

The Use of Red Blood Cell Distribution Width (RDW) as Mortality Predictor in the Intensive Therapy Unit (ITU) at Hospital Ángeles Del Pedregal

Humberto Ochoa Salmorán^{1*}, Ivonne Martínez Martínez², Silvia Del Carmen Carrillo Ramírez³ and Juan Gerardo Esponda Prado⁴

¹ITU Medical Resident at Hospital Ángeles del Pedregal, Universidad La Salle Medical School, Mexico City, Mexico

²Intensive Medicine Resident at Hospital Ángeles del Pedregal, Universidad La Salle Medical School, Mexico City, Mexico

³ITU Attending Physician at Hospital Ángeles Pedregal, Mexico City, Mexico

⁴ITU Chief Physician at Hospital Ángeles Pedregal, Mexico City, Mexico

***Corresponding Author:** Humberto Ochoa Salmorán, ITU Medical Resident at Hospital Ángeles del Pedregal, Universidad La Salle Medical School, Mexico City, Mexico.

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Abstract

Introduction: Red Blood Cell Distribution (RDW) consists in an index used to determine heterogeneity for red blood cells, which measures anemia or malnutrition disorders. However, its statistical elevation was associated with other inflammation biomarkers. Values above 15% are associated with increased mortality rate in critically ill patients.

Objective: To determine the RDW increase and mortality ratio, in this environment, for patients in the Intensive Therapy Unit.

Methodology: Control group consisted of hospitalized patients between March 2018 and August 2018, and the following data was included in the statistical analysis: SOFA, SAPS 3, hemoglobin, hematocrit, leucocytes, platelets, RDW, creatinine, albumin, as well as demographic data. The values assessed by the laboratory team in this unit were considered to be within normal levels.

Results: Regarding the Chi-squared distribution statistical test, a p value of 0.048 was obtained when linking the number of deaths in the ITU to the RDW values, which proves the relationship between these variables.

Conclusion: The RDW increase is highly associated with a higher mortality rate and is useful for risk stratification in critically ill patients.

Keywords: Red Cell Distribution; Intensive Therapy Unit; Mortality Rate

Introduction

Red Blood Cell Distribution (RDW) consists in an index used to determine heterogeneity for red blood cells. This has been broadly used as a mortality biomarker in patients with severe diseases, such as heart failure, pulmonary embolism (PE), acute coronary syndrome (ACS) and peripheral arterial disease (PAD) [1]. The RDW value is influenced by several factors. During the Kim., *et al.* [1] study, it was reported that elevated RDW [1] values are considered independent mortality indicators in sepsis and septic shock patients [1].

In the case of malnutrition disorders, this indicator can be used to measure chronic conditions [2]. Age is an expected physiological cause, which results in RDW decreased values [3]. Characteristic oxidative stress and inflammation states, during a severe disease play, play an important role that fosters pathological physiology, which normally connects RDW and mortality. The increased levels of oxidative stress can be attributed to inflammation-mediated cytosine, which also results in iron immobilization and the following RDW increase [4]. Regardless of being used for diagnosing anemia' differential, RDW's statistical elevation is linked to additional inflammation biomarkers, such as C-creative protein, ESR, Interleukin 6 (IL-6) and tumor necrosis factor alpha.

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In 2007, Michael Felker, *et al.* [6] found that RDW was an independent predictor of mortality in heart failure patients; later, this was also linked to other medical conditions [6]. Several studies have proven the relationship between high RDW levels and mortality rate in community-acquired pneumonia, sepsis and septic shock patients [6].

RDW represents a variable circulating red blood cell volume. During any physiological event, it is determined that erythropoiesis increases, which results in the occurrence of immature red blood cell forms. This is a secondary feature to inflammation and reactive systems, which not only affect the half-life but also the membranes in red blood cells; therefore, red blood cells capacity to mature is affected and reticulocytosis increases [5].

Statistical abnormalities are found in values above 15%. Recently, evidence suggesting a relationship between RDW and mortality in critically ill patients was demonstrated, which fails to differentiate medical and surgical pathology [2]. Furthermore, it was proven that the predictor value, which is limited in its qualities and consecutive lecture series [2], consists in the first time that the patient was hospitalized. These characteristics are supported by the half-life count of blood cells, found in the blood stream, which is 120 days within healthy subjects and possibly, 30 days in patients showing pathological conditions [2]. RDW consecutive measurements are only believed to have a significant value when used for chronic conditions, where patients are monitored for long periods of time; to be considered medically relevant, a 30-day interval is proposed to measure and interpret RDW [2].

There is a great need for a risk stratification system, in the Emergency Room and Intensive Therapy Units, that would funnel patients. This is aimed at fostering the efficient use of institutional resources from hospitals, where patient admission is limited [5]. RDW consists in a routine study, which can be performed, in terms of cost-effectiveness, in patients to predict mortality rates, as these metrics were studied for a 90-day period after the moment the patient is admitted to the actual provision of these services [2]. The ITUs are focused on a highly heterogenous group; therefore, at the moment of patient's entry, risk stratification must be determined, which will also optimize the use of the resources available [7].

For surgical patients, a group of 00 patients was used, 47% (237 patients), showed an RDW increase and a mortality rate of 28% (140 patients). In this group, it was observed that the mortality rate and RDW increase are independent values from normally used inflammation systems or score in critically ill patients². RDW impact was also assessed in pneumonia patients, as widely-used scores, such as CURB - 65 or PSI, were developed in the Emergency Room to calculate mortality rates for patients treated in the Emergency Room. For 60-year-old senior patients showing an RDW increase outside the reference scope, a relationship between mortality and mobility was observed in patients with no elevated levels [8]. Furthermore, the ratio in senior patients of more than 65 years old increased, based on several facts like an atypical occurrence of infectious processes, and even though it was proven to be linked to mortality, it is not yet a widely-used tool for these purposes; one of the goals is to determine the relationship between these three factors: RDW and mortality rate in senior patients of more than 65 years old. Unless there are more studies supporting these findings, the previous information must be taken into account to efficiently use this method [9,10].

Materials and Methods

Materials and sample: In this study, a sample comprising patients admitted in the Intensive Therapy Unit (ITU) at Hospital Ángeles del Pedregal, from March to August 2018, was assessed; except in the case of incomplete medical records, the patients' full blood count (CBC), blood chemistry and liver function tests (LFT) were available at the time of admission. In case of re-entry, the laboratory results from the patient's first hospitalization are used as the study baseline values.

A longitudinal study was performed to determine the existing RDW increase and mortality ratio for patients in this environment.

The following data was included in the statistical analysis: SOFA, SAPS 3, hemoglobin, hematocrit, leucocytes, platelets, RDW, creatinine, albumin, as well as demographic data. SOFA and SAPS 3 indexes, which are valid scores for multi-center studies, are normally used during the entry process to ITUs, as a mortality predictor. SOFA score is employed for a daily assessment of the patients' response to treatment, as well as a patient mortality predictor in these units.

The values assessed by the laboratory team in this unit were considered to be within normal levels.

Statistical analysis

For quantitative variables, the mean absolute deviation (MAD) and standard deviation (SD) were used as the first step of an analysis of the descriptive statistics; the Shapiro-Wilk test was also performed to see if the variables fitted a normal distribution and determine, based on the results, the suitable type of test for the a bivariate analysis.

Consequently, the observed frequency was used and the pertinent valid percentage for quantitative variables in each group, as an analysis of the descriptive statistics.

To perform a bivariate analysis, contingency tables were undertaken for binary variables, which resulted in squared 2 x 2 tables, to verify the hypothesis on variable independence; the Pearson's chi-squared distribution statistical test (χ^2) was used and Fisher's exact test was employed when frequency grids were not enough for these purposes. For quantitative variables, the verification process was obtained through a non-parametric Mann-Whitney *U* test when variables were not within normal distribution values, while the equality of variances were assessed by a Levene's test when variables were within normal distribution values, which complied with the use of a Student's *t*-test for independent samples. For all the bivariate analyses, the test statistical review was reported, as well as the statistical significance value (p value). OR value and the confidence interval (CI) were obtained when contingency tables were employed.

For a multivariate analysis (MVA), logistic regression models and a Hosmer-Lemeshow test were performed to assess favorable characteristics for the model adjustment.

For all testing, a level of alpha significance level of 0.05 was adopted and all statistical analyses were conducted RStudio computing software.

Results

In this study, a sample of 175 male and female patients, with an average age of 62.78 (SD = 16.84), was used, where the minimum age was 17 years old and the maximum age was 92 years old. The general sample laboratory results are mentioned in table 1.

The first bivariate analysis result from sample and death demographic variables is explained in table 2. There is no statistical evidence showing a variable relationship.

Major origin sites are Emergency Rooms with 35.1% (60 patients) and Operating Rooms with 32% (56 patients), while minor origin sites are the Hemodynamic Laboratory with 2.3% (4 patients). Entry conditions are classified in tow main categories: type A (organ failure) with 43.9% (75 subjects) and type B (risk of organ failure) with 21.1% (36 subjects). Entry CPR levels are determined to be at 98.2%, due to all the support provided, in contrast to the clearly differentiated 92.4% (157 patients) that was not subject to this procedure.

	Total sample
	Mean (SD)
SAPS3	33.67 (26.23)
SOFA	6.22 (8.76)
RDW	13.92 (2.44)
Leucocytes	12.4 (6.96)
Hemoglobin	12.63 (2.86)
Hematocrit	38.16 (8.19)
Platelet	223.91 (104.88)
Creatinine	1.41 (1.87)
Albumin	3.17 (0.79)
Globulin	4.25 (18.38)
Total CO ₂	19.11 (4.49)

Table 1

	Deaths		Statistical index ^a	p	IC
	Applicable (n = 29)	NA (n = 146)			
	n (%)				
Age	64.07 (15.93) ^c	62.53 (17.05) ^c		0.942	
Sex			0.139	0.709 ^b	0.79 (0.32,1.9)
Female	16 (55)	72 (49)			
Male	13 (45)	74 (51)			
Re-entry	2 (7)	11 (8)		1 ^b	0.91 (0.09,4.53)
Code 77 ^d	2 (7)	12 (8)		1 ^b	0.83 (0.09,4.05)
Code blue ^e	1 (3)	4 (3)		1 ^b	1.27 (0.02,13.43)
a: Pearson’s chi-squared distribution statistical test (χ^2) b: Fisher’s exact test c: Mean absolute and standard deviations d: Code 77, patient showing a medical deterioration on site, admitted to the ITU e: Code blue, patient subject to CPR and admitted to the ITU					

Table 2

Regarding chronic degenerative diseases, the following values were obtained: a prevalence for Systemic Hypertension with 38.6% (66 subjects); secondly, Diabetes Mellitus (DM) with 15.8% (27 subjects); thirdly, Chronic Kidney Disease with 7.6% (13 subjects); in fourth place, Chronic Obstructive Pulmonary Disease (COPD) with 9.4% (16 subjects); in fifth place, Hypothyroidism with 7.6% (13 subjects), and lastly, other medical conditions with 76% (130 subjects). The prophylaxis for stress ulcers and deep vein thrombosis were identified in all the patients.

In table 3, the results from the bivariate analysis, which were obtained from the reviews of the laboratory variables, and death and survival groups, are explained.

Considering that the RDW value is within a risk parameter when it is equal or above 15%, a binary analysis was conducted, which included this cut point and an independent verification was performed between the RDW variable and the patient mortality rate, through a Pearson’s chi-squared distribution statistical test that yielded a result of $p = 0.082$ and $\chi^2 = 3.025$, which indicates that both variables are independent.

When comparing both qualitative variables per sex (Table 3) sample, the following values were obtained for chronic degenerative diseases: a prevalence for Systemic Hypertension with 45.3% (39 subjects) in the male group and 31.8% (27 subjects) in the female group; secondly, Diabetes Mellitus (DM) has higher percentage of 16% (14 subjects) in the female group; thirdly, Chronic Kidney Disease with no participation from the female group and 15.1% (13 subjects) in the male group; in fourth place, Chronic Obstructive Pulmonary Disease (COPD) with 12.9% (11 subjects); in fifth place, Hypothyroidism with 10.6% (9 subjects), and lastly, Delirium with 20.9% (18 subjects).

	Deaths		Statistical index ^a	P
	Applicable (n=29)	NA (n=146)		
	Mean (SD)			
SAPS3	60.93 (27.56)	28.25 (22.38)		< 0.001 ^b
SOFA	12.24 (13.78)	5.02 (6.84)		< 0.001 ^b
RDW	14.73 (2.31)	13.76 (2.44)		0.014 ^b
Leucocytes	14.94 (9.34)	11.9 (6.31)		0.156 ^b

Hemoglobin	11.87 (2.9)	12.78 (2.84)	57.159	< 0.001
Hematocrit	36.1 (8.2)	38.57 (8.16)	61.297	< 0.001
Platelet	177.18 (88.16)	233.06 (105.72)		0.015 ^b
Creatinine	1.71 (1.88)	1.35 (1.87)		0.058 ^b
Albumin	2.8 (0.69)	3.24 (0.78)		0.004 ^b
Globulin	2.85 (0.68)	4.52 (20.11)		0.908 ^b
Total CO ₂	17.47 (4.57)	19.44 (4.42)	55.653	< 0.001
a: Student's <i>t</i> -test				
b: Mann-Whitney <i>U</i> test				

Table 3

Increased RDW diagnosis are highly relevant in the female group with 32.9% (28 patients) and in the case of the performance status, it has a greater representation in the male group with 83.7% (72 patients).

Regarding the ITU patient deaths that took place (Table 4), only the most relevant cases are presented as evidence. Systemic Hypertension with 35.7% (10 subjects); secondly, Diabetes Mellitus (DM) with 17.9% (5 subjects); thirdly, Chronic Kidney Disease with 14.3% (4 subjects); in fourth place, Chronic Obstructive Pulmonary Disease (COPD) with 14.3% (4 subjects); in fifth place, other medical conditions with 78.6% (22 subjects), and, lastly, Delirium with 17.9% (5 patients).

Model adjustment in:	IC	Standard Error (SE)	Statistical index z	p	Hosmer-Lemeshow test	
					Statistical index	p
SAPS3	1.052	0.01	5.265	< 0.001	5.927	0.655
SOFA	1.142	0.049	2.693	0.007	20.634	0.008
RDW	1.159	0.078	1.904	0.057	7.0312	0.533

Table 4

For the Chi-squared distribution statistical test, a p value higher than 0.048 (Table 5) when obtaining an ITU patient mortality rate and RDW values ratio, which proves that there is a relationship between those variables.

RDW diagnosis	ITU deaths				p*
	Yes		No		
	Frequency	Percentage	Frequency	Percentage	
High	11	39.3	31	21.7	0.048
Bajo	17	60.7	112	78.3	0.048

Table 5: ITU deaths and RDW ratio.

*A relevant p value less than 0.05 was established through the Chi-squared distribution statistical test.

Predictive models for patient mortality are used, where only SAPS3, SOFA and RDW values are adjusted in each model, respectively.

The only model considered unsuitable for these reviews is the SOFA-adjusted model, which indicates that it is not a proper model to predict mortality. While the RDW-adjusted model proves that this variable is not statistically related to the model, for the p value is $p > 0.05$, it is inferred that a higher sample number could be required, as the gap between the observed and fixed significance levels is minimal.

For the Chi-squared distribution statistical test, a p value higher than 0.048 (Table 5) when obtaining an ITU patient mortality rate and RDW values ratio, which proves that there is a relationship between those variables.

Discussion

In the last years, there has been a growing interest for discovering new diagnosis methods for critically ill patients in the Intensive Therapy Unit (ITU). Early diagnosis and on-time risk stratification are particularly important in this type of patients. In this study, it was found that an RDW value is highly associated to ITU patient mortality. This study confirmed all findings observed by Zhang, *et al.* [1] and concludes that the RDW is linked to a higher mortality risk in hospitals for critically ill unselected patients [1].

RDW is also useful to allocate limited ITU resources by assessing the severity of critical illnesses, determining the pertinent healing effects, comparing the performance in different facilities and making medical decisions [2]. Physicians from the Emergency Room also need a precise tool to identify patients that will benefit from hospitalization, especially those admitted to the ITU. In the last years, a great amount of studies tried to find new predictors [11,12].

An RDW increase contemplates a greater heterogeneity in the red blood cells volume. Disorders related to an inefficiency in the coefficient of variation (CV) of circulating red blood cells (iron-deficiency anemia, vitamin B12, folate deficiency, bone marrow suppression and hemoglobinopathy), the breakdown of red blood cells (hemolysis) or blood transfusion cause an RDW increase [13]. Furthermore, an RDW change is affected by several factors, such as liver or kidney failures, malnutrition, cancer, thyroid disease, acute or chronic inflammatory responses, the use of some drugs, the activation of the renin-angiotensin system (RAS) and ethnic group [14-16]. Consequently, as of now, RDW was mainly used to detect iron-deficiency anemia, but it is dismissed when the possibility for this condition is disregarded.

Nevertheless, some authors, like Felker, proved that RDW is one of the strongest morbidity and mortality predictors for several cardiovascular diseases, such as Coronary Artery Disease (CAD), Pulmonary Hypertension, Acute Heart Failure, Peripheral Arterial Disease (PAD), strokes or Pulmonary Embolism, and is considered independent from hemoglobin levels [17-21].

Currently, the relationship between RDW and mortality rates is supported by several studies; however, the exact underlying mechanism is not completely understood yet. Some authors indicate that bone marrow function and human iron metabolism are constantly influenced by the systemic inflammatory response [22,23].

Otero corroborated the relationship between increased RDW levels and mortality rates for postoperative patients of major surgeries, after 90 days of being admitted to the Critical Care Unit (CCU). An IC estimate of 2.28 was established (IC 95%: 1,20 - 4,33, $p = 0,012$) in the patient group, with an RDW rate of $> 14.5\%$, compared to the group with an RDW value of $11.5-14.5\%$ [5]. Several researches concluded that there is a narrow relationship between RDW and mortality and determined the need of more studies to predict future events [14].

Nevertheless, this ratio is modified by several medical conditions; therefore, it is necessary to conduct an analysis with the lowest amount of intervening variables possible. During this research, the authors attempted to standardize the studied sample by analyzing a similar male and female percentage within the control groups.

The RDW predictor value is still considered an important factor, even though RDW was included to the previously established predictive models, such as SOFA, APACHE II and SAPS 3, which considerably improves their discriminatory power [3].

The study results are overall aligned with the literature information. Consequently, Oh, *et al.* [24] discovered that RDW was an independent predictor of mortality in critically ill patients after 28 days. There are several published studies, as well as others that consistently show a significant bond between RDW and mortality [25-27]. The same results are replicated in this research.

In conclusion and based on previous evidence, this study confirms that the documented RDW increase, at the time of ITU admission, is linked to a higher hospital mortality rate. However, the diagnostic performance to predict mortality still needs to be researched in the future.

Conclusion

The RDW increase is highly associated with a higher mortality rate and is useful for risk stratification in critically ill patients. Furthermore, as it is a routine procedure, there are no additional expenses for it. This study's findings and limitations provide an essential objective for future research by establishing definitive cut points and continuously evaluating their relationship with other scores.

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