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The Predictive Value of Red Blood Cell Distribution width (RDW) in Critically ill Children . A Cross sectional study

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ABSTRACT

Background: RDW has been demonstrated to have an important predictive role and an evaluative role, regarding the severity and the outcome in critically ill pediatric patients

Aim: The objective of the study was evaluating the role of RDW as an indicator for severity of the illness in diseased children with a critical condition

Patients and methods: This cross-sectional hospital-based study included 111 children, 55 males (49.5 %). . All diseased children with critical condition met the following requirements were included in the research , 2 month to 14 years old age, whose were admitted to the PICU, at Sohag University Hospital, during a period of 6 months, from the date of protocol acceptance, the following laboratory tests were performed to the patients during their stay ; Complete Blood Count, Serum electrolytes, Liver functions , kidney functions, CRP, Blood gases, Serum lactate, Coagulation profile, serum fibrinogen, and Blood urea nitrogen (BUN) . All the followings were demonstrated, the need of patients for mechanical ventilation or for inotropes , the hospital stay peroid and the outcome patients. Critical illness scores were calculated including, pediatric sequential organ failure assessment (PSOFA), pediatric logistic organ dysfunction-2 (PELOD-2). pediatric multiple organ dysfunction syndrome (PMODS) and the pediatric risk of mortality (PRISM)

Results: In the study participants there was a negative correlation between RDW level and the period of stay at PICU with a statistical significance with p-value= 0.005 and also show a positive correlation between RDW level and serum lactate and CRP levels with a statistical significance with(p-value <0.007 and<0.006) respectively .There was a significant association between elevated RDW >16.9 with mortality rate among patients and R DW level had a positive correlation with the prognostic severity scores , which had previously been mentioned with a statistical significance with (p-value <0.008 , p-value<0.005 , p-value<0.005 and p-value <0.007) .

Conclusion: RDW is a non-invasive and simple easily applicable marker and it can be used as an additional prognostic factor and a good predictor for illness severity among critically ill children as it has a significant correlation with the prognostic severity scores.
Keywords: RDW, ill children , PICU, severity scores.

1- INTRODUCTION

Red cell distribution width (RDW) is a parameter commonly used to measure the variations in the size of RBCS, ranging from 11.5 to 15.5. The common field of study regarding RDW is the diagnosis of different types of anemia like chronic hemolytic anemia and iron deficiency anemia .[(2)] Elevated RDW has been associated with increased morbidity rate among different body systems and mortality in patients with severe septicemia and septic shock at PICU.

Several studies have proposed it as a potentially useful prognostic marker in this population but these studies were conducted on adults, while a few studies have examined the predictive role of RDW in critically ill children . [4][5] However many prognostic scoring systems in critically ill children were demonstrated in many researches such as (PELOD- 2), (p-MODS), (PRISM) and (pSOFA). [1].

The exact pathophysiologic explanation for why RDW can serve to be an effective indicator of mortality and morbidity is not completely understood but there were many contributing situations with high RDW, such as malnutrition, renin-angiotensin system activation, and chronic kidney injury, sepsis, cardiovascular disease, malignancies and chronic lung disease [9]. The prognostic role of RDW in children with infectious diseases was enrolled by some studies in comparison to some classical indexes [4].

The link between the hematological and the inflammatory systems is an area of interest for many researches , it was demonstrated that inflammatory cytokines affect the RBCs maturation by decreasing the effect of erythropoietin and by shortening of the RBCs survival by impairing the iron metabolism leading to the elevated RDW [6]

Inflammatory cytokines as, interleukin-1ß, have a direct and negative effect on the RBCs survival by causing a disruption in the integrity of RBCs membrane , and affect its maturation leading to a new and large reticulocytes and increase the RDW, indicating that RDW is an indicator for severity of the inflammatory process [6][7] The stressful oxidizing situations affect the homeostasis of RBC and affect its integrity and the span of its life, reducing its survival, also it stimulate the process of apoptosis and disrupt the RBC regarding size resulting in RDW rise [8]

The objective of the study was evaluating the role RDW as an indicator for severity of the illness in diseased children with a critical condition.

2- PATIENTS AND METHOD

This cross-sectional hospital-based study included 111 children, 55 males (49.5 %). . All diseased children with critical condition met the following requirements were included in the research , 2 months to 14 years old age, whose entered the (PICU) , at Sohag University Hospital, during a period of 6 months, from the date of protocol acceptance, Cases who received a transfusion by blood before PICU admission and patients with incomplete data for,(sofa), (PRISM) (PMODS) and (PELOD- 2) scores were excluded from the study.

The next data was collected from all the research participants. History focusing on demographic data , and history of underlying diseases in different body systems. Clinical examination included, all items of general examination, Neurological examination, heart and abdominal examination . Parents or guardians of children provided written or oral consent for their children's participation in the research, after obtaining the ethical approval

All the next laboratory test were done for all participants during the admission in (PICU). All parameters of the CBC specially, HB level and RDW. Blood gases, sodium, potassium and calcium serum levels, serum fibrinogen. Blood urea nitrogen (BUN), Liver and Renal functions, CRP and Serum lactate

The need of patients for mechanical ventilation and or inotropic vasoactive drugs was observed and demonstration of the hospital stay duration and the outcome of patients. C alculation the following scores PRISM III, PSOFA, PELOD II, PMODS. [1]

3- Statistical analysis:

The SPSS program (Statistical Package for Social Science) version24 was used to analyze the collected data . The Shapiro Walk test used to test its normal distribution. The chi- square test ($\chi 2$) and Fisher exact were used to detect the difference between the qualitative data while the Quantitative data were expressed as median and range. Kruskal-Wallis Test was used to calculate the difference between the quantitative variables in two groups for non-

normally distributed variables

Areas under ROC curves and their standard errors were determined using the method of Centor and compared using the normal distribution, with correction for correlation of observations derived from the same cases. The time to death of cases in PICU was estimated by Kaplan and Meier's method and The Cox proportional hazards model was used for univariate regression analysis.

4- Results

The study was conducted on 111 critically ill children with a range of age from 1 month to 14 years, with female to male ratio 1.02:1.**Figure1**, shows that critically ill pediatric patient with a low RDW <16.9 had a longer period of stay at PICU admission with a statistical significance with p-value =0.018 and **Table 1**, show a negative correlation between RDW level and the period of patient stay at PICU with a statistical significance with p-value =0.005 and also show a positive correlation between RDW level and serum lactate and CRP levels with a statistical significance with (p-value <0.007 and<0.006) respectively . As regard the relation between the RDW and the fibrinogen level there was a negative correlation with statistical significance a with p- value <0.006 This study found a significant negative correlation between RDW and Hb level with p-value =0.009. Regarding the correlations between RDW level with FiO2 and SPO2, were significantly positive with the first and significantly negative with the second. Regarding the correlation between RDW level and (PRISM III, SOFA, PLEOD II, and PMODS) scores, it was significantly positive with (p-value <0.008 , p-value<0.005 , p-value<0.005 and p-value <0.007), respectively , so high RDW > 16.9 was a predictor for the survival of patients with p-value <0.001 .Also a lower GCS of patients during their admission at PICU was associated significantly with elevated RDW > 16.9 with a p-value <0.008.

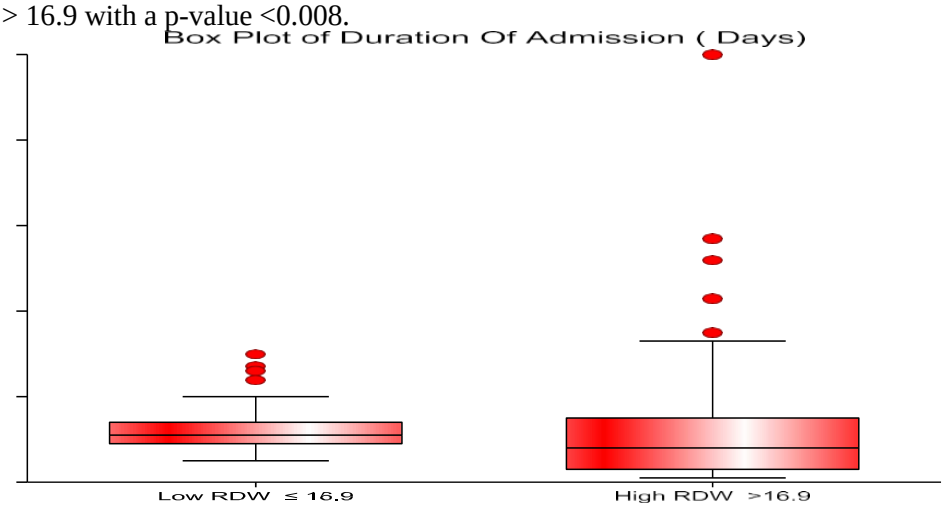

Figure 1. The range of Duration of Admission (Days) based on ROC curve-derived RDW levels

Table 1. Correlations between RDW % level and parameters of patients

Parameters of cases	Red cell distribution width(%)	
	(r)	P
Age (months)	0.022	0.830
Weight (kg)	-0.033	0.751
Height (Cm)	0.012	0.910
The period of Admission (Days)	-0.309	0.005
Systolic blood pressure (mm hg)	-0.119	0.220
Diastolic blood pressure (mm hg)	-0.145	0.133
Glascow coma scale	-0.560	<0.008
WBCS(White blood Cells) (X1000/ML)	-0.019	0.90
Mean corpuscular volume (FL)	-0.138	0.158
HGB (G/DL)	-0.259	0.009

Platelet number (X1000/ML)	-0.099	0.317
serum lactate (mmol/l)	0.330	<0.007
serum fibrinogen (mg/dl)	-0.360	<0.006
blood urea nitrogen(mg/dl)	0.555	<0.008
PH	-0.093	0.346
PAO2 (MM HG)	-0.001	0.98
PACO2(MM HG)	0.188	0.068
HCO3(MMOL/L)	0.063	0.578
FIO2	0.745	<0.009
SPO2 %	-0.366	<0.005
CRP(C Reactive Protein) (MG/L)	0.490	<0.006
Na(Mmol/L)	0.095	0.339
K(Mmol/L)	-0.149	0.127
Ionized Ca level(Mmol/L)	-0.069	0.488
Total Ca level(Mg/Dl)	0.075	0.449
serum.Creatinine. (mg/dl)	0.105	0.290
ALT(U/L)	0.014	0.910
AST(U/L)	0.017	0.885
Serum Albumin(g/dl)	-0.150	0.123
PRISM III (Pediatric risk of mortality)	0.798	<0.008
PSOFA(Pediatric sequential organ failure assessment)	0.809	<0.005
PELOD II (Pediatric logistic organ dysfunction-2)	0.825	<0.005
PMODS (Pediatric multiple organ dysfunction syndrome)	0.780	<0.007

r = Correlation Coefficient P ≤ 0.05= significant P <0.001 highly significant and P >0.05 NS

The high RDW >16.9 was associated significantly with the mortality among in the cases, with p-value<0.001. as shown in **Figure 2**. Also The high RDW >16.9 was significantly associated with the needs of cases at PICU for mechanical ventilation and inotropic vasoactive drugs with P value<0.001 **Table 2)**

Table2: Comparison between the patients need for Ventilators and Inotropic support and RDW levels (ROC curve derived)

		Red cell distribution width(RDW)level		X2 Test	P Value
		Low RDW ≤ 16.9 N=51	High RDW >16.9 N=60		
Ventilators	No	50(98,04%)	12(20%)	65.469	<0.001
	Yes	1 (.5%)	48(80%)		
Inotropic supports	No	49 (96.07)	10 (16.6%)	67.080	<0.001
	Yes	2 (3.9%)	50 (83.4%)		

(ROC) The Receiver operating characteristic

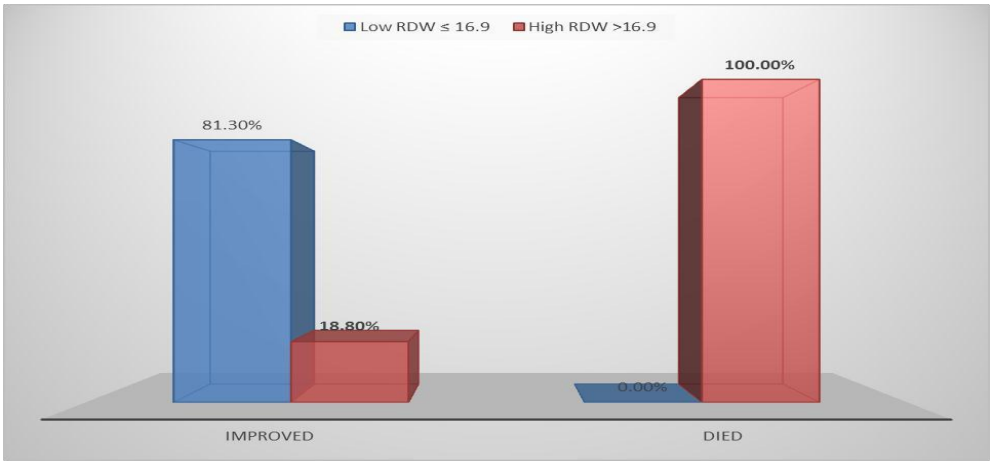

Figure 2. ROC curve derived RDW levels based on survival outcome

Inotropes at cutoff >17.6 had an AUC of 0.925 with a sensitivity and specificity of (96.5% and 83.61%) respectively. The PPV and the NPV were (83% and 96.4%) respectively with P value <0.001. MV at cutoff >18.4 had an AUC of 0.926 with a sensitivity and specificity o f (93.64% and 87.6%) respectively . The PPV and the NPV were (84.7% and 94.8%) respectively with (P value <0.001). For mortality at cutoff >16.8 had an AUC of 0.95 with a sensitivity and a specificity of (99% and 81%) respectively. The PPV and the NPV were (79.6% and 100%) respectively with (P= <0.001)(Table 3).

Table 3: Analysis of RDW as a predictive marker by (ROC) curve for patients outcomes at PICU

	Cut-Off	Sensitivity % 95% CI	Specificity % 95% CI	PPV 95% CI	NPV 95% CI	AUC 95% CI	P
Inotropes	>17.6	96.5 86.5 - 99.6	83.61 71.9 - 91.8	83 73.4 - 89.7	96.4 86.8 - 99.1	0.925 0.858 - 0.966	<0.001
MV	>18.4	93.64 82.6 - 98.8	87.6 76.9 - 94.5	84.7 74.1 - 91.4	94.8 86.1 - 98.1	0.926 0.860 - 0.968	<0.001
Mortality	>16.8	99 92.2 - 100.0	81 69.4 - 89.8	79.6 70.1 - 86.6	100	0.94 0.900 - 0.986	<0.001

	β: regression coefficient	SE: standard error	P	HR (hazard ratio)	95.0% CI confidence interval, for HR
PRISM III	0.482	0.079	<0.006	1.619	1.389-1.886

(ROC) The Receiver operating characteristic, (RDW) Red cell distribution width, (MV) Mechanical ventilation The 95%CI: 95% confidence interval, Positive predictive value (PPV), and negative predictive value (NPV)

The Univariate regression analysis show a significant effects of RDW% and the following severity prognostic scores (PRISM III, PSOFA, PLEOD II, PMODS,) on the patient' outcome regarding their survival at PICU with (p-value <0.006 , p- value <0.005 , p- value <0.007 , p- value <0.005 and <0.008) respectively (Table 4)

Table 4 Analysis of RDW % , prognostic scores for survival by Univariate Cox-regression

PSOFA	0.486	0.075	<0.005	1.623	1.405-1.875
PELOD II	0.314	0.046	<0.007	1.367	1.251-1.494
PMODS	0.535	0.088	<0.005	1.708	1.442-2.020
RDW %	0.350	0.048	<0.008	1.419	1.295-1.554

5- DISCUSSION

Red cell distribution width (RDW) is a parameter commonly used to measure the variations in the size of RBCS, ranging from 11.5 to 15.5. The common field of study regarding RDW is the diagnosis of different types of anemia like chronic hemolytic anemia and iron deficiency anemia .[2] Elevated RDW has been associated with increased morbidity rate among different body systems and mortality in patients with severe septicemia and septic shock at PICU. Several studies have proposed it as a potentially useful prognostic marker in this population but these studies were conducted on adults, while a few studies have examined the predictive role of RDW in critically ill children . [4][5] However many prognostic scoring systems in critically ill children were demonstrated in many researches such as (PELOD- 2), (p-MODS), (PRISM) and (pSOFA). [1]. The exact pathophysiologic explanation for why RDW can serve to be an effective indicator of mortality and morbidity is not completely understood but there were many contributing situations with high RDW, such as malnutrition, renin-angiotensin system activation, and chronic kidney injury, sepsis, cardiovascular disease, malignancies and chronic lung disease [9]. The prognostic role of RDW in children with infectious diseases was enrolled by some studies in comparison to some classical indexes [4].

Considering the fact that the RDW is included in the routine automated complete blood count (CBC) analyses with no additional cost, this makes our study of RDW as a marker was efficacious and interesting .Regarding the duration of PICU admission of cases , our study has proven, that a low RDW <16.9 was associated with a longer period of patient stay at PICU with a statistical significance with p-value =0.018 ,a negative correlation between RDW level and the duration of admission was found in our study with a statistical significance , that was consistent with **Shaimaa M et al,** that found a statistically significant relation between lower RDW and longer duration of admission of critically ill children in PICU with p value = 0.015 [21]. But our results differ from the research that conducted by **Said et al**. that found a significant relation between elevated RDW >14.8 and a longer duration of PICU stay with p-value <0.001[13]. The reason for the difference with this study may be that it was conducted on a larger sample of cases which is 3913 critically ill children admitted at PICU.

Our study reported a positive correlation between RDW level and serum lactate and CRP levels with a statistical significance with (p-value <0.007 and<0.006) respectively . That may be due to the increase of CRP and lactate in similar situations like the RDW , as critical hypoxemic and inflammatory diseases , which are found in critically ill pediatric patients , that was in line with **Sukewanti et al** and **Shaimaa M et al** studies , regarding the significant relation between higher RDW and elevated lactate and CRP levels among critically ill children, also our study was consistent with **Ha et al. study** which reported a strong relation between inflammatory mediators and elevated RDW, that explained by entering numerous and a new reticulocytes in the circulation by the effect of inflammatory mediators that lead to elevation of RDW, which reflect the relation between the RDW and the inflammation severity [1][15]

A negative correlation between RDW and Hb level was reported by our study with a statistical significance with p-value =0.009. This was consistent with **Sukewanti et al.** and **Shaimaa M et al** , those found the same relation between the RDW and the hemoglobin level

with (p- value=0.002 and p=0.007) respectively . This can be explained by that proinflammatory cytokines those associated with the inflammatory process suppressing RBC maturation, leading to elevated RDW[20].

This study found a significant correlations between RDW level with FiO2 and SPO2, that were significantly positive with the first and significantly negative with the second and also we found that high RDW >16.9 was significantly associated with the needs of cases at PICU for mechanical ventilation, that was in line with **Hartawan et al. and Shaimaa M et al** those had evaluated the correlation between RDW and duration of stay on Ventilators and the FiO2 needs at PICU and found a positive correlation between RDW and FiO2 and the duration of stay on ventilators with a statistical significance [16][21] , that can be explained that elevated RDW decrease the PaO2 transiently leading to release of the erythropoietin which trigger the immature reticulocytes release into the circulation. [16]

Schepens et al. also reported that patients with elevated RDW during their stay at PICU were associated with a great needs for ventilators and for vasoactive drugs ([5], that was in line with our study , that found , high RDW >16.9 was significantly associated with the needs of cases at PICU for ventilators and inotropic vasoactive drugs with P value<0.001

This research has proven that high RDW >16.9 was associated with the mortality among critically ill cases with a statistical significance with (p-value<0.001), that was consistent with **Ramby et al** , **Sukewanti et al** and **Shaimaa M et al** , those have proven a significant e levation o f RDW among children whose died in PICU with p- value =0.001[11] [12] [21]. The result of the research conducted by **Sachdev et al**. on 101 critically ill children was in line with the research we conducted , regarding the elevated RDW among non-survived pediatric patients in PICU with p-value =0.007 [10].

Bazick et al and **Khanbabaee et al.** were reported that elevated RDW was an important predictor of mortality in the critically ill pediatric patient and had a significant association with septicemia and septic shock with with a p-value =0.017 and p –value=0.019 respectively, the previous studies were consistent with our results regarding prediction of PICU mortality assessment depending on the RDW.

Our study found a positive correlation between RDW level and (PRISM III, SOFA, PLEOD II, and PMODS) prognostic scores with (p-value <0.008 , p-value<0.005 , p-value<0.005 and p-value <0.007), respectively, so high RDW > 16.9 was a predictor for the patients survival outcomes with p-value <0.001,this was consistent with the **Ha et al.** study which reported a significant relation between the elevated RDW >16.5 and the prognostic severity scores with p-value <0.019, 0.005, 0.018 and <0.015) [14],also our results were consistent with **Shaimaa M et al** which was conducted on 120 critically ill pediatric patients who were entered PICU to evaluate the predictive role of RDW in the severity of critical illness among children admitted at PICU and found a strong correlation between RDW and the prognostic severity scores.[21]

6- CONCLUSION

RDW is a non-invasive and simple easily applicable marker and it can be used as an additional prognostic factor and a good predictor for illness severity among critically ill children as it has a significant correlation with the prognostic severity scores.

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