Research Article

Red Blood Cell Distribution Width as a Pragmatic Marker for Outcome in Pediatric Critical Illness

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Abstract
Background: Red cell distribution width (RDW) measures variability in red blood cell size. It may also be useful as a biomarker of disease severity and clinical outcomes in critically ill patients. An increased RDW is an independent predictor of all-cause mortality in sepsis, congestive heart failure and has been shown to improve acute physiology scoring for risk prediction in critically ill adults. **Patients and Methods:** The medical records of 100 critically ill patients were reviewed for a CBC, including RDW, measured within 24 hours of PICU admission. **Results**: There was significant increase in PIM-2, RDW and the frequency of anemia compared with others without mortality, while there was significant decrease in Hb and MCV levels, all are Risk factors for mortality. The optimal cutoff value of PIM-2 to predict mortality rate in the studied patients was >5.8% with a very high sensitivity 97.67% and specificity 98.25%, and the optimal cutoff value of RDW to predict mortality rate in the studied patients was >14.7% with a high sensitivity 81.4% and specificity 85.96%. **Conclusion:** RDW is a predictor of mortality in critically ill PICU patients. Taking into consideration the fact that RDW is routinely measured in complete blood count with no additional cost, this can serve as an "inexpensive prognostic marker" in critically ill patients.
Keywords: PICU, RDW and mortality.

Introduction
Red cell distribution width (RDW) measures variability in red blood cell size and is a simple, low cost, and widely available measure routinely reported as part of a complete blood count (CBC) (Qurtom et al., 1998).

Several recent studies suggest that RDW may also be useful as a biomarker of disease severity and clinical outcomes in critically ill patients. An increased RDW is an independent predictor of all-cause mortality in sepsis (Ku et al., 2012; Jo et al., 2013), congestive heart failure (Felker et al., 2007; Forhecz et al., 2009) and has been shown to improve acute physiology scoring for risk prediction in critically ill adults (Al-Najjar et al., 2009).

Similarly, sustained RDW elevation may also be seen in cases of protracted inflammation, as in adults with chronic illnesses (Allen et al., 2010; Koma et al., 2013).

Patients and Methods
The present study was conducted at Minia Children University Hospital PICU Unit, during the period from August 2016 to August 2017.

This study is included 100 critically ill children were evaluated as critically ill children which is defined as is any disease process which causes physiological instability leading to disability or death within minutes or hours. The history of patients included the following points:

Medical history:
1. Prenatal, natal and post-natal history of diseases and medications were taken by mother. Prenatal and natal care.
2. Gestational age, Mode and place of delivery
3. Family history of any medical problems.
4. Developmental history and feeding history
5. Previous hospital admission with dates and diagnoses. Current medications and Immunization status.

Clinical assessment to determine:

1. Age, sex and weight.
2. Vital signs, Level of consciousness: Glascow coma scale.
3. Head (size and shape), fontanelles (size and tension) and pupils.
4. Signs of sepsis as (tachycardia, tachypnea, bronchial breathing, etc), Signs of organ failure.

Laboratory Investigations:

Subjects were tested under complete aseptic condition, by sterile venipuncture, venous blood was withdrawn from each subject complete blood count including (Hb, MCV and RDW). The Pediatric Index of Mortality (PIM)-2 score was determined.

Statistical methodology

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 20. Descriptive statistics were done for numerical data by mean and standard deviation, while they were done for categorical data by number and percentage.

Results

This study included 110 critically ill patients admitted to pediatric intensive care unit (PICU). Baseline characteristics of the study population are presented in Table 1.

Table1: Characteristics of studied patients admitted to pediatric intensive care unit (PICU):

Characteristic		Descriptive statistics (n=100)
Age	Range	(0.1-13)
	Mean ± SD	2.2±2.4
	Median	1.5
Gender	Male	60(60%)
	Female	40(40%)
Admitted category	Respiratory	33(33%)
	Sepsis	14(14%)
	CNS	26(26%)
	Cardiac	4(4%)
	GIT	17(17%)
	Surgical	2(2%)
	Endocrine	4(4%)
PIM-2	Range	(0.6-97.5)
	Mean ± SD	15±20.7
	Median	3.9
Hemoglobin	Range	(5.6-14.8)
	Mean ± SD	10.7±2
MCV	Range	(65.3-98.2)
	Mean ± SD	77.2±6.8
RDW	Range	(12.6-20)
	Mean ± SD	14.7±1.4
PICU LOS	Range	(1-14)
	Mean ± SD	4.6±2.4
Death	No	57(57%)
	Yes	43(43%)

The age of studied patients was between 0.1-13 years. The mean age of the patients was 2.2±2.4year. The frequency of males was slightly higher than the frequency of females (60% versus 40%, respectively). The most frequent admitted categories at PICU was respiratory system (33%), followed by CNS (26%), GIT (17), sepsis (14), cardiac (4%), endocrine (4%) and then surgical (2%). The LOS in the PICU of the studied patients was ranged from 1 day to 14 days. In our PICU, the mortality rate of

the studied patients was 43% (43 out of 100). The median RDW for all patients was 14.7% (12.6-20). PIM2 score range from (0.6%-97%).

Table 2 showed the characteristics of the studied patients according to mortality (yes or no). There were insignificant differences between both groups regarding age and gender ($p > 0.05$). As regarding PICU LOS there was significant increase in patient with mortality compared with patient without mortality ($p < 0.01$).

Table 3 showed the PIM2 and laboratory data of the studied patients according to mortality (yes or no). There was significant increase in PIM-2, RDW and the frequency of anemia compared with others without mortality, while showed significant decrease in Hb and MCV levels, all are Risk factors for mortality.

Table (2): Characteristics of the studied patients according to mortality in both (surviving and non-surviving).

		Mortality		P value
		Surviving (n=57)	**Non-surviving (n=43)**	
Age	Range Mean ± SD Median	(0.1-12) 2.3±2.5 1.4	(0.1-13) 2±2.2 1.6	0.981
Gender	Male Female	35(61.4%) 22(38.6%)	25(58.1%) 18(41.9%)	0.742
Admitted category	Respiratory Sepsis CNS Cardiac GIT Surgical Endocrine	21(36.8%) 2(3.5%) 16(28.1%) 0(0%) 12(21.1%) 2(3.5%) 4(7%)	12(27.9%) 12(27.9%) 10(23.3%) 4(9.3%) 5(11.6%) 0(0%) 0(0%)	**0.001***
PICU LOS	Range Mean ± SD	(2-9) 3.9±1.6	(1-14) 5.7±2.8	**<0.001***

: Significant level at P value < 0.05

Comparison between RDW and other parameters in patient without mortality is shown in table (4). RDW showed insignificant positive correlation with PIM-2, age, Hb and MCV while showed significant moderate correlation with PICU LOS (P value < 0.001). so RDW is a good indicator of severity.

Comparison between RDW and other parameters in patient with mortality is shown in table (5). RDW showed insignificant positive correlation with PIM-2, MCV and PICU LOS and showed insignificant negative correlation with age and Hb.

Table (3): PIM2 and laboratory data in relation to mortality two groups surviving and non-surviving.

		Mortality		P value
		Surviving (n=57)	Non-surviving (n=43)	
PIM-2	Range Mean ± SD Median	(0.6-7.6) 2.6±1.3 2.5	(2.7-97.5) 31.4±22.8 23.9	**<0.001***
Hemoglobin	Range Mean ± SD	(7.3-14.8) 11.6±1.8	(5.6-12.8) 9.6±1.8	**<0.001***
MCV	Range Mean ± SD	(65.3-98.2) 78.7±7.2	(66.5-89.4) 75.1±5.8	**0.006***
RDW	Range Mean ± SD	(12.6-15.5) 13.9±0.8	(13.6-20) 15.8±1.2	**<0.001***

: Significant level at P value < 0.05

Table (4): Correlation between RDW and other parameters in patient without mortality.

Without mortality	RDW	
	R	P value
PIM-2	0.150	0.265
Age	0.002	0.987
Hemoglobin	0.027	0.843
MCV	0.065	0.632
PICU LOS	0.526	<0.001*

Table (5): Correlation between RDW and other parameters in patient with mortality.

With mortality	RDW	
	R	P value
PIM-2	0.155	0.321
Age	-0.135	0.389
Hemoglobin	-0.045	0.775
MCV	0.083	0.598
PICU LOS	0.175	0.260

: Significant level at P value < 0.05

Simple logistic regression analysis revealed that the most predicting factors of mortality are RDW (OR=9.28), PIM-2(OR=2.79), PICU LOS (OR=1.47) in the studied patients (Table 6).

As shown in ROC curve (Table 7), the optimal cutoff value of PIM-2 to predict mortality rate in the studied patients was >5.8% with a very high sensitivity (97.67%) and specificity (98.25%) (AUC =0.99, p <0.001). and the optimal cutoff value of RDW to predict mortality rate in the studied patients was >14.7% with a high sensitivity (81.4%) and specificity (85.96%) (AUC =0.919, p <0.001).

Table (6): Simple logistic regression analysis of factors predicting the mortality:

	OR	95% CI	P value
PIM-2	2.79	1.53-5.11	0.001*
MCV	0.917	0.86-0.98	0.010*
RDW	9.28	3.82-22.54	<0.001*
PICU LOS	1.47	1.18-1.83	0.001*

Simple logistic regression analysis
OR: Odds Ratio
CI: Confidence Interval
*: Significant level at P value < 0.05

Table (7): ROC curve analysis of PIM-2 and RDW predicting the mortality:

	Optimal cutoff	AUC	P value	Sensitivity	Specificity	PPV	NPV	Accuracy
PIM-2	>5.8	0.99	<0.001*	97.67	98.25	97.7	98.2	98
RDW	>14.7	0.919	<0.001*	81.4	85.96	81.4	86	84

Discussion

RDW which is a part of a standard complete blood count (CBC) is a measure of variations in the volume of red blood cells. An elevation in RDW is known as anisocytosis. An increased level of RDW has been found in patients with vitamin B12, iron, and folate deficiency. RDW has also been observed after blood transfusion and hemolysis (Sertoglu et al., 2015).

The present study was done in EL- Minia University Children's Hospital during the period from August 2016 to August 2017 and included 100 critically ill patients (60 males and 40 females) who were collected from children admitted to pediatric intensive care unit (PICU) at our hospital, their age ranged from 0.1 to 13 years .

Regarding the clinical data of the current study, the frequency of males was higher than the frequency of females with ratio (60% versus 40% respectively). This was consistent with Siddiqui et al., (2018) who enrolled 167 children admitted to the PICU with 58.6% being males and 41.3% were females. The explanation for this is that females have stronger humoral and cellular immune responses to infection or antigenic stimulation which can be beneficial in protection and clearance of various pathogens. This male predominance may be due to a gene located on the X chromosome involved with the function of the thymus or with synthesis of immunoglobulin (Muenchhoff and Goulder, 2014), so males are more susceptible to infections and hence PICU administration.

Moreover, among 100 children admitted to the PICU, the most common admitted category was those with respiratory diseases 33%, CNS 26%, GIT 17%, sepsis 14%, cardiac or endocrine 4% and those admitted for surgical purposes were at the bottom 2%, and this agrees with *Qiu et al.*, (2017); who reported that the majority of the PICU patients had respiratory diseases, then nervous system diseases, and finally other miscellaneous conditions. But, this contrasted with the result of *Ramby1 et al.*, (2015) who reported the cardiovascular as the commonest admitted category 27%, followed by sepsis 17.4%, respiratory 16.3%, neurologic 12.9, airway surgery 5.9%, GIT/hepatic 4.7%, renal 3.7%, hematologic/oncologic 3.5%, orthopedic 3.4%, trauma was the least common admitted category 1.3%, and 3.9% were admitted for other purposes.

This could be explained by the results of previous studies that showed that incidence

of patients hospitalized for moderate or severe acute respiratory infections was reported as 290/100 000 population, with higher rates in very young children aged 1–11 months (5135/100 000 population overall for the period 2009–2012) (Rowlinson et al., 2017).

Pediatric Index of Mortality-2 (PIM2) score in our study ranged from 0.6 to 97%, with mean value of 15, and median value 3.9. This was in contrast to Qiu et al., (2017); who reported the median of PIM-2 as 2.20%. This could be explained by the very late referral of patients may lead to severe complicated disease course, and hence, increased mortality.

In our study, RDW value ranged from 12.6 to 20, with mean value of 14.7. This was in consistent with Said et al., (2017), who reported the mean RDW as 14.12% .

RDW as a widely available, "inexpensive prognostic marker" which if increased in a clinical setting is suggestive of an underlying complex hyperinflammatory pathologic process. Considering the fact that the RDW is routinely included in the automated complete blood count (CBC) analyses and has no additional cost, this makes our study of RDW as a prognostic marker efficacious and interesting. Intensive Care Unit has a very heterogeneous patient population with an extended spectrum of illness (Wang et al., 2011).

PICU mortality was 43% of our study patients, and this was against Ramby1 et al., (2015) who recruited 596 PICU patients with only 6.5% of them died and *Said et al.,* (2017), who reported mortalities in 2.91% of PICU patients. But, our result was not so far from Siddiqui et al., (2018) who reported mortalities in 32.3% of PICU patients .
This difference in PICU mortalities could be explained by our presence in a developing country with deficient facilities (e.g. many PICUs may have one or no mechanical ventilator) and supplementations to PICU, the decreased number of qualified doctors for critical care management. Also, the very late referral of patients may lead to severe complicated disease course. In addition to the limited PICU places in general hospitals and the untolerable expensive cost of the nights in private hospitals, hence the prognosis of the late admitted cases would be worse from the start

When we compared PICU LOS the characteristics of the studied patients according to mortality and there was a significant increase of PICU LOS in patients with mortality compared to patients without mortality ($p < 0.01$), and this was against Siddiqui et al., (2018) who compared the characteristics of PICU patients according to mortality finding no significant differences between both groups regarding PICU LOS.

The PIM2 and laboratory data of the studied patients according to mortality (yes or no) were investigated in our study finding that; there were significant increase in PIM-2, RDW and the frequency of anemia in mortality patients compared with others without mortality, while showed significant decrease in Hb and MCV levels in mortality compared to others without mortality. This agreed with *Shukla et al.*, (2014) who observed that PIM2 score was significantly higher ($P < 0.001$) in patients who died (243) as compared to those who survived (496) (mean = 6.12, SD = 15.05).

The pathophysiologic basis to explain RDW-mortality association is not clear. It has been suggested that the association between RDW and mortality can be explained by RDW being a marker of inflammation because an increase in RDW can be seen with multiple processes that release reticulocytes into the circulation. An increase in RDW can be used to represent the extent of systemic inflammation present as an elevated RDW is associated with increased biomarkers of inflammation, including erythrocyte sedimentation rate, interleukin (IL-6), C-reactive protein, and tumor necrosis factor receptors I and II. These cytokines cause defective erythropoiesis resulting in structural and functional changes of erythrocytes, with volume variations and increased RDW. High values

of RDW can also appear in nutritional deficiencies such as iron deficiency anemia, vitamin B12 or folate deficiency anemia, or in blood transfusions (Orfanu et al., 2017). It has been also hypothesized that an increased oxidative state attributed to the release of inflam-matory cytokines leads to iron immobili-zation which may play a pivotal role in increasing the RDW (Lorente et al., 2014).

Then, we performed simple logistic regression analysis that revealed the most predicting factors of mortality were RDW, then anemia, PIM-2, PICU LOS in the studied patients. This was in accordance to (Shukla et al., 2014) who reported that PIM2 was significantly associated with mortality. Moreover, (Safdar et al., 2017) reported RDW as a predictor of mortality in PICU patients.

Finally, we found that the optimal cutoff value of PIM-2 to predict mortality rate in the studied patients was >5.8% with a very high sensitivity (97.67%) and specificity (98.25%), and the optimal cutoff value of RDW to predict the mortality rate in the studied patients was >14.7% with a high sensitivity (81.4%) and specificity (85.96%). These values were in accordance to (Shukla et al., 2014) who followed 739 PICU patients for two years reporting that cutoff value of PIM-2 was at 1.9 with the sensitivity for the first-year data was 65.8%, and the specificity was 71%. (AUC = 0.724). This cutoff was validated for the second-year data, which yielded the similar sensitivity (70.6%) and specificity (65%), and agrees with (Safdar et al., 2017), who reported the optimal cutoff value of RDW to predict mortality rate in the studied PICU patients was 15.75% with a high sensitivity (71%) and specificity (89%).

The exact pathophysiology that makes increased RDW a potential marker of prognosis of mortality in acute illness is not very clear. In conditions related to increased red blood cell destruction, blood loss, or after blood transfusions, RDW can be elevated (Fujita et al., 2015, Safdar et al., 2017). However, previous studies in the medical literature have revealed that the relationship between RDW and mortality of RDW is independent of anemia (Loveday et al., 2015, Safdar et al., 2017). A plausible explanation is that RDW is a surrogate marker of inflammation-related oxidative stress. Severe inflammatory conditions such as severe pneumonia and sepsis have been known to increase the degree of aniso-cytosis by causing a disruption in erythro-poiesis, changing the red blood cell membrane deformability and red blood cell circulation half-life, and this eventually causes an increased RDW (Shteinshnaider et al., 2015, Safdar et al., 2017).

Bion suggested that RDW can also be possibly used to give some insight into the ICU patient's degree of physiological reserve, one of three main determinants of clinical outcome (Ramby et al., 2015). Hunziker et al., suggested that the physio-logical reserve is a reflection of the collective cellular response to an acute stressor state of hypoxia and ischemia (Hunziker et al., 2012).

Conclusion and Recommendations

In conclusion, RDW is a predictor of mortality in critically ill PICU patients. Taking into consideration the fact that RDW is routinely measured in complete blood count with no additional cost, this can serve as an “inexpensive prognostic marker” in critically ill patients. On the basis of our findings in this study and in conjunction with that from previous studies, we suggest that:

(1) Additional studies on large number of cases in association with assessment of RDW & other parameters to find correlation between each parameter and mortality to evaluate the exact relation between RDW and PICU patient’s mort-ality,

(2) Including a study sample composed of patients under the care of multiple tertiary centers, a large sample size, and an increased number of deaths

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