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Original Research Article

RED BLOOD CELL DISTRIBUTION WIDTH AS A PROGNOSTIC BIOMARKER FOR CLINICAL OUTCOMES AND MORTALITY IN ACUTE RESPIRATORY DISTRESS SYNDROME

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ABSTRACT

Background: The objective is to determine whether admission Red Blood Cell Distribution Width (RDW) predicts the clinical course and in-hospital mortality among patients with acute respiratory distress syndrome (ARDS) admitted to the Chest Intensive Care Unit (ICU).

Materials and Methods: This prospective observational study was conducted in Ward-12 Chest Intensive Care Unit (ICU), Jinnah Postgraduate Medical Centre (JPMC), Karachi, over six months. A total of 193 adult patients diagnosed with acute respiratory distress syndrome (ARDS) according to the Berlin Definition were enrolled using consecutive non-probability sampling. Admission Red Blood Cell Distribution Width (RDW) was measured from the complete blood count, and patients were followed until hospital discharge or death. Clinical outcomes included duration of mechanical ventilation, ICU length of stay, multiorgan dysfunction, and in-hospital mortality. Data were analyzed using SPSS version 26.0, and multivariable logistic regression was performed to identify independent predictors of mortality.

Results: The mean age of participants was 55.2±14.8 years, and 61.7% were male. Seventy-two (37.3%) patients had an admission RDW ≥16.4%. Patients with elevated RDW had significantly longer ICU stay (12.1±4.8 vs. 8.3±3.9 days; $p<0.001$), prolonged mechanical ventilation (9.4±4.5 vs. 6.1±3.4 days; $p<0.001$), higher frequency of multiorgan dysfunction (43.1% vs. 19.8%; $p=0.001$), and greater in-hospital mortality (45.8% vs. 23.1%; $p=0.001$). Elevated RDW independently predicted mortality (adjusted OR 2.63, 95% CI: 1.36–5.09; $p=0.004$).

Conclusion: Elevated admission RDW is independently associated with adverse clinical outcomes and increased in-hospital mortality in patients with ARDS. As an inexpensive and routinely available laboratory parameter, RDW may serve as a practical prognostic biomarker for early risk stratification in critically ill patients.

Keywords: Acute respiratory distress syndrome; Red blood cell distribution width; Mortality; Intensive care unit; Prognostic biomarker; Mechanical ventilation.

INTRODUCTION

The severe form of acute hypoxemic respiratory failure is called Acute Respiratory Distress Syndrome (ARDS). It is associated with widespread inflammatory damage to the lung, with the lung's blood vessels becoming more permeable and with the presence of pulmonary infiltrates on both sides of the body and is not explained by the presence of heart failure or high hydrostatic pressure. Although there have been numerous advances in lung-protective mechanical ventilation, prone positioning, extracorporeal membrane oxygenation (ECMO), and other aspects of critical care management, ARDS is still associated with considerable morbidity and mortality throughout the world. New studies have shown that ARDS is present in about 10% of those patients admitted to an intensive care unit (ICU), and in about 23% of patients who require mechanical ventilation. The mortality rate of these patients is reported to be in the range of 35% to 46%, and is determined by the severity of the ARDS and the cause of the syndrome.[1,2] Identifying these patients early in the course of ARDS allows for the best use of limited resources and has the potential to choose and administer therapies that may alter the course of the syndrome and improve survival. Although there are multiple widely judged prognostic indicators of ARDS such as the SOFA score, APACHE II and the Simplified Acute Physiology score (SAPS II), these scores are complex, and require numerous clinical and laboratory evaluations which are often not performed at the time of admission to the ICU.[3] Therefore, there is great interest in the development of low cost and readily accessible biotechnologies that could help identify patients at risk for the acute syndrome in a timely fashion. Almost all complete blood counts (CBCs) also include Red Blood Cell Distribution Width (RDW). RDW is a measure of the variation in red blood cell size (anisocytosis). RDW has been traditionally employed to evaluate different anemias. Recently, RDW has been used as a predictor of poor prognosis in a number of critical disorders such as sepsis and heart failure. In the context of these diseases, rising RDW values may be indicative of the complex combination of succumbing inflammation, oxidative stress and nutrient deficiency, as well as impaired erythropoiesis.[4] A recent meta-analysis has found that an RDW value that rises above the reference range upon ICU admission is suggestive of a significantly higher risk of developing ARDS and of a higher risk of mortality. Further, in a large study of 1,037 ARDS patients, an RDW level at admission ≥ 16.4 % was correlated with an increased risk of ICU mortality, longer mechanical ventilation and longer ICU stay.[5,6]

MATERIALS AND METHODS

This prospective observational study was carried out in Ward-12 Chest Intensive Care Unit (ICU), Jinnah Postgraduate Medical Centre (JPMC), Karachi, for six months after approval from the Institutional Review Board (IRB). The Chest ICU is a specialized tertiary-care unit where patients with Acute Respiratory Distress Syndrome (ARDS) requiring advanced respiratory support, including invasive mechanical ventilation, are routinely admitted and managed. This study was conducted on adult patients (≥18 years) with the diagnosis of Acute Respiratory Distress Syndrome (ARDS) according to the Berlin Definition. The number of patients who fulfilled the selection criteria was 193. The WHO sample size formula was used to determine the sample size with a 7% margin of error, 95% confidence level and a presumed mortality rate of 54.1% in parent study. The selection of the participants was done using non-probability sampling and was done consecutively until the sample size was fulfilled. This study included both males and females diagnosed with ARDS, within one week of a known clinical insult, and fulfilling the diagnostic criteria of the Berlin definition. These patients were excluded from the study because they had a blood transfusion within 3 months; hematological disease that would modify the morphology of red blood cells; chronic liver disease; end-stage kidney disease requiring dialysis; pregnant; and/or incomplete clinical records. After obtaining written informed consent from the patient or the patient's legal representative, a structured data collection proforma was filled out and included demographic data, comorbidities, smoking history, ARDS etiology, and relevant clinical information. Admission Red Blood Cell Distribution Width (RDW) was obtained from the complete blood count which was performed on an automated hematology analyzer as a routine part of the admission blood work. ICU patients were followed throughout their length of stay to document clinical course. This encompassed mechanical ventilation time, length of stay in the ICU, organ dysfunction, and mortality within the hospital. The independent variable was the RDW at admission and the main outcome was the mortality rate during the hospitalization. Other outcomes of interest were mechanical ventilation duration and length of stay in the ICU. The data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0. The Shapiro-Wilk test was used to assess the normal distribution of continuous data. Data were presented as mean ± SD or median (IQR). Categorical data were presented as numbers and percentages. Independent-samples t-test or Mann-Whitney U test were used for the comparison of study groups for continuous data; Chi-square test or Fisher's exact test were used for categorical data. Multivariable logistic regression was used to determine independent risk factors for in-hospital mortality after controlling potential confounders. The p-value of less than 0.05 was considered statistically significant. The confidentiality of all participants was ensured and all procedures followed the principles of the Declaration of Helsinki.

RESULTS

A total of 193 patients with acute respiratory distress syndrome (ARDS) were enrolled in the study. The mean age was 55.2 ± 14.8 years (range: 18–84 years). There were 119 (61.7%) males and 74 (38.3%) females. Hypertension was the most common comorbidity (81, 42.0%), followed by diabetes mellitus (66, 34.2%) and chronic obstructive pulmonary disease (29, 15.0%). Pneumonia accounted for 98 (50.8%) cases of ARDS, sepsis for 54 (28.0%), aspiration pneumonitis for 23 (11.9%), and other causes for 18 (9.3%). The mean admission RDW was 15.8 ± 1.7%. Baseline demographic and clinical characteristics are presented in [Table 1].

Using an admission RDW cut-off of 16.4%, 121 (62.7%) patients were categorized into the RDW <16.4% group and 72 (37.3%) into the RDW ≥16.4% group. Patients with elevated RDW had significantly longer ICU stay (12.1 ± 4.8 vs. 8.3 ± 3.9 days; p<0.001) and prolonged duration of mechanical ventilation (9.4 ± 4.5 vs. 6.1 ± 3.4 days; p<0.001). Vasopressor requirement (44.4% vs. 24.8%; p=0.006) and multiorgan dysfunction (43.1% vs. 19.8%; p=0.001) were also more frequent among patients with RDW ≥16.4% [Table 2].

Overall, 61 (31.6%) patients died during hospitalization, while 132 (68.4%) survived. Mortality was significantly higher among patients with RDW ≥16.4% than those with RDW <16.4% (45.8% vs. 23.1%; p=0.001) [Table 3].

Multivariable logistic regression analysis demonstrated that RDW ≥16.4% remained an independent predictor of in-hospital mortality after adjustment for age, gender, hypertension, diabetes mellitus, smoking status, and ARDS etiology (adjusted OR 2.63; 95% CI: 1.36–5.09; p=0.004). Increasing age (adjusted OR 1.04 per year; 95% CI: 1.01–1.07; p=0.011) and diabetes mellitus (adjusted OR 1.89; 95% CI: 1.01–3.56; p=0.047) were also independently associated with mortality, whereas gender, hypertension, smoking status, and ARDS etiology were not significant predictors [Table 4].

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Value
Sample size	193
Age (years), mean ± SD	55.2 ± 14.8
Male	119 (61.7%)
Female	74 (38.3%)
Hypertension	81 (42.0%)
Diabetes mellitus	66 (34.2%)
Admission RDW (%)	15.8 ± 1.7

Table 2: Clinical Course According to RDW

Variable	RDW <16.4%	RDW ≥16.4%	p-value
ICU stay (days)	8.3 ± 3.9	12.1 ± 4.8	<0.001
Mechanical ventilation (days)	6.1 ± 3.4	9.4 ± 4.5	<0.001
Organ dysfunction	24 (19.8%)	31 (43.1%)	0.001

Table 3: Association Between RDW and Mortality

RDW	Survived	Died	Total	p-value
<16.4%	93	28	121	
≥16.4%	39	33	72	
Total	132	61	193	0.001

Table 4: Logistic Regression for Mortality

Variable	Adjusted OR	95% CI	p-value
RDW ≥16.4%	2.63	1.36–5.09	0.004
Age	1.04	1.01–1.07	0.011
Diabetes mellitus	1.89	1.01–3.56	0.047

DISCUSSION

This study also demonstrates that acute respiratory distress syndrome (ARDS) patients with a higher RDW at admission (>16.4%) were more likely to have longer mechanical ventilation and multiorgan dysfunction and to remain in the intensive care unit (ICU) longer, besides being at higher risk of dying while hospitalized. For this group of patients, an increase in RDW might be an effective marker for mortality. RDW was found to be a predictor of mortality even after adjusting for other variables, so this measurement can be done to help identify high-risk patients.[7] In the study done by Menk et al., the authors noted similar findings. Patients with ARDS and an elevated RDW (> 16.4%) had a longer duration of mechanical ventilation, a longer length of stay in the ICU and increased in-ICU mortality. Furthermore, the authors noted that the use of RDW could be a useful additional measurement for risk stratification of ARDS patients.[7] In the recent meta-analysis, an increased RDW at the time of admission to the ICU was shown to have a significant positive correlation with an increased mortality risk and an increased severity of illness for patients with ARDS. As a simplified and easily available prognostic

marker, RDW also had a significant positive correlation with the mortality risk for those with ARDS in the study by Yu et al which also included other clinical variables. Also reported in that study was an increase in RDW, which was prognostic.[8,9] The poor clinical outcomes and elevated RDW may be the result of a myriad of factors. Increased levels of chronic inflammation and the presence of oxidative stress; dysregulation of erythropoiesis, iron, and nutrition; and finally poor treatment may all play a role. In patients in critical condition, these mechanisms unravel the association between elevated RDW levels and the RDW levels and the severity of disease.[10–12] The remaining study, diabetes mellitus, and advanced age were also predictors of mortality and were also independently associated with the mortality of ARDS, and these results were consistent with previously published studies.[13,14] Advanced age and diabetes were independent risk factors. Gender, hypertension and smoking and ARDS were not independent causes of death. This means that RDW could be more predictive than the conventional clinical parameters. The main strengths were prospectiveness, sample size, and clinically relevant outcomes, while the main limitations were single-center design, and no repeated measures of RDW. Future multi-center studies should assess the addition of RDW to existing ARDS severity scores (e.g. APACHE II, SOFA) to assess the potential value of predicted mortality and RDW for informing ARDS patient care.[15]

CONCLUSION

This research found that when patients with Acute Respiratory Distress Syndrome (ARDS) are admitted with an elevated Red Blood Cell Distribution Width (RDW; reflective of an RDW ≥ 16.4%), they are at greater risk for a longer ICU stay, a longer duration of mechanical ventilation, increased multiorgan deterioration, and greater mortality. Also, RDW was an independent mortality risk factor after the potential confounders were controlled for. The RDW is a relatively simple, cheap and widely available laboratory test and can serve as a biomarker in identifying early those patients at risk of developing ARDS and in assessing prognosis in ARDS. More and larger studies, and prospective studies, are needed to confirm these findings and the usefulness of RDW to guide the practice of medicine.

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