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 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 were 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. 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. 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. 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. 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
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 $63.2 \pm 15.5$ 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. 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
injury treated with continuous renal replacement therapy. More recently, studies have identified RDW as a very good prognostic marker in esophageal carcinoma and ulcerative colitis.

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. 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.

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 antibiotics such as cefotaxime and meropenem was the most common therapeutic intervention in our study. These results are consistent with previous studies which have shown that RDW is a good prognostic marker in ICU patients.
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. However, many studies in the medical literature have revealed that the relationship between RDW and mortality of RDW is independent of anemia. 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.

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

### 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

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.

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