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Research Article

RED BLOOD CELL DISTRIBUTION WIDTH IN BRONCHIAL ASTHMA AND PNEUMONIA PATIENTS IN INTENSIVE CARE UNIT AT BENGHAZI CHILDREN HOSPITAL, 2020-2021

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Abstract

Background: The red cell distribution width (RDW) is a widely available, inexpensive, and highly reproducible test that reflects the range of the red cell sizes. Any process that releases reticulocytes in the circulation will result in an increase in RDW**.** RDW is a routine laboratory measure associated with poor outcomes in adult critical illness. **The aims of study**: We performed a retrospective study to describe the association between RDW with morbidity and mortality in children with bronchial asthma and clinically diagnosed pneumonia and we determined the utility of RDW as an early pragmatic biomarker for outcome in those children admitted to ICU of Benghazi children hospital. **Materials and methods**: Retrospective study to all patients admitted to Benghazi children hospital with bronchial asthma and clinically diagnosed pneumonia between January 2021 and January 2022 were considered eligible for inclusion with some exclusions. We collected demographics, laboratory values, hospitalization characteristics and outcomes. We calculated the relative change in RDW from admission (A-RDW) to the last RDW(R-RDW) which either repeated days later or before mortality. **Results:** Over a13-month period, 100 patients had RDW measure done in the first day of PICU admission. The mean age of the patients was years, equal gender distribution by 50% of both. All patients were Libyans. Causes of admissions were Bronchial asthma (35%), Pneumonia (46%) and Bronchial asthma superimposed by pneumonia (19%). We noted a severe respiratory distress in most of cases according to PRESS score (68.3%).Reported complications of this study were sepsis (13%), association of more than one complications (13%), pleural effusion (1%), empyema (1%) and respiratory failure (4%). Regarding the route of oxygen therapy was by mask in 100% of patients on admission and 13% 0f these patients connected to MV. The A-RDW mean was 13.44% and R-RDW 14.219%. There were significant correlations between RDW on admission and severity of respiratory distress, length of hospital stay and outcome of patients. 87% of our patients were discharged in good general condition. **Conclusions and recommendations:** We conclude that there is a reliable correlation between RDW and respiratory diseases, and elevated RDW is a significant predictors of mortality, complication and prolonged staying in hospital. We recommend further studies to evaluate the correlation between RDW and other diseases in pediatric age group, correlation between RDW and inflammatory markers and also we recommend further study to evaluate prolonged complication with RDW readings.

Keywords: Pediatric ICU, Red Cell Distribution width, Respiratory diseases, Mortality.

INTRODUCTION

Red Cell Distribution Width "RDW" is one of the parameters in complete blood count (CBC) that measures variation in red blood cell size or volume (anisocytosis)[(1)]. The most common cause of an elevated RDW is anemia [evaluated in association with mean corpuscular volume (MCV) in differential diagnosis]. Regardless of that higher than normal RDW has also been described as a risk factor for unfavorable clinical course in various diseases in children [(2)]. The word "width" in the RDW test doesn't mean the size of individual red blood cells. Instead, it refers to the difference in size from largest to smallest red blood cell. A low RDW means red blood cells are all about the same size. A high RDW means you have both very small and very large red blood cells [(3)]. Red blood cells (RBC) serves as the vehicle for delivering oxygen to peripheral tissues in the human body. Unequal size of RBCs in the circulation, termed anisocytosis, is observed in several conditions, such as nutritional deficiencies, anemia (sickle cell anemia, hemolytic anemia), myelodysplastic syndrome, and other hematological disorders. As such, characteristics of human RBCs are utilized in the differential diagnosis of various clinical settings [(4)]. In recent years, some clinical studies have shown that there is a correlation between RDW and some acute diseases, such as brain infarction, sepsis, infective endocarditis and diabetic ketoacidosis. In addition, several studies have reported the predictive effect of RDW on lung disease [(5)]. Red cell distribution width (RDW) is a frequently overlooked parameter in routine hematological reports. It is a simple and inexpensive test which has been found by many adult studies to be a prognostic indicator of mortality in intensive care units [(6)]. RDW may elevated for many reasons. First, increased RDW may reflect an imbalance between hematopoiesis and RBC survival. Specifically, delayed clearance of senescent RBCs from the circulation leading to RBC underproduction, resulting in an increase in the plasma levels of RDW. Second, elevated RDW may suggest an underlying inflammation through multiple mechanisms, for instance, pro-inflammatory cytokines, such as interferon γ and tumor necrosis factor α, may affect iron metabolism and the capacity of RBC production by the bone marrow, which leads to anemia and increased RDW. Alternatively, RDW may increase due to shortened RBC lifespan and premature release of RBCs from the bone marrow in the presence of increased oxidative stress associated with inflammation. Third, RDW could also increase in other physiologic events, such as aging, pregnancy, or following erythropoietin stimulation and exercise [(7).] The usual red blood cell (RBC) volume is approximately 80-100 fl [(8)]. However, the size can vary significantly [(9)]. The degree of anisocytosis or size variability is quantified by the red cell distribution width or RDW [(10)]. The

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RDW equals the coefficient of variation of the mean corpuscular volume (MCV). The actual formula for calculating the RDW is the standard of deviation (SD) of the red blood cell volume divided by the MCV [(11)]. The RDW is routinely calculated by virtually all automated hematologic analyzers, so the values are reported for almost every complete blood count [(12)]. The results are usually expressed as a percentage with the usual upper limit of normal in the 11.5% to 14.4% range [(13)].
Red blood cell distribution width (RDW) is a parameter commonly used to identify different types of anemia and reactive bone marrow states and it is also a simple, widely used, and inexpensive parameter [(14)]. RBC distribution width (RDW) is a commonly used measure to quantify the variation of individual RBC volumes as it circulates during the approximate lifespan of 115 days [(15)]. In practice, elevated RDW levels are utilized as a diagnostic tool for differentiating an early stage of nutritional deficiency or megaloblastic anemias from thalassemia [(16)].

The potential value of RDW as a rapid and easy prognostic tool among high-risk patients, if effective, will vastly benefit timely intervention because RDW levels are measured as part of routine measures of complete blood count (CBC) by automated instruments in hematology laboratories [(17)]. Patients with a respiratory problem such as pneumonia and asthma experience oxygen exchange disturbance that causes tissue hypoxia. Hypoxia in tissue can increase the RDW in conjunction with acute fall of partial pressure of oxygen (PaO_2) mechanism, which triggers the renal cortex to excrete erythropoietin (EPO). EPO induces erythropoiesis in renal marrow by suppressing apoptosis and therefore increasing the number of red blood cells (RBCs) [(18)]. Although the precise pathophysiological mechanism of the correlation between higher RDW and mortality is vague, it seems that chronic subclinical inflammation affects iron metabolism as well as bone marrow function and its response to erythropoietin. On the other hand, erythrocyte maturation is suppressed by the inflammatory cytokines and high oxidative stress leading to the entry of newer, larger reticulocytes into the circulation and elevation of RDW. Additionally, RBC membrane glycoproteins and ion channels are altered by inflammation contributing to the change of RBC morphology [(19)]. Data on the utility of RDW as a biomarker of clinical outcomes in the pediatric population are more limited. One study demonstrated that preoperative RDW levels were associated with outcomes in children with cardiac disease [(20)]. However, there are no studies examining RDW as a biomarker in bronchial asthma and pneumonia in a general pediatric intensive care unit (PICU) in Benghazi children hospital. The characterization of such a readily available biomarker may provide a simple, pragmatic tool to stratify patients by severity of illness and identify those at risk for increased resource utilization and poor outcomes to facilitate novel laboratory assay [(21)] .

Aim of study

Red blood cell distribution width (RDW) is reported to be an independent predictor of outcome in adults with a variety of conditions. We sought to determine if RDW is associated with morbidity or mortality in children with bronchial asthma and pneumonia .We therefore studied the association of RDW at PICU admission with length of stay and mortality to determine its potential application as a pragmatic biomarker in bronchial asthma and pneumonia in pediatric population.

MATERIALS AND METHODS

Study design and setting: This retrospective study was conducted at Benghazi Children's hospital, during the period from January 2021-January 2022.

Selection of participating patients: A total of 100 children were enrolled in the study. Children were eligible if fulfilling the following criteria, their age between 1-14year, admitted to Pediatric intensive care with clinical picture of an acute infection of the pulmonary parenchyma, with bronchial asthma or both. Children were excluded if they had another comorbidities (as congenital heart disease or renal disease) those with hemoglobinopathies (as thalassemia), those who received a blood transfusion prior to ICU admission, patients younger than 1 year and older than 14 years and non-Libyans patient.

Data collection: Data were collected from the files to obtain demographic data as (age, sex), clinical data and examination of the patients with evaluation of the severity by using The Pediatric Respiratory Severity Score (PRESS). The PRESS assessed tachypnea , wheezing, retraction (accessory muscle use), Partial Oxygen Saturation (SpO2), and feeding difficulties, with each component given a score of 0 or 1, and total scores were classified as mild (0–1), moderate (2–3), or severe (4–5), and assessment of the outcomes, in addition to the length of stay in the hospital, complications which develop either on admission or during stay in the hospital (pleural effusion, empyema, pneumothorax, respiratory failure or signs of severe sepsis or septic shock) . Chest X-ray was done for every child admitted.

Laboratory data: Complete blood count (CBC) including; RDW was done to all participating children in the first 24 hours of admission and repeated on next days during hospital stay. The normal reference range for RDW in our hospital laboratory was 11.5-14.4%. Patients were categorized into four RDW quintiles: quintile1 RDW (13.4%), quintile 2(13.4–14.3%), quintile3 (14.4–15.7%), and quintile 4 (>15.7%).

Blood sampling: Two ml of blood put into an EDTA tube for the determination of CBC ' including RDW".

Methods: Complete blood picture was done using an automated blood counter (Sysmex KX21N) used in our hospital lab.

Data analysis: All data were coded, tabulated, and statistically analyzed using SPSS software version 25.0 (Statistical Package for Social Sciences). Descriptive statistics were done for non-parametric quantitative data by mean, standard deviation (SD) and minimum and maximum of the range, and median, while they were done for categorical data by number and percentage.

RESULTS

This retrospective study was done in Benghazi Children Hospital, Benghazi (Libya), during the period from January 2021 to January 2022. The results of our study were compatible with the literature that elevated RDW in pediatric patients admitted in PICU is associated with a higher risk for morbidity and mortality in critically ill pediatric patients.

Table 1. Comparison between survivors and Non-survivors groups as regard demographic & baseline data

Demographic and baseline data		Survivors (n=87)	Non-survivors (n=13)	p- value
Age in years	Range	0.75-14	1-14	0.124
	Mean±sd	4.52±3.800	3.371±3.54	
	Median	2.54	2.00	
Gender	Male	45(52%)	5(38%)	0.049
	Female	42(48%)	8(62%)	
Weight	Range	8-41	9.5-40	0.076
	Mean±sd	17.64±8.800	15.008±8.089	
	Median	13.00	12.5	
PRESS	Range	2-5	4-5	0.000
	Mean±sd	2.6436 ± 0.4816	3.000±0.000	
	Median	3.00	3.00	
LOS/Hospital	Range	3-20	2-14	0.002
	Mean±sd	1.563±0.499	1.692± 0.4803	
	Median	2.00	2.00	
Complications	Nil	68(78.8 %)	0(0.0%)	0.278
	Sepsis	13(15.2%)	0(0.0%)	
	Pl. effusion	1(1.6%)	0(0.0%)	
	Empyema	1(1.6%)	0(0.0%)	
	Respiratory failure	0(0.0%)	4(31%)	
	Sepsis with others	4(4.8%)	9(69%)	
RDW	Range	10.7-20.5	13.3-21.5	0.112
	Mean±sd	13.94±2.084	16.077±2.519	
	Median	14.5	15.5	

A total of 150 patients were collected, 5o of them were excluded according to our exclusion criteria, and the other 100 pediatric patients with PICU admissions over the 13 months of study period were included in the study. As regards baseline and demographic data of both survivors and non-survivors groups are showed in Table1.The age range was between 9 months to 14 years. There was statistically significant difference in the mean age between both groups Figure1. The mean age of all patients was years. In this retrospective study, it was reported that males and females were equal, as showed in Table2. Over all PICU mortality was 13%.

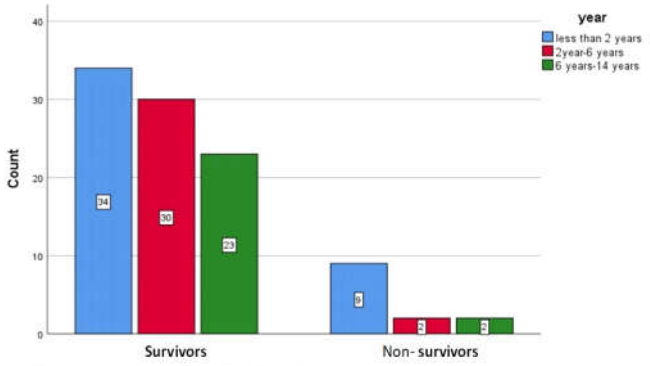

Figure1: outcome and age distribution in survivors and Non-survivors groups

Table 2. Gender percentage % in studied group

	Frequency	Percent%
Male	50	50
Female	50	50
Total	100	100

The clinical causes of admission were pneumonia (46%) followed by Bronchial asthma (35%), then bronchial asthma superimposed with pneumonia (19%) which are summarized in Table 3. The laboratory characteristics (CBC) of the patients at admission are summarized in Table4, and repeated CBCs are summarized in Table5. The mean of A-RDW was 13.44OO 2.28159 and mean of R-RDW was 14.219 .There was no correlation between RDW and leukocyte counts and also with platelet count. Pulmonary infiltrations on chest x-rays were in 64.3% of patients, while others had free chest x-rays.

Survivors and Non- survivors were 87% and 13%, respectively, Figure2. The RDW range of our studied patients was between 10.6%-23.6%. However, there was a significant increase in mortality across RDW quartiles, the rate of mortality in the quartile 3 and 4 was 69.2% .Our results indicated respiratory distress was severe according to PRESS in most of the cases (69%), Figure3. Oxygen saturation on admission in most of the cases (74%) was between 85-90%, Figure 4. Mask was the commonest mode of oxygen therapy used with studied patients, only 13% of them were connected to mechanical ventilator.

Table 3. Causes of admission in studied groups

	Frequency	Percent %
Bronchial Asthma	35	35.0
Pneumonia	46	46.0
Br.asthma with pneumonia	19	19.0
Total	100	100.0

Table 4. Hematological indices of studied group at admission

Hematological indices	Mean ± SD
HB	12.043000 ± 1.104377
MCV	75.389000 ± 4.477416
MCH	27.417000 ± 1.832482
MCHC	35.915000 ± 1.646200
RBC	4.242000 ± 0.612196
WBC	12.389000 ± 4.676632
Platt	342.780000 ± 132.578209
RDW	14.2190 ± 2.25037

Table 5. Repeated Hematological indices of studied group

Hematological indices	Mean ± SD
MCV	75.0370 ± 4.44292
MCH	27.0790 ± 1.52138
MCHC	35.7810 ± 1.58003
RBC	4.4683±.69763
WBC	14.7120 ± 5.84139
Platt.	370.4100 ± 139.33131
RDW	13.4400 ± 2.28159

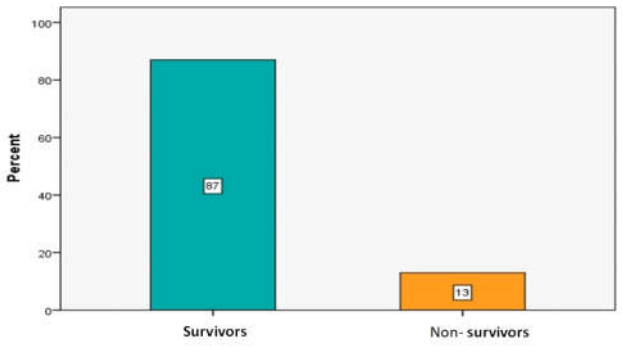

Figure2: Outcome in studied groups

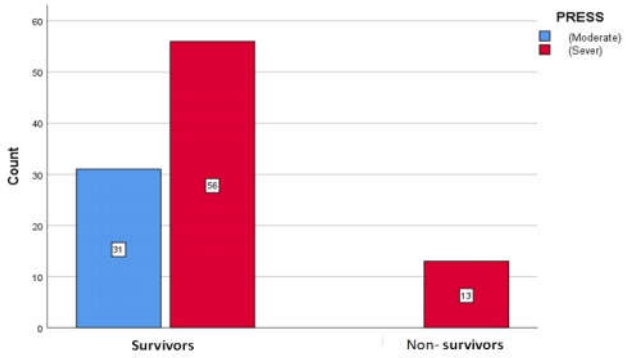

Figure3: Relation between outcome and PRESS

Table 6. List of Complications

	Frequency	Percent %
Nil	68	68.0
Sepsis	13	13.0
Pl. effusion	1	1.0
Empyema	1	1.0
Respiratory failure	4	4.0
Sepsis with others	13	13.0

Table 7. Complications and RDW quartiles Cross-tabulation

			RDW Quartiles				Total
			<13.4%	13.4-14.3%	14.4-15.7%	>15.7%	
Complications	Nil	Count	26	11	24	7	68
		% within RDW Groups	89.7%	78.6%	68.6%	31.8%	68.0%
	Sepsis	Count	1	0	4	8	13
		% within RDW Groups	3.4%	.0%	11.4%	36.4%	13.0%
	pl. effusion	Count	1	0	0	0	1
		% within RDW Groups	3.4%	.0%	.0%	.0%	1.0%
	empyema	Count	0	0	0	1	1
		% within RDW Groups	.0%	.0%	.0%	4.5%	1.0%
	respiratory failure	Count	1	1	1	1	4
		% within RDW Groups	3.4%	7.1%	2.9%	4.5%	4.0%
	sepsis with others	Count	0	2	6	5	13
		% within RDW Groups	.0%	14.3%	17.1%	22.7%	13.0%
			29	14	35	22	100
			100.0%	100.0%	100.0%	100.0%	100.0%

Table 8. LOS and RDW quartiles Cross-tabulation

			RDW Quartiles				Total
			<13.4%	13.4-14.3%	14.4-15.7%	>15.7%	
days in hosp.	<7 days	Count	26	12	2	2	42
		% within RDW Groups	89.7%	85.7%	5.7%	9.1%	42.0%
	≥7days	Count	3	2	33	20	58
		% within RDW Groups	10.3%	14.3%	94.3%	90.9%	58.0%
Total		Count	29	14	35	22	100
		% within RDW Groups	100.0%	100.0%	100.0%	100.0%	100.0%

Table 9 Outcome and RDW quartiles Cross-tabulation

			RDW Quartiles				Total
			<13.4%	13.4-14.3%	14.4-15.7%	>15.7%	
Outcome	Survivors	Count	28	11	31	17	87
		% within RDW Groups	96.6%	78.6%	88.6%	77.3%	87.0%
	Non-survivors	Count	1	3	4	5	13
		% within RDW Groups	3.4%	21.4%	11.4%	22.7%	13.0%
Total		Count	29	14	35	22	100
		% within RDW Groups	100.0%	100.0%	100.0%	100.0%	100.0%

54% of patients received steroids and 65% received antibiotics. Out of complications , Sepsis was the commonest(26%), half of them were only Sepsis and the other half were Sepsis with other complications (such as empyema ,pleural effusion and respiratory failure) ,as listed in Table6. Sepsis was associated with increased RDW values as stated in Table7. The main complication in the non- survivors group was respiratory failure in 13 patients.

The median length of hospital stay was 7 days. LOS in hospital was strongly correlated to RDW, 58 patients stayed at hospital 7days or more Figure5, 53 of them (91.4%) had high RDW Table8. In this study, we found that in the non- survivors group(13 cases), 9 patients (69.2%) had high RDW and 4 patients (30.8%) had RDW within normal range; while in the survivors group (87 patients) ; 48 of them(55.2%) had high RDW, Table9. 43% of patients in our study were younger than

two years, Figure6. There was a strong correlation between high RDW, younger age and mortality; out of non-survivors group (13 patients), 8 patients who were younger than 2 years old had high RDW (61.5%). The survivors group who developed complications were 19 patients (21.8%); out of them, 17 patients had high RDW Figure 7. Most of patients in our study were discharged in good general conditions (87%).

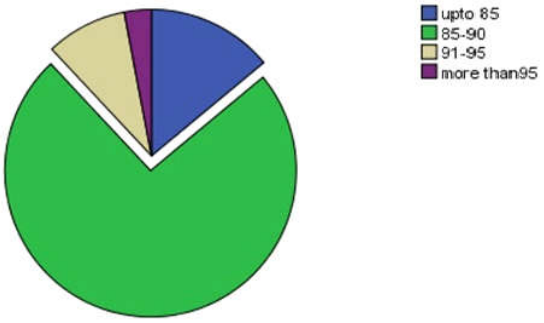

Figure 4. . Oxygen % of patients at admission

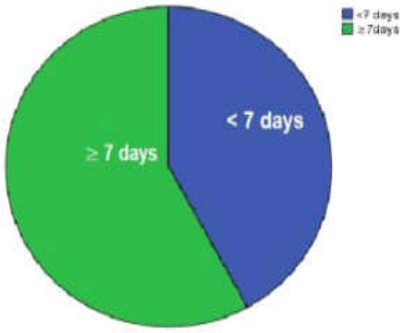

Figure 5. LOS at hospital

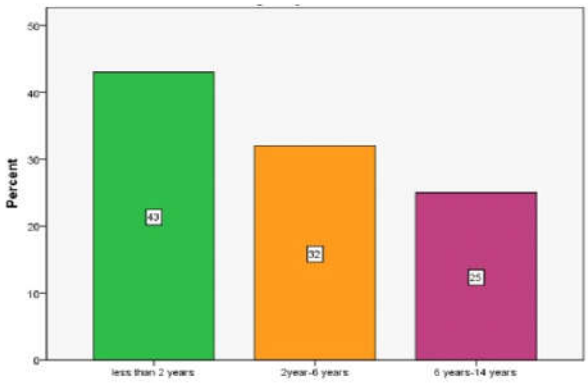

Figure 6. Age distribution of patients

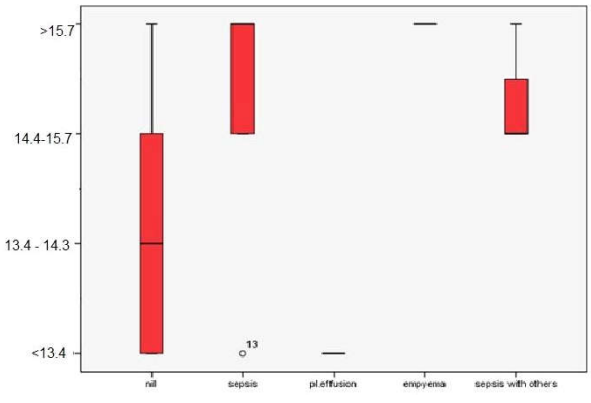

Figure 7. Relation between RDW and complication in survivors

DISCUSSION

Respiratory diseases in children exert a great burden in developing countries and still associated with a higher incidence and mortality rates. We hypothesized that readily available clinical parameters can be used to assess the risk of morbidity and mortality in children with acute respiratory diseases. Our results support this hypothesis in as much as the RDW and the PRESS had significant predictive characteristics and warrants further investigation. The present study examined the relation between RDW and bronchial asthma and clinically diagnosed pneumonia in children admitted to ICU of Benghazi children hospital. RDW at the time of PICU admissions is associated with different validated parameters for patients with clinically diagnosed pneumonia and bronchial asthma. Elevated RDW reflects anisocytosis and higher variability in size of circulating RBCs .The need for oxygen by masks, mechanical ventilation or both in PICU patients are associated with RDW values on admission. Song Mao has demonstrated that RDW was a non-invasive, low-cost, and widely available predictor for the risk and progression of RTIs. RDW level may reflect the disease course among RTIs (Song Mao, 2018). Seyedeh observed that higher RDW was strongly linked to higher mortality risk in pediatric patients admitted in PICU. Higher RDW was associated with longer duration of PICU admission (Seyedeh, 2017). Our study also showed similar association. There is a significant correlation between severity of respiratory distress and RDW. We study the demographical information (e.g. age, sex) and patients admitted with pneumonia, bronchial asthma or both to ICU and complications which include pneumothorax, pleural effusion, sepsis, empyema and respiratory failure. Therapeutic interventions such as the use of steroids, oxygen, and the use of broad-spectrum antibiotics were also studied .A recent study by Nasren Gamal has demonstrated there is a strong correlation between RDW and respiratory diseases as pneumonia, acute bronchiolitis, and others. There is also a strong relation between RDW and duration of oxygen therapy and length of hospital stay (Nasren Gamal, 2020).

A high RDW on admission was associated with an increased risk of long-term mortality in patients with Acute Respiratory Failure(ARF) (Tom Schepens,2017) .RDW may provide an alternative indicator to predict the prognosis and disease progression and it is easy to get. Until recently, the value of RDW in children admitted to the PICU had not been reported. A recent study by (Said et al, 2017) in critically ill children showed that admission RDW is associated with pediatric ICU mortality and morbidity, independent of illness severity. There are several theoretical mechanisms to explain the increase of RDW, and further studies are needed to validate the relationship between Erythropoietin (EPO), pro-inflammatory factors, reticulocytes, and RDW in the serum of patients with Acute Respiratory Failure (ARF); (Wei Zhang, 2020). The independent association of RDW with the outcome may imply that anisocytosis itself may be a possible causable factor in organ dysfunction (Bujak *et al.,* 2015). The presence of anemia is the most likely cause of a change in RDW (Bujak *et al.,* 2015). Which is the reason we exclude patients with anemia in this study, another factor potentially causing a change in RDW is vitamin D3 deficiency (Wang, 2011). Vitamin D3 plays an important role in erythropoiesis and cell proliferation, so a small change in vitamin D3 concentration will affect bone marrow erythropoiesis (Nasren Gamal, 2020). In our study, Vitamin D3 was not done. Many confounding factors should

be taken into account when considering the prognosis of a patient's disease, e.g. the underlying disease and inflammatory markers like CRP. RDW is possibly influenced or associated with these factors. Several studies have compared RDW to other inflammatory markers such as interleukin 6, C-reactive protein and ESR; they found a correlation between them. In our analysis, we have exclude inflammatory markers because of insufficient data. RDW is attractive as a pragmatic clinical biomarker for respiratory dysfunction by its low cost and universal availability compared to other proposed biomarkers. RDW could be a future prognostic tool or an additional biomarker for monitoring critically ill children. Many studies have evaluated diverse prognostic markers for early recognition of ICU patients who have high morbidity and mortality risk. A variety of approaches including clinical scoring systems such as the Pediatric Risk of Mortality (PRISM) score, and Pediatric Respiratory Severity Score (PRESS) also specific routine laboratory tests have been evaluated in former studies for identifying their potential role in prediction of outcome in critically ill pediatric patients (Seyedeh,2017). RDW has been proposed to be a prognostic factor influencing mortality in a spectrum of diseases including cardiovascular, pulmonary, renal, infectious and oncologic diseases and also in critically ill patients. Although the precise pathophysiological mechanism of the correlation between higher RDW and mortality is vague, it seems that chronic subclinical inflammation affects iron metabolism as well as bone marrow function and its response to erythropoietin. On the other hand, erythrocyte maturation is suppressed by the inflammatory cytokines and high oxidative stress leading to the entry of newer, larger reticulocytes into the circulation and elevation of RDW. Additionally, RBC membrane glycoproteins and ion channels are altered by inflammation contributing to the change of RBC morphology (Büyükkoçak, 2014). Previous studies have established that RDW values increased with age. This relationship; although not fully defined, could depend on several factors including inflammation, anemia, nutritional status and age associated diseases (Büyükko- çak, 2014). The correlation between RDW and age in patients admitted in ICU was significant especially among the patients who had expired (Song Mao, 2018). In our study, we found no relationship between age and RDW. In the study by (Ramby *et al.,* 2019). Al in Italy the Overall PICU mortality was 6.5% which was much less than what we had in our hospital. They also found that there was a significant increase in mortality rate across all RDW quartiles and RDW measured within 24 hours of PICU admission was independently associated with PICU duration of admission >48 hours and higher mortality in a general PICU population. In our patients, elevated RDW was also associated with LOS at hospital. Different cohorts reveal that poor medical conditions requiring mechanical ventilation is one of the most important risk factors of mortality in PICU patients' .In our study, the all non-survivors group (13%) were connected to mechanical ventilator.

Conclusion

Elevated RDW values on admission can be used to predict cases at high risk of mortality for early management and to decrease children death from acute respiratory diseases. PRESS is a simple and trustable score for initial evaluation of children in the emergency department and PICU. We conclude from this retrospective study that there is a significant correlation between RDW with pneumonia and bronchial asthma and outcome of patient in our hospital. There is also a strong relation between RDW and duration of oxygen therapy and length of hospital stay.

Recommendation

- Further studies to evaluate the correlation between RDW and other diseases in the pediatric age group.
- Further prospective prolonged study to evaluate patient during admission and after discharge to compare prolonged complication with RDW readings.
- Further studies to evaluate relation of RDW and inflammatory markers as ESR and CRP and outcome of patients.
- Further studies about RDW as a prognostic value in all critically ill pediatric patient admitted to ICU.
- Further studies to confirm the correlation between RDW, morbidity and vitamin D levels in pediatrics.

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