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ORIGINAL ARTICLE

Red Cell Distribution Width as a Predictor of Outcome in Pediatric Intensive Care Unit

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ABSTRACT

Background: The Red blood Cell Distribution Width (RDW or RCDW) is a measure of the Red Blood Cell (RBC) volume that was reported as a part of the standard complete blood count. In the past, RDW was used for the differential diagnosis of anaemia. RDW has been demonstrated to be significantly associated with mortality and other different outcomes in various clinical conditions. Our study aimed to study the prognostic effect of red cell distribution width and it's clinical implications on critically ill children admitted to the Pediatric Intensive Care Unit (PICU).

Methods: This was a prospective cohort study of critically ill children admitted to Pediatric Intensive Care Unit (ICU), Zagazig University Hospitals during the period of 6 months Including 40 critically ill children, their age from 1 month to 14 years. We limited our analysis to include patients under 14 years, and in which complete blood count (CBC) including RDW was obtained at a 1st day,4th day and 7th day of PICU admission.

Results: This study showed that statistically significant difference between the studied patients regarding RDW on 1st, 4th, 7th days and RDW with different hematological indices and different outcomes.

Conclusions: RDW is a significant prognostic factor for hospital mortality in critically ill-patients.

Keywords: erythrocyte indices, intensive care units, mortality, pediatrics.

BACKGROUND

Critically ill child means a child who is in a clinical state which may result in cardiac arrest or severe neurological complication if not recognized promptly. Patients are admitted to pediatric intensive care unit because they require a very high level of monitoring of vital signs and other body functions not available in other parts of the hospital. These patients may need mechanical ventilation, invasive intravascular monitoring, and frequent attention by both nursing and medical staffs [1]. The Red blood Cell Distribution Width (RDW or RCDW) is a measure of the variation of the Red Blood Cell (RBC) volume that is reported as a part of a standard complete blood count. In the past, RDW was used for the differential diagnosis of anemia. RDW has been demonstrated to be significantly associated with mortality and other different outcomes in various clinical conditions, including chronic and acute diseases such as chronic and acute heart failure, acute dyspnea, acute pancreatitis, severe sepsis and septic shock, trauma, and acute pulmonary embolism [2].

RDW is highly associated with hospital mortality in deselected severely ill-patients [3].

In the critically ill children, it is crucial to promptly and accurately assess the severity of the illness and organ dysfunction and predict outcomes for prompt management. For this purpose, many studies have been investigating for proper prognostic factors including several scoring systems such as the pediatric risk of mortality (PRISM). The association between the red cell distribution width (RDW) and mortality in critically-ill children admitted in pediatric intensive care unit (PICU) [4]. They concluded that high (≥18.6%) RDW at admission and its persistent high levels were associated with high mortality and prolonged stay in PICU, respectively. RDW used as a marker for different samples that may need manual peripheral blood smear examination, since higher RDW may reflect the red cell fragmentation, agglutination, or

dimorphic red cell changes **[5]**. This study aimed to study the prognostic effect of elevated red cell distribution width and its clinical implication on critically ill children admitted to the Pediatric Intensive Care Unit (PICU) at Zagazig University Hospitals.

METHODS

This was a prospective cohort study of critically ill children admitted to Pediatric Intensive Care Unit (ICU), Zagazig University Hospitals during the period of 6 months Including 40 critically ill children, their age from 1 month to 14 years, divided according to reason for admission into [Cardiac problem >>8 persons, Respiratory problems >>8 persons, Neurology problems >>20 persons, GIT problems >>3 persons, Multi organ failure >>1person]. Including Criteria: Male and female, age group of infancy and childhood (from one month to 14 years). Patient admission due to any causes either medical or surgical. Exclusion criteria: Patients who died within 24 hours of PICU admission, discharged to ward within 24 hours, history of blood transfusion during the last 3 months, patients with proven hematological or oncological, patients whose relatives refused to participate in the study.

Written Informed consent was taken from the parents of the patient and/or their caregivers. The permission for the study was received from the pediatrics Departments of Zagazig University Hospitals after the permission of the Institutional Review Board (IRB). The research was carried out in compliance with the Code of Ethics of the World Medical Association (Deceleration of Helsinki) for studies involving humans.

All participants in the study had subjected to complete history taking regarding socio demographic characteristics such as sex, age, weight. Complete clinical examination, Laboratory tests, including Complete Blood Counting (CBC). Complete blood count includes the red blood cells (RBCs), hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), white blood cell (WBC), platelets, serum Creatinine, prothrombin time (PT), partial thromboplastin time (PTT), serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase (SGPT, SGOT) and C-reactive protein (CRP). RDW performed on 24 hours of PICU admission, on day 4 of admission and on day 7 of admission by using automated blood analyzer (Cell-DYN Emerald) (SYSNEXKX-ZIN).

Complete Blood Count (CBC); 5 ml venous blood sample was anti coagulated in EDTA tubes (vecutainer) and analyzed by Sysmex XP 300. The instrument measures the following indices: total white cell, red blood cell count, hemoglobin, mean cell volume, mean cell Hb, MCHC, and platelets.

C-reactive protein (CRP); It is agglutination reaction in which inert particles aggregated in presence of specific antibody. CRP can be done by passive agglutination using latex particles coated with anti–CRP, a negative reaction is indicated by uniform milky suspension with no agglutination, positive reaction is indicated by any observable agglutination in reaction mixture, CRP was done by qualitative test.

STATISTICAL ANALYSIS

Data was entered checked and analyzed using Epi-Info version 6 and SPSS for Windows version 8 (Dean, 2006). For a comparison of means of more than two groups it was used F-value (ANOVA of F test). Correlation between variables was done using correlation coefficient "r", This test detects if the change in one variable was accompanied by a corresponding change in the other variable or not. It was used Mann Whitney-U test for comparison between the 2 groups (successful and weaning) for the not normally distributed data. It was used t test when comparing two means. The threshold of significance is fixed at 5% level (p-value). Significant when the probability of error is less than 5% ($p < 0.05$). Non-significant when the probability of error is more than 5% ($p > 0.05$). Highly significant when the probability of error is less than 0.1% ($p < 0.001$). The smaller the p-value obtained, the more significant are the results.

RESULTS

Age of the studied patients ranged from 61 days to 14 years old with a mean age 3.18 years. About half of the studied patients had neurological diseases. More than half of the studied patients were undergo mechanically ventilated, while only three of them died at the end of the study (Table 1).

There was statistically significant difference between the studied patients regarding RDW and there outcomes over different days of admission : RDW on first day was higher among studied patients than those outcome , on the other hand, there is a non-significant difference between them regarding RDW on fourth or seventh day. In each group, there was non-significant change in RDW overtime (Table 2).

There was significant negative correlation between RDW on the first day and all of MCV, MCH, MCHC values on the same day.

There was significant negative correlation between RDW on the fourth day and all of MCV, and MCH values on the same day.

There was significant negative correlation between RDW on the seventh day and all hemoglobin, MCV, and MCH values on the same day. There was significant positive correlation between it and WBCs on the same day, also there was non-

significant change in Hb, PCV, MCH and MCHC on the fourth and the seventh days (Table 3).

There was significant positive correlation between RDW on each of the studied days and RDW values on other days (Table 4). There was non-significant correlation between RDW value on first, or seventh days, and either liver, kidney function tests or bleeding profile There was significant positive correlation between RDW on 1st and 4th day and CRP while there is non-significant correlation between it and either liver, kidney function tests or bleeding profile (Table 5).There was statistically non-significant difference between the studied patients who underwent MV or not regarding RDW on first, fourth, or seventh day. In each group, there is non-significant change in RDW overtime (Table 6).

The best cutoff of RDW at the first day in prediction of mortality is ≥17.6 with area under curve 0.896 with sensitivity 100%, specificity 75.7%, positive predictive value 25%, negative predictive value 100%, positive likelihood ratio 4.12, negative likelihood ratio 0, accuracy 77.5% ($p<0.05$) (Table 7). The best cutoff of RDW at the fourth day in prediction of mortality is ≥18.05 with area under curve 0.622 with sensitivity 66.7%, specificity 75.7%, positive predictive value 20%, negative predictive value 96.7%, positive likelihood ratio 3.09, negative likelihood ratio 0.42, accuracy 77.5% (Table 7). The best cutoff of RDW at the seventh day in prediction of survival is ≥15.55 with area under curve 0.532 with sensitivity 62.2%, specificity 100%, positive predictive value 100%, negative predictive value 88.5%, positive likelihood ratio 0, negative likelihood ratio 0.38, accuracy 57.5% (Table 7).

Table 1: Distribution of the studied patients

	Mean ± SD	**Median (range)**
Age (years)	**3.18 ± 3.72**	**1.4 (61 days – 14 years)**
	***N*=40**	**%**
Diagnosis:		
Cardiac	**8**	**20**
Respiratory	**8**	**20**
Neurological	**20**	**50**
GIT	**3**	**7.5**
Multiorgan failure	**1**	**2.5**
Mechanical ventilation:		
Yes	**22**	**55**
No	**18**	**45**
Outcome		
Survivors	**37**	**92.5**
Dead	**3**	**7.5**

Table 2 : Comparison between RDW in the studied patients and patient's outcomes

RDW %	**Results**		**Test**	
	Studied patients	**Outcomes**	**t**	***p***
	Mean ± SD	**Mean ± SD**		
First day	**20.93 ± 2.76**	**15.9 ± 3.23**	**2.616**	**0.013***
Fourth day	**18.23 ± 5.51**	**16.21 ± 3.39**	**0.954**	**0.346**
Seventh day	**16.13 ± 0.75**	**16.65 ± 3.33**	**-0.263**	**0.794**
***p* (F)**	**0.418**	**0.196**		

*, $p<0.05$ is statistically significant; t, Independent sample t test; F, repeated measure ANOVA

Table 3: Correlation between RDW at each day and hematological indices on the same day among the studied patients

	RDW first day		**RDW fourth day**		**RDW seventh day**	
	r	***p***	**r**	***p***	**r**	***p***
WBCs ×10³/mm³	**0.229**	**0.156**	**0.09**	**0.581**	**0.426**	**0.006***
RBCs million/mm³l	**0.243**	**0.13**	**0.125**	**0.443**	**-0.019**	**0.91**
Hemoglobin g/dl	**-0.14**	**0.388**	**-0.101**	**0.535**	**-0.43**	**0.006***
PCV (%)	**0.051**	**0.755**	**-0.195**	**0.228**	**-0.29**	**0.069**

	RDW first day		RDW fourth day		RDW seventh day	
	r	*p*	r	*p*	r	*p*
MCV (fl)	-0.566	<0.001**	-0.599	<0.001**	-0.441	0.004*
MCH (pg)	-0.324	0.041*	-0.341	0.031*	-0.356	0.024*
MCHC (g/dl)	-0.434	0.005*	0.088	0.587	-0.298	0.061
Platelet count ×10³/ml	-0.198	0.22	-0.186	0.249	-0.252	0.117

*, p<0.05 is statistically significant; **, p≤0.001 is statistically highly significant; WBCs, white blood cells count; RBCs, red blood cells count; PCV, packed cell volume; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCH, mean corpuscular hemoglobin concentration

Table 4: Correlation between RDW values over different days among the studied patients

RDW %	RDW first day		RDW fourth day		RDW seventh day	
	r	*p*	r	*p*	r	*p*
1st day	1		0.697	<0.001**	0.64	<0.001**
4th day	0.697	<0.001**	1		0.672	<0.001**
7th day	0.64	<0.001**	0.672	<0.001**	1	

*, p<0.05 is statistically significant; **, p≤0.001 is statistically highly significant

Table 5: Correlation between RDW and CRP, kidney function tests, liver function tests, bleeding profile over different days among the studied patients

	RDW first day		RDW fourth day		RDW seventh day	
	r	*p*	r	*p*	r	*p*
CRP (mg/l)	0.444	0.004*	0.358	0.023*	0.042	0.795
S. Creatinine (mg/dl)	-0.049	0.763	0.106	0.516	0.029	0.858
BUN (mg/dl)	0.042	0.795	0.102	0.531	0.045	0.781
ALT (U/l)	-0.044	0.786	-0.088	0.588	0.031	0.848
AST (U/l)	0.2	0.217	0.161	0.322	0.147	0.346
PT (Sec)	0.028	0.865	-0.005	0.974	-0.092	0.572
PTT. (Sec)	0.101	0.534	0.273	0.089	0.05	0.758
INR	0.065	0.69	0.163	0.316	0.084	0.605

CRP, C-reactive protein; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio

Table 6 : Relation between RDW on different days and mechanical ventilation among the studied patients

RDW %	Mechanical ventilation		Test	
	No (*n*=18)	Yes(*n*=22)	t	*p*
	Mean ± SD	Mean ± SD		
First day	16.72±3.63	15.92±3.31	0.727	0.472
Fourth day	16.87 ± 2.87	15.95±4.01	0.823	0.415
Seventh day	17.08 ± 3.6	16.22 ± 2.87	0.846	0.403
p (F)	0.868	0.877		

Table 7: Performance of RDW on first, fourth and seventh days respectively in prediction of mortality among the studied patients

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	+LR	-LR	Accuracy	*p*
≥17.6	0.896	100	75.7	25	100	4.12	0	77.5	0.024*
≥18.05	0.622	66.7	78.4	20	96.7	3.09	0.42	77.5	0.488
≥15.55	0.532	62.2	100	100	88.5	0	0.38	57.5	0.857

*, P<0.05 is statistically significant; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio

DISCUSSION

RDW had been referred to as an inflammatory biomarker in the different illnesses such as cardiovascular diseases, acute and chronic kidney diseases, chronic pulmonary diseases, and critically ill-patients. In these illnesses, a higher RDW level could predict relatively severe morbidity and mortality [6]**.** Based on the hypothesis that RDW measured on ICU entry was an independent predictor of in-hospital mortality among critically ill-patients, our study aimed at studying the prognostic effect of elevated red cell distribution width and it's clinical implications on critically ill children admitted to the pediatric intensive care Unit (PICU) at Zagazig University Hospitals. Our studied cases admitted to PICU ranged from 0.17 (61 days) to 14 years old with a mean age 3.18 years. About half of the studied patients had neurological diseases. More than half of the studied patients were ventilated while only three of them died by the end of the study.

Sachdev et al.[4] studied the association between red cell distribution width (RDW) and mortality in one hundred fifteen critically-ill child admitted to the Pediatric intensive care unit (PICU); 14 patients were excluded (9 stayed in PICU for <24 hours and 5 had hematological disorders) and 42 patients were under 2 years of age. Twenty-five patients presented with shock at admission; 11 (16.9%) children died during study period. Regarding RDW in our study, there was a statistically significant difference between dead patients and survivors regarding RDW on the first day; on the other hand, there was a non-significant difference between them regarding RDW on the fourth or the seventh day. In each group, there was a non-significant change in RDW overtime.

The mechanism of association between high RDW and mortality was not known: any condition resulted in the release of reticulocytes into the circulation would result in an increase in RDW and these elevations in RDW may had negative impact on the patient survival by reflecting the extent of the inflammation, also higher RDW was associated with increasing levels of inflammatory markers in outpatients, and also direct association was found in outpatients between RDW and CRP that was independent of age, sex, mean corpuscular volume, hemoglobin, and ferritin **[7]**.

Sachdev et al. [4] found that percent of hemoglobin at admission was inversely related to RDW D1 but there was no significant difference in the hemoglobin levels between survivors and death. High RDW at admission (RDW D1) correlated significantly with mortality. The odds of death increased to 15 to 23 times with a rise in RDW D1 from 18% to more than 21%. Of the 11 patients who died, 10 had RDW D1 >18.6%.

High RDW had been also shown to be associated with blood inflammatory marker like interleukin-6, C reactive protein (CRP), raised erythrocyte sedimentation rate, impaired iron mobilization, oxidative stress, ineffective red cell production and increased red cell destruction. Pro-inflammatory cytokines suppress erythrocyte maturation and inhibit the half-life and deformability of the RBC membrane allowing larger reticulocytes to enter the peripheral circulation and increase RDW **[8]**.

In our study, there was a significant negative correlation between RDW on the first day and all of MCV, MCH and MCHC values on the same day. There was a significant negative correlation between RDW on the fourth day and all of MCV, and MCH values on the same day. Also, there was a significant negative correlation between RDW on the seventh day and all hemoglobin, MCV, and MCH values on the same day, but there were a significant positive correlation between it and WBCs on the same day and a significant positive correlation between RDW on each of the studied days and RDW values on other days. Also, there was significant positive correlation between RDW and CRP on the 1st and the 4th day, while there was a non-significant correlation between it and either liver, kidney function tests or bleeding profile. There were significant differences between dead patients and survivors regarding a percent change in MCV on the 4th day and RDW at 7th day.

Oh et al. [9] clarified that whether RDW was associated with mortality in Acute Kidney Injury (AKI) patients. They found that higher RDW could be independently related to all causes of mortality in AKI patients. They founded that RDW may help in risk stratification and can introduce a cheap tool to predict outcomes in critically ill -patients with AKI. RDW was higher among 1st day of patients admission rather than different days of admission or results of patients admission, it was related to severity of clinical condition of the patients from the start of their admission and begin to improve with improving clinical condition of them or worsen with deterioration of them [2].In our study, there was a statistically non-significant difference among patients with different outcome regarding acute phase reactants, liver, kidney function tests.

Sachdev et al. [4] found that the optimal RDW D1 cut-off value for mortality was 18.6% with sensitivity 90.9%, specificity 70.8%, positive predictive value 27.8% and negative predictive value 98.4%. The area (95% CI) under the ROC was 0.83.The most favorable properties of RDW as a pragmatic clinical biomarker were its relative low cost, and universal availability compared to other biomarkers in this generation. The upper limit of lower RDW quartile (<13.4%) achieved a NPV of 96.7% to rule out mortality, which was comparable

to the 97% NPV reported in a validation study of a multi-biomarker algorithm generated using a sophisticated genome-wide expression algorithm in pediatric septic shock **[10]**.

In our study, ROC curve showed performance of RDW at first, fourth and seventh days in prediction of mortality among the studied patients. The best cutoff of RDW at the first day in prediction of mortality was ≥17.6 with area under the curve 0.896 with sensitivity 100%, specificity 75.7%, positive predictive value 25%, negative predictive value 100%, positive likelihood ratio 4.12, negative likelihood ratio 0, accuracy 77.5% ($p<0.05$). The best cutoff of RDW at the fourth day in prediction of mortality was ≥18.05 with area under curve 0.622 with sensitivity 66.7%, specificity 75.7%, positive predictive value 20%, negative predictive value 96.7%, positive likelihood ratio 3.09, negative likelihood ratio 0.42, and accuracy 77.5%.

The best cutoff of RDW at the seventh day in prediction of survival was ≥15.55 with area under the curve 0.532 with sensitivity 62.2%, specificity 100%, positive predictive value 100%, negative predictive value 88.5%, positive likelihood ratio 0, negative likelihood ratio 0.38, accuracy 57.5%.

From a prediction perspective, it appeared that RDW was a helpful pragmatic and prognostic estimate for PICU outcome and mortality.

Persistence elevation of RDW may also be seen in cases of protracted inflammation, as in patients with chronic conditions [11].

CONCLUSIONS

Increased variation in the size of erythrocytes on admission to ICU, as indicated by RDW, together with significant positive correlation between group of patients with different outcome regarding percent change in MCV at 4Th day, also the statistically significant difference between dead patients and survivors regarding White blood cell count on fourth day and significant positive correlation between RDW and CRP on 1st and 4th day ensures that RDW is a helpful pragmatic and prognostic estimate for PICU outcome, in addition to being cheap and widely available laboratory measurement.

Conflict of Interest: None.

Financial Disclosures: None.

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