4 (13)	0.62 (0.20-1.95)	0.602
ESRD, *n* (%)	10 (8)	2 (6)	0.79 (0.16-3.82)	1.000
CHF, *n* (%)	19 (15)	3 (10)	0.60 (0.16-2.16)	0.570
Dementia, number and %	8 (6)	4 (13)	2.17 (0.61-7.73)	0.257
History of CAD, *n* (%)	9 (7)	2 (6)	0.89 (0.18-4.34)	1.000
History of CVA, *n* (%)	9 (7)	4 (13)	1.91 (0.55-6.67)	0.291
History of thyroid disease, *n* (%)	6 (5)	2 (6)	1.66 (0.31-8.97)	0.626
Dyslipidemia, *n* (%)	11 (9)	0 (0)	0.16 (0.009-2.76)	0.123
Presence of DVT or PE, *n* (%)	1 (1)	1 (3)	4.13 (0.25-68.04)	0.359
Presence of GERD, *n* (%)	1 (1)	3 (10)	13.29 (1.33-132.60)	0.025
Median RDW	15.70	17.20	N/A	0.007

GFR: Glomerular filtration rate, HIV: Human immunodeficiency virus, ESRD: End-stage renal disease, CHF: Congestive heart failure, CAD: Coronary artery disease, CVA: Cerebrovascular accident, DVT: Deep vein thrombosis, PE: Pulmonary embolism, GERD: Gastroesophageal reflux disease, RDW: Red cell distribution width, N/A: Not available

Table 2: Primary Intensive Care Unit diagnosis

Primary diagnosis	Alive group (*n*=125), *n* (%)	Deceased group (*n*=31), *n* (%)
Respiratory failure	35 (28)	8 (26)
Cardiovascular	12 (10)	7 (23)
Septic shock	70 (56)	15 (48)
Pancreatitis	4 (3)	1 (3)
Acute renal failure	4 (3)	0 (0)

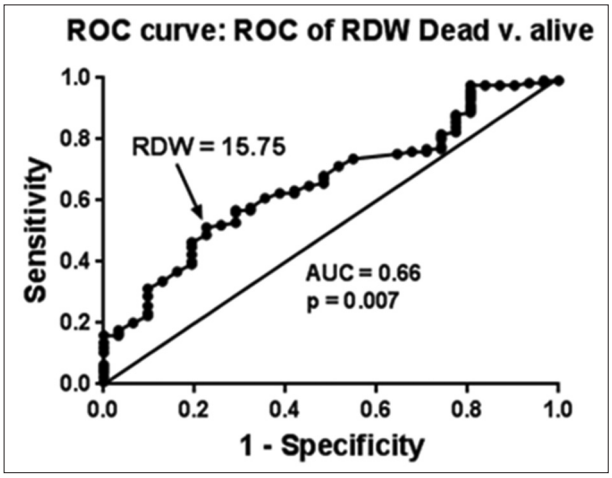

Figure 1: Receiver operating characteristic curve: Receiver operating characteristic of red cell distribution width dead versus alive

injury treated with continuous renal replacement therapy.[2-10] More recently, studies have identified RDW as a very good prognostic marker in esophageal carcinoma and ulcerative colitis.[3-4]

In our study, we measured and calculated the multivariable, including the demographical information and different patient comorbidities, which we commonly encounter in the ICU setting. This includes hypertension, diabetes mellitus, human immunodeficiency virus infection, chronic obstructive pulmonary disease, end-stage renal disease, congestive cardiac failure, coronary artery disease, cerebrovascular accident, thyroid disease, dyslipidemia, deep venous thrombosis, and the presence of GERD. Therapeutic interventions such as the use of steroids, HAART, anticonvulsants, oral hypoglycemics, diuretics, sedatives, nebulizers, calcium channel blocker, and use of broad-spectrum antibiotics were also studied. The above variables were included in the study essentially to investigate the independent association of RDW with the mortality, making our findings more unique since this was not done in prior studies.

In this study, we included patients with end-stage renal disease. It is important to note that renal dysfunction is classically associated with reduced erythropoietin production. The decreased erythropoietin levels affect erythrocyte maturation, which leads to an increase in RDW.[10-13] These patients also have elevated levels of inflammatory cytokines, such as interleukin 1 or interleukin 6, which upregulate hepcidin, a molecule that regulates iron homeostasis by inhibiting iron absorption from the intestine and iron release from reticuloendothelial stores. This also contributes to inhibiting erythrocyte maturation and increasing RDW.[11]

Our results show that the RDW value at the time of admission to the ICU is significantly associated with increased risk of 30-day mortality with $P = 0.050$. The mean RDW in the deceased group is 17.20 and 15.70 in the alive group, validating the RDW cutoff value as 15.70. The use of broad-spectrum

Table 3: Patient interventions with univariable analysis

Patient interventions	Alive group (*n*=125), *n* (%)	Deceased group (*n*=31), *n* (%)	OR with 95% CI	*P*
Use of steroids, *n* (%)	30 (24)	4 (13)	2.13 (0.68-6.64)	0.190
Patients on highly active antiretroviral therapy, *n* (%)	7 (6)	1 (3)	1.78 (0.21-15.07)	0.603
Patients on anticonvulsants, *n* (%)	14 (11)	2 (6)	1.83 (0.40-8.44)	0.443
Patients on oral hypoglycemics, *n* (%)	2 (1)	0	0.89 (0.3275-2.4183)	0.821
Use of diuretics, *n* (%)	28 (22)	6 (19)	1.20 (0.45-3.20)	0.714
Use of sedatives, *n* (%)	33 (26)	11 (35)	0.65 (0.28-1.51)	0.320
Calcium channel blockers, *n* (%)	16 (13)	3 (10)	1.51 (0.41-5.51)	0.540
Use of nebulizers, *n* (%)	36 (29)	4 (13)	2.79 (0.91-8.53)	0.074
Use of broad-spectrum antibiotics, *n* (%)	41 (33)	22 (71)	0.20 (0.08-0.47)	0.002

OR: Odds ratio, CI: Confidence interval

Table 4: Highlighting the multivariable analysis

Patient factors	OR with 95% CI	*P*
Age, with cutoff of 67.5 years	0.97 (0.93-1.01)	0.109
Median GFR, with cutoff of 57.2 mL/min	1.001 (0.99-1.01)	0.322
Presence of GERD	0.97 (0.39-2.44)	0.940
Median RDW, with cutoff of 15.75	0.40 (0.15-1.004)	0.050
Use of nebulizers	0.97 (0.73-8.59)	0.146
Use of broad-spectrum antibiotics	0.27 (0.11-0.68)	0.004

GERD: Gastroesophageal reflux disease, RDW: Red cell distribution width, GFR: Glomerular filtration rate, OR: Odds ratio, CI: Confidence interval

antibiotics also has a significant $P = 0.004$. This can be explained by the fact that the use of broad-spectrum antibiotics is usually reserved for patients with severe infection or sepsis-related multiorgan dysfunction who have an increased risk of mortality. The remaining variables that were considered had no significant association, thereby eliminating its role as a confounding factor.

The exact pathophysiology that makes increased RDW a potential marker of prognosis of mortality in acute illness is not very clear. In conditions related to increased red blood cell destruction, blood loss, or after blood transfusions, RDW can be elevated.[2,10-15] However, many studies in the medical literature have revealed that the relationship between RDW and mortality of RDW is independent of anemia.[12,16-20] A plausible explanation is that RDW is a surrogate marker of inflammation-related oxidative stress. Severe inflammatory conditions such as severe pneumonia and sepsis have been known to increase the degree of anisocytosis by causing a disruption in erythropoiesis, changing the red blood cell membrane deformability and red blood cell circulation half-life, and this eventually causes an increased RDW.[9-14]

Bion suggested that RDW can also be possibly used to give some insight into the ICU patient's degree of physiological reserve, one of three main determinants of clinical outcome.[21] Hunziker *et al*. suggested that the physiological reserve is a reflection of the collective cellular response to an acute stressor state of hypoxia and ischemia.[2] This results in a cascade of necessary events to improve the delivery of oxygen to target organs including increasing erythropoietin production which in turn leads to the increased manufacture and release of mature erythrocytes from the bone marrow into the bloodstream. The faster and more efficient process of reactive erythropoiesis carried out under oxidative stress, the more effective will be the patient's ability to physiologically deal with the acute stressor event. This is interesting because the release of large immature red cells that possess poor oxygen-binding capacity, which manifests as an increased RDW, implies suboptimal and ineffective response to the oxidative stress such as sepsis.[2-7] It may also give a tenable explanation for why an increased RDW is associated with increased mortality in patients admitted to the ICU.

The current study does, however, have some limitations. Although RDW is significant as a cheap and effective prognostic marker, its underlying mechanism is still unclear. Several studies have compared RDW to other inflammatory markers such as interleukin 6, C-reactive protein, as well as iron mobilization and anemia of chronic disease. In our analysis, we have not included other inflammatory markers, as they are not routinely measured on admission. The second limitation is that recommendations for standardization of cell sizing have not been uniformly adopted, so the measurement of RDW might vary to some extent between the manufacturers. As it is usually measured only in one occasion, at the time of admission as part of the complete blood cell count, measurement error, biologic variability, and other chronic disease may limit its use. Third, there might be a possibility of additional confounding factors from conditions and patient interventions that were not included in our analysis. Other limitations worth mentioning include the lack of transfusion data, vitamin B12, and iron studies. Nutritional deficiencies such as B12 and iron are the most common causes of anemia in the United States, and they can cause a concomitant elevation in RDW.

Conclusion

RDW as a prognostic marker in ICU patients helps to improve the decision regarding the urgent timing and use of effective therapeutic intervention. This also helps in making clinical decisions with regard to early discharges by stratifying the

patients on admission. Furthermore, taking the fact into consideration that RDW is routinely measured as part of the admission CBC analysis and thus is free of additional expensive costs. Future studies may be considered to include RDW in the severity illness score (Acute Physiology and Chronic Health Evaluation 4 and Simplified Acute Physiology Score 3). Our findings and its limitations also provide an indispensable target for future translational research.

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Conflicts of interest

There are no conflicts of interest.

References

1. Zhang Z, Xu X, Ni H, Deng H. Red cell distribution width is associated with hospital mortality in unselected critically ill patients. J Thorac Dis 2013;5:730-6.
2. Hunziker S, Celi LA, Lee J, Howell MD. Red cell distribution width improves the simplified acute physiology score for risk prediction in unselected critically ill patients. Crit Care 2012;16:R89.
3. Otero TM, Canales C, Yeh DD, Hou PC, Belcher DM, Quraishi SA. Elevated red cell distribution width at initiation of critical care is associated with mortality in surgical Intensive Care Unit patients. J Crit Care 2016;34:7-11.
4. Wang F, Pan W, Pan S, Ge J, Wang S, Chen M. Red cell distribution width as a novel predictor of mortality in ICU patients. Ann Med 2011;43:40-6.
5. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK, *et al.* Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail 2010;16:230-8.
6. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009;133:628-32.
7. Muhlestein JB, Lappe DL, Anderson JL, Muhlestein JB, Budge D, May HT, *et al.* Both initial red cell distribution width (RDW) and change in RDW during heart failure hospitalization are associated with length of hospital stay and 30-day outcomes. Int J Lab Hematol 2016;38:328-37.
8. Özdogan HK, Karateke F, Özyazici S, Özdogan M, Özaltun P, Kuvvetli A, *et al.* The predictive value of red cell distribution width levels on mortality in intensive care patients with community-acquired intra-abdominal sepsis. Ulus Travma Acil Cerrahi Derg 2015;21:352-7.
9. Shteinshnaider M, Barchel D, Almoznino-Sarafian D, Tzur I, Tsatsanashvili N, Swarka M, *et al.* Prognostic significance of changes in red cell distribution width in an internal medicine ward. Eur J Intern Med 2015;26:616-22.
10. Fujita B, Franz M, Figulla HR, Pfeifer R, Kabisch B, Fritzenwanger M, *et al.* Red cell distribution width and survival in patients hospitalized on a medical ICU. Clin Biochem 2015;48:1048-52.
11. Sicaja M, Pehar M, Đerek L, Starcevic B, Vuletic V, Romic Ž, *et al.* Red blood cell distribution width as a prognostic marker of mortality in patients on chronic dialysis: A single center, prospective longitudinal study. Croat Med J 2013;54:25-32.
12. Pascual-Figal DA, Bonaque JC, Redondo B, Caro C, Manzano-Fernandez S, Sánchez-Mas J, *et al.* Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients. Eur J Heart Fail 2009;11:840-6.
13. Weng CL, Wang CH, Chen IC, Hsiao KY, Chang KP, Wu SY, *et al.* Red cell distribution width is an independent predictor of mortality in necrotizing fasciitis. Am J Emerg Med 2014;32:1259-62.
14. Braun E, Kheir J, Mashiach T, Naffaa M, Azzam ZS. Is elevated red cell distribution width a prognostic predictor in adult patients with community acquired pneumonia? BMC Infect Dis 2014;14:129.
15. Meynaar IA, Knook AH, Coolen S, Le H, Bos MM, van der Dijs F, *et al.* Red cell distribution width as predictor for mortality in critically ill patients. Neth J Med 2013;71:488-93.
16. Pérez-Martín A, Horrillo-Sánchez de Ocaña L, Satué-Bartolomé JA, Belinchón Paraíso JC, Gonzalo-Pascua S, Marrero-Francés J, *et al.* Red cell distribution width and mortality following hospital discharge in patients over 70 years of age. Med Clin (Barc) 2014;143:49-56.
17. Oh HJ, Park JT, Kim JK, Yoo DE, Kim SJ, Han SH, *et al.* Red blood cell distribution width is an independent predictor of mortality in acute kidney injury patients treated with continuous renal replacement therapy. Nephrol Dial Transplant 2012;27:589-94.
18. Förhécz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskuti L. Red cell distribution width in heart failure: Prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J 2009;158:659-66.
19. Loveday S, Sinclair L, Badrick T. Does the addition of RDW improve current ICU scoring systems? Clin Biochem 2015;48:569-74.
20. Ramby AL, Goodman DM, Wald EL, Weiss SL. Red blood cell distribution width as a pragmatic marker for outcome in pediatric critical illness. PLoS One 2015;10:e0129258.
21. Bion JF. Susceptibility to critical illness: Reserve, response and therapy. Intensive Care Med 2000;26 Suppl 1:S57-63.