ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 7(C), pp. 27891-27895, July, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

THE PROGNOSTIC POTENTIAL OF RED BLOOD CELL DISTRIBUTION WIDTH VALUES IN INTENSIVE CARE UNIT PATIENTS

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DOI: http://dx.doi.org/10.24327/ijrsr.2018.0907.2353

ARTICLE INFO

Article History:
Received 15th April, 2018
Received in revised form 7th May, 2018
Accepted 13th June, 2018
Published online 28th July, 2018

Key Words:
Intensive Care Unit,
APACHE II, RDW, mortality

ABSTRACT

Aim: In several diseases, a relationship has been shown between mortality and a high level of red blood cell distribution width (RDW). The aim of this study was to investigate the relationship between mortality and RDW measured in patients in the Intensive Care Unit (ICU), and to compare the RDW values with the Acute Physiology and Chronic Health Evaluation (APACHE-II) score, which is accepted as an independent risk factor for mortality.

Material and Method: A retrospective evaluation was made of the demographic data, disease diagnoses, laboratory data and APACHE-II scores of ICU patients between January 2013 and December 2014.

Results: A total of 233 patients were included in the study. The mean age was 74 years (range, 19-96 years) and the mortality rate was 25.32%. The RDW value and APACHE-II score at the time of admission to ICU were determined to be higher in the patients with mortality than in those who survived ($p<0.001$). In the multivariable logistic regression analysis, a ROC curve was drawn for each patient to determine the diagnostic accuracy of the RDW ($p<0.05$, OR=0.870) and APACHE II ($p<0.001$, OR=0.723) values determined as independent markers of mortality status, and mortality predictive capability was examined. In the prediction of mortality, sensitivity was 66.1% and specificity was 66.1% for RDW (AUC = 0.689, optimal cutoff value = 14.5), and for APACHE II scores, sensitivity was calculated as 86.4% and specificity as 81% (AUC = 0.902, optimal cutoff value = 17.5).

Conclusion: The results of this study determined a relationship between increased RDW values and mortality in ICU patients. Although the rates of predicting mortality were not as high as those of the APACHE II score, RDW alone, which is a low-cost and readily available test, can be considered an extremely valuable parameter for the prediction of mortality rates.

INTRODUCTION

Various scoring systems are used in the prediction of prognosis and mortality of patients in the Intensive Care Unit (ICU). Patients in ICU are most often evaluated according to the Acute Physiology and Chronic Health Evaluation (APACHE-II) scoring system, which was first established in 1981.This scoring system defines a value for the patient calculated from variables such as vital signs, laboratory values, consciousness status and presence of chronic diseases. Higher scores are related to an increased risk of mortality (1).

Red cell distribution width (RDW) is a measurement of the variability of the volume of erythrocytes and is examined in a routine full blood count. The normal range of RDW is 11%-14.5%. An increase in RDW shows a great variation in erythrocyte volumes (2). It has recently been reported that RDW is a marker of mortality and a high value indicates a poor prognosis in many diseases (3, 4). Moreover, increases in RDW have been found to be related to increased inflammatory markers (5, 6).

The aim of this study was to retrospectively examine the RDW values of ICU patients and determine the potential for prediction of morbidity and mortality.

MATERIAL AND METHOD

Approval for the study was granted by the Local Ethics Committee. A retrospective examination was made of the records of patients in the General Surgery ICU between January 2013 and December 2014. Patients were excluded if

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laboratory or clinical data were incomplete, if they were aged <18 years, pregnant or postpartum, had any malignancy or a history of blood transfusion in the previous 15 days.

A total of 357 patients were screened. The exclusion criteria applied to 124 patients and 233 patients were included in the study. The patients were categorised as survivor or non-survivor, and according to the RDW levels as Low RDW for those with ≤14% and High RDW for those with >14%, taking 14% as the reference value of the 50th percentile of RDW %. Biochemical and hematological data and all the clinical results of the patients were obtained from the hospital database and patient records.

Statistical Analysis

The data obtained in the study were statistically analysed using the Statistical Package for Social Sciences (SPSS) version 22.0 software. Conformity of the data to normal distribution was examined visually (histogram and probability graphs) and with the analytical method of the Kolmogorov-Smirnov test. In descriptive analyses, variables with normal distribution were stated as mean ± standard deviation (SD), and variables not showing normal distribution were stated as median, minimum and maximum values. Continuous variables were reported as mean±SD, and categorical variables as number (n) and percentage (%). In the comparison between group of continuous variables, the Student's t-test or the Mann Whitney U-test was applied according to whether distribution was normal or not. In the comparison of categorical variables between groups, the Chi-square test was applied.

To determine the independent predictive variables of mortality, forward stepwise multivariate logistic regression analysis was applied, including all the variables determined as $p<0.1$ in the univariate analysis and the results were presented showing the Odds Ratio (OR) and Confidence Interval (CI). For all the tests a value of $p<0.05$ was accepted as statistically significant. The cutoff values of independent predictors found to be significant were analysed with the receiver operating characteristic (ROC) curve. The ROC curve analysis and the area under the curve (AUC) were evaluated with the Hanley and McNeil method.

RESULTS

Evaluation was made of a total of 233 patients comprising 50.6% females and 49.4% males. The mortality rate was determined as 25.32%, with 59 patients in the non-survivor group. When the patients were grouped according to the mortality and survivor status, the probabilities of death in hospital were found to be similar for female gender ($p>0.05$). The patients in the non-survivor group were determined to be significantly older ($p<0.005$), have a higher APACHE II score and to have a longer length of stay in hospital than the survivor group ($p<0.05$). The probability of survival was higher in the diagnosis groups of poisoning, trauma, digestive disease, infectious disease /sepsis, cardiovascular disease and renal insufficiency, and the probability of mortality was higher in pulmonary and neurology group patients (Table 1). According to the laboratory parameters, the mean values of RDW ($p<0.001$), WBC ($p<0.05$), and CRP ($p<0.001$) were significantly higher and the mean albumin (g/L) value was calculated to be lower ($p<0.001$) in the non-survivor group. The Hb levels of both groups were similar ($p>0.05$). The basal demographic data, clinical and laboratory values of both groups are shown in Table 1.

The patients were categorised into 2 groups of 135 and 98 patients according to the RDW values. No difference was determined between the groups in respect of age and gender ($p>0.05$). The High RDW group were determined to have a higher mean APACHE II score and a longer length of stay in hospital ($p<0.001$). The number of non-survivor patients in the High RDW group was found to be significantly high ($p<0.001$) and the 90-day mortality rates were calculated as 50% and 9% respectively (Figure 3). According to the laboratory parameters, the mean CRP was determined to be higher ($p>0.001$) and the albumin (g/L) level ($p<0.001$) was lower in the High RDW group. The mean WBC ($\times 10^3$ /µl) and hemoglobin (g/dL) values were similar in both groups ($p>0.05$). The differences between the groups in respect of the clinical and laboratory parameters are shown in Table 2.

Table 1 Comparison of demographic clinical variables and laboratory parameters between survivors and non-survivors

Variables Total	Total (n=233)	Survivors (n=174)	Non-survivors (n=59)	*P*
Sex (male, %)	115(49,4)	80(34,3)	35(15)	0,076
Age (years)	74(19-96)	68,15(19-94)	76(44-96)	0,028
Apachi II	15,28(7,48)	12,57(5,98)	23,25(5,55)	<0,001
Principal diagnosis (n, %)				<0,001
Neurological disease	55(23,6)	37(15,9)	18(7,7)	
Pulmonary disease	83(35,6)	54(23,2)	29(12,4)	
Cardiovascular disease	15(6,4)	14(6,0)	1(0,4)	
Digestive disease	24(10,3)	23(9,9)	1(0,4)	
Infectious disease/sepsis	12(5,2)	9(3,9)	3(1,3)	
Renal insufficiency	18(7,7)	12(5,2)	6(2,6)	
Poisoning	7(3,0)	7(3,0)	0(0)	
Trauma	8(3,4)	7(3,0)	1(0,4)	
Other	11(4,7)	11(4,7)	0(0)	
Hemoglobin (g/dL)	12,34(2,37)	12,26(2,34)	12,57(2,45)	0,389
RDW (%)	14,50(10-29)	13(10-27)	15(11-29)	<0,001
WBC (×103 /µl)	11,57(3,9-27,9)	11,06(4-27,6)	12,82(3,9-27,9)	0,026
CRP (mg/L)	1,9(0,02-28)	1,3(0,02-28)	5,6(0,2-25)	<0,001
Albumin (g/L)	3,05(0,73)	3,12(0,71)	2,82(0,75)	0,007

Apachi II score: Acute Physiology and Chronic Health Evaluation II score, *RDW*: Red blood cell Distribution Width, *WBC*: White Blood Cell, *CRP*: C-Reactive Protein

Table 2 Comparison of demographic clinical variables and laboratory parameters between RDW range

Variables Total	Total (n=233)	Low-RDW (n=135)	High-RDW (n=98)	*P*
Sex (male, %)	115(49,4)	66(28,3)	49(21)	0,867
Age (years)	74(19-96)	73(19-93)	76(22-96)	0,053
Mortality(%)	59(25,3)	9(3,9)	50(21,5)	<0,001
TLSH(days)	5(1-90)	4(1-86)	8,5(1-90)	<0,001
Apachi II	15,28(7,48)	13,11(6,98)	18,27(7,15)	<0,001
Hemoglobin (g/dL)	12,34(2,37)	12,59(2,20)	12(2,55)	0,389
WBC (×103 /µl)	11,57(3,9-27,9)	11,05(4-27,6)	12,71(3,9-27,9)	0,088
CRP (mg/L)	1,9(0,02-28)	0,9(0,02-28)	4,8(0,02-23)	<0,001
Albumin (g/L)	3,05(0,73)	3,15(0,68)	2,9(0,77)	0,007

TLSH: Total Length of Stay in Hospital, *Apache II score*: Acute Physiology and Chronic Health Evaluation II score, *RDW*: Red blood cell Distribution Width, *WBC*: White Blood Cell, *CRP*: C-Reactive Protein

Table 3 Univariate odds ratios of variables for predicting *ICU* mortality and Independent predictors of *ICU* mortality by multivariate logistic regression analysis.

	Univariate odds ratios			Multivariate odds ratios		
Variables	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
Male	1,714	0,941-3,119	0,078			
Age (years)	0,968	0,946-0,990	0,005			
RDW (%)	0,852	0,772-0,940	0,001	0,870	0,762-0,995	0,041
Apachi II	0,733	0,673-0,797	<0,001	0,723	0,660-0,793	<0,001
Hemoglobin (g/dL)	0,942	0,831-1,066	0,343			
WBC (×103 /µl)	0,944	0,896-0,995	0,031			
CRP (mg/L)	0,955	0,915-0,998	0,039			
Albumin (g/L)	1,762	1,162-2,672	0,008			

Apachi II score: Acute Physiology and Chronic Health Evaluation II score, RDW: Red blood cell Distribution Width, WBC: White Blood Cell, CRP: C-Reactive Protein

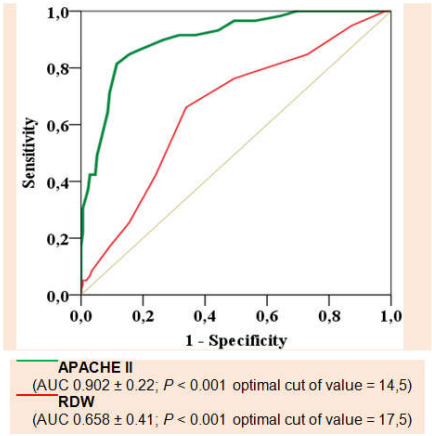

Figure1 *ROC* curve with Area Under the Curve *(AUC)* for Acute Physiology and Chronic Health Evaluation *(APACHE)* II score, and Red blood cell Distribution Width *(RDW)* predicting Intensive care unit *(ICU)* mortality for 90 days

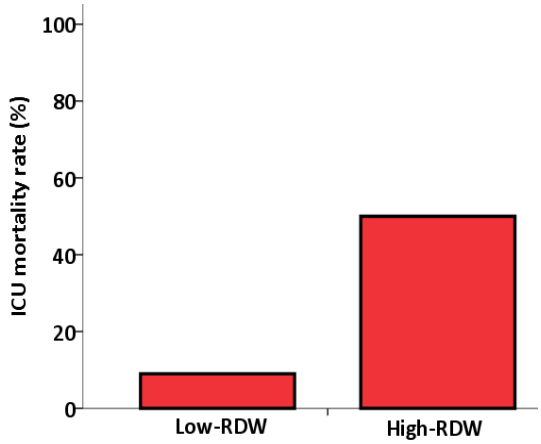

Figure 2 Intensive care unit *(ICU)* mortality rate for 90 days

The results of the univariate analysis applied to determine the predictors of mortality are shown in Table 3. With the aim of determining independent predictors of mortality, analysis was made of an advanced stage risk model including these variables. In the multivariate logistic regression analysis, a ROC curve was drawn for each patient to determine the diagnostic accuracy of the RDW ($p<0.05$, OR=0.870) and APACHE II ($p<0.001$, OR=0.723) values determined as independent markers of mortality status (Table 3), and the mortality predictive capability of each was examined separately. In the prediction of mortality, sensitivity was 66.1% and specificity was 66.1% for RDW (AUC = 0.689, optimal cutoff value = 14.5), and for APACHE II scores, sensitivity was calculated as 86.4% and specificity as 81% (AUC = 0.902, optimal cutoff value = 17.5). The predictive value of APACHE II for mortality was determined to be higher than that of RDW.

DISCUSSION

In this study of ICU patients, the relationship of RDW level with mortality was investigated and was compared with the APACHE II score, which is a multifactorial marker of mortality. The results of the study showed a higher mortality rate and longer length of stay in hospital in the High RDW group. The RDW level was an independent risk factor for mortality in ICU patients. In addition, an independent association was found between RDW and length of stay in hospital in surviving patients. RDW together with other scoring systems of severity seems to be a practical means of evaluation of elderly patients who require hospitalisation. To the best of our knowledge, the current study is one of a limited number of studies that have presented high RDW as a possible prognostic marker in ICU patients.

Although various prognostic markers have been evaluated for the early diagnosis of ICU patients at high risk of morbidity

and mortality, the most widely used is the APACHE II score (7). In recent studies related to the mortality prediction of RDW values, mortality in groups with high RDW values has been found to be high, similar to the rates in groups with high APACHE II scores. Thus, the association of RDW with mortality has been well-documented in patients with common cardiovascular diseases such as heart failure, acute myocardial infarct, coronary artery disease, pulmonary embolism, cardiac arrest and stroke (3, 8-11). In the current study, the mortality rate was determined to be 25.32%, which was found to be consistent with literature that the prognostic value does not lie in the RDW curve in patients with high RDW values (11-14).
Although the exact pathophysiological mechanism of the relationship between mortality and high RDW indexes is not clear, it is widely accepted that there is a significant relationship between inflammatory response in ICU patients and adverse clinical results such as mortality. Correctly conducted studies have confirmed the relationship between morbidity, mortality and increasing levels of acute phase reactants such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (5, 15-17). Similarly, in a limited number of studies, RDW, which is a measurement of variations in red blood cell dimensions affected by the inflammatory response, has been found to be a strong marker of mortality (18, 19). That the CRP values were significantly high in the RDW group of the current study was consistent with literature, and similarly, elevated CRP has been associated with mortality and length of stay in hospital (5, 20).

There were some limitations to this study, primarily that it was a cross-sectional study. The effects of RDW on mortality might be able to be better clarified with longitudinal studies. The patient group of this study was limited in number and heterogenous in respect of diagnoses. There is a need for further studies with specific patient groups. Another limitation of the study was that B12 and iron levels were not defined in the data. B12 and iron deficiencies are frequently seen in Turkey and this coud have caused an increase in the RDW level.

In conclusion, even if the estimated mortality associated with APACHE II in ICU patients is not 100% successful in showing clinical mortality, it has high predictive value. However, as RDW is a readily available and low-cost method, and the sensitivity and specificity of the mortality predictive rates of RDW as a single parameter are close to the rates of APACHE II, which is calculated from multiple parameters, the predictive value is increased. It can be considered that in the future, RDW could be added to the calculation of disease severity scoring.

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How to cite this article:

Hüseyin Avni Fındıklı *et al*.2018 , The Prognostic Potential of Red Blood Cell Distribution Width Values In Intensive Care Unit Patients. *Int J Recent Sci Res.* 9(7), pp. 27891-27895. DOI: http://dx.doi.org/10.24327/ijrsr.2018.0907.2353

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