Research Article

Red Cell Distribution Width Elevation and Sepsis in Pediatric Critically Ill Patients

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Abstract

Background: Recently, a relationship has been demonstrated between red blood cell distribution width (RDW) and mortality risk in critically ill patients although the exact mechanism of this association is still vague. However, the impact of changes in RDW on sepsis and its outcome in critically ill patients has not been widely studied. Therefore, we studied the prognostic impact of changes in RDW in critically ill pediatric patients with sepsis.

Methods: A total of 304 patients who were admitted to pediatric intensive care unit were selected to participate in this study. The changes in RDW on the day of admission and 4 and 8 days after admission in PICU were documented and their relationship with SIRS positivity, sepsis, and mortality were analyzed.

Results: The mortality rate in our patients was 10.5%. In total, 39.8% of patients were SIRS positive and 50.4% fulfilled the criteria of sepsis. The mean of RDW at the time of admission, on Day 4 and on Day 8 of admission was 14.8%, 16.1%, and 16.6%, respectively. At the time of admission, RDW had a significant correlation with mortality and SIRS positivity, but RDW measured on Days 4 and 8 of admission did not correlate with neither of them. Neither of RDW0, RDW4, nor RDW8 did correlate with sepsis criteria fulfillment. ΔRDW day 4-adm > 0.2%, ΔRDW day 8-adm > 0.2%, ΔRDW day 8-day 4 > 0.2% exhibited no correlation with SIRS positivity, sepsis, and mortality.

Conclusions: We found that an increase in RDW from baseline during the first 4 and 8 days after admission of critically ill pediatric patients did not correlate with their mortality, SIRS positivity, and sepsis. However, elevated baseline RDW is a valuable prognostic marker in patients with sepsis.

Keywords: Sepsis, RDW, Mortality, SIRS

1. Background

Sepsis is characterized by systemic inflammatory response syndrome (SIRS), dysregulation of immune system, derangements of microcirculation, and end-organ damage (1). Globally, the total burden of illness from pediatric sepsis is high, particularly in intensive care units. Mortality rates could be as high as 80% in systemic inflammatory response syndrome (SIRS) and sepsis (2, 3). Therefore, early identification of SIRS and sepsis is essential to achieve satisfactory outcomes in children. Several studies have examined factors associated with morbidity and mortality due to sepsis in patients in intensive care units (4). Various biomarkers have been evaluated to act as a predictor of prognosis in septic patients, but most results are contradictory. Due to difficulties in test methods and unavailability or expensiveness, most of these markers have not made it to routine clinical practice (5-7). Studies have shown that red cell distribution width (RDW), which is reported as part of complete blood count and is routinely assessed in nearly all hospitalized patients, can predict critically ill patients' prognosis. Not thoroughly understood pathophysiological mechanisms are responsible for this relationship. Iron metabolism and bone marrow function are affected by systemic inflammatory responses (8). Proinflammatory cytokines can lead to elevation of RDW by down-regulating the expression of erythropoietin receptor and inhibiting erythrocyte maturation and proliferation induced by erythropoietin (9). High oxidative stress, which is present in sepsis, induces an increase in RDW by reducing RBC sur-

vival and increasing the release of large premature RBCs into the peripheral circulation.

In our study, we evaluated the correlation among RDW, SIRS, sepsis, and mortality in pediatric patients admitted to intensive care units and we also studied whether changes in Red cell distribution width could act as a predictor in pediatric septic patients.

2. Methods

This study was an observational study conducted from September 2015 to February 2016, at a pediatric intensive care unit of a teaching hospital in Tehran. Our ICU has 12 beds and is managed by fellowships of pediatric ICU and anesthesiologists 24/7.

Approval for the study was settled by the Institutional Review Board of Mofid Children's Hospital.

Patients with age more than 16 years, chronic renal failure, chronic metabolic disease, cancer, chronic hematologic diseases with the potential to change RDW, history of red blood cell (RBC) transfusion within 72 hours were excluded from the study.

The medical records of all patients were reviewed for the following data: demographics and vital signs including body temperature, blood pressure, respiratory rate, and pulse rate, and CBC including RDW, measured within 24 hours of PICU admission on Day 4 of admission and on Day 8 of admission. Also, changes between values (Delta RDW) were calculated for each patient. Blood gas results, blood bank reports, microbiology reports, mortality, and duration of PICU admission were also documented.

RDW is reported as a coefficient of variation (percentage) of red blood cell volume. The normal reference range for RDW in this hospital laboratory is 11.5% to 14.5%. Patients were categorized in to 4 RDW quartiles based on a previously published priori cut points (RDW < 13.4, 13.4 - 14.3, 14.4 - 15.7, and > 15.7) (10, 11).

The systemic inflammatory response syndrome (SIRS) and sepsis were defined according to the international consensus conference on pediatric sepsis definitions (1, 12).

2.1. Statistical Analysis

Qualitative data were represented in the form of frequency and percentage. Association between qualitative variables was assessed using chi square test. Quantitative data were represented using mean $\pm$ SD. Analysis of Quantitative data between the 2 groups was done using unpaired t test and Mann-Whitney test. SPSS software Version 16 was used for data analysis.

3. Results

We enrolled 306 pediatric patients who were admitted to ICU during the 6 months of our study; of whom, 55.8% were males. The mean age of our patients was 2.9 years. Patients' characteristics are summarized in Table 1.

The history of tracheal intubation during their PICU admission was present in 34% of patients and correlated significantly with SIRS positivity, sepsis, and mortality.

In 87.8% of patients, blood pressure was within normal limits for age, in 50% respiratory rate was within normal limits for age, and in 38.4% pulse rate was within normal limits for age.

Fever (core temperature above 37.8) was present in 26.5% of patients and 9.9% of patients had hypothermia.

According to patients' CBC, 24.1% of patients had leukocytosis, 51.7% anemia according to age, and 11.3% had thrombocytopenia.

Considering the microbiology reports, 21.3% had positive blood cultures (The most common organism being coagulase negative Staphylococci, followed by *Pseudomonas* spp., *Klebsiella* spp. and *Acintobacter*.). Blood culture positivity significantly correlated with SIRS positivity and sepsis, but it did not correlate with mortality (Table 2).

In view of the SIRS criteria, 39.8% of patients were SIRS positive and 50.4% fulfilled the criteria of sepsis.

The mortality rate of our patients was 10.5%. Mortality rate was significantly higher in patients in the SIRS positive and sepsis group (P = 0.004). The difference between mortalities in the SIRS positive and sepsis group are summarized in Table 3.

The mean RDW at the time of admission (RDW0) was 14.8% $\pm$ 2.4. In 24.7% of patients, RDW was above 15.7%. The correlation of mean RDW at the time of admission (RDW0) with other variables is summarized in Table 4.

In 93 patients, the second RDW was measured on Day 4 of PICU admission (RDW4), and in 56 patients, the third RDW was measured on Day 8 of PICU admission (RDW8). The mean of RDW4 was 16.1%, and the mean of RDW8 was 16.6%. In measuring RDW4 and RDW8, 49.5% and 51.8% of patients were, respectively, in the RDW > 15.7% group.

RDW0 had a significant correlation with mortality (P = 0.01), and the mean of RDW in patients who died was more than patients who did not die during their PICU admission (15.9% vs. 14.7%), but RDW4 and RDW8 did not correlate with mortality.

RDW0 had a significant correlation with SIRS positivity (P = 0.0001), and the mean of RDW in patients who were SIRS positive was more than those who were SIRS negative at the time of their PICU admission (15.4% vs. 14.4%), but RDW4 and RDW8 did not correlate with SIRS positivity.

Table 1. Patients' Characteristics According to RDW Quartiles

Characteristic	All Patients	< 13.4	13.4 - 14.3	14.4 - 15.7	> 15.7	P Value
No. (%)	304	85 (28)	75 (24)	68 (22)	76 (25)	
Age, y	2.9 (0.1 - 16)	3.4 (0.15 - 16)	2.13 (0.1 - 14)	2.1 (0.1 - 13)	3.1 (0.1 - 16)	0.046
Gender, %						0.9
Male	169 (55.6)	50 (58.8)	41 (54.7)	36 (52.9)	42 (55.3)	
Female	135 (44.4)	35 (41.2)	34 (45.3)	32 (47.1)	34 (44.7)	
Admit category, %						0.004
Medical	140 (46.1)	37 (43.5)	26 (34.7)	31 (45.6)	46 (60.5)	
Surgery	94 (30.9)	20 (23.5)	28 (37.3)	23 (33.8)	23 (30.3)	
Neurosurgery	70 (23)	28 (32.9)	21 (28)	14 (20.6)	7 (9.2)	
SIRS, %						
Negative	185 (60.9)	57 (67.1)	53 (70.7)	40 (58.8)	35 (46.1)	0.009
Positive	119 (39.1)	28 (32.9)	22 (29.3)	28 (41.2)	41 (53.9)	
Sepsis						0.448
Negatie	58 (48.7)	16 (57.1)	12 (54.5)	14 (50)	16 (39)	
Positive	61 (51.3)	12 (42.9)	10 (45.5)	14 (50)	25 (61)	
Positive blood culture, %	16 (21.3)	1 (7.1)	2 (11.1)	4 (21.1)	9 (37.5)	0.08
Positive any culture	50 (52.6)	5 (29.4)	12 (52.2)	12 (50)	21 (67.7)	0.08
CRP						0.01
< 10	68 (58.6)	22 (73.3)	12 (66.7)	23 (63.9)	11 (34.4)	
≥ 10	48 (41.4)	8 (26.7)	6 (33.3)	13 (36.1)	21 (65.6)	
Mortality, %	34 (11.1)	8 (9.4)	5 (6.6)	5 (7.3)	16 (21.1)	0.016

Table 2. The Relationship Between Blood Culture Positivity and Other Variables

	Blood Culture		P Value
	Positive	Negative	
SIRS			
Positive	17	45	0.02
Negative	0	14	
Sepsis			
Yes	16	28	0.01
No	1	17	
Mortality			
Yes	7	13	0.1
No	10	46	

Table 3. The Difference Between Mortalities in the SIRS Positive and Sepsis Group

	Mortality		P Value
	Yes	No	
SIRS			
Positive	29	94	0.000
Negative	9	182	
Sepsis			
Yes	21	41	0.007
No	8	53	

Neither of RDW0, RDW4, nor RDW8 did correlate with sepsis criteria fulfillment.

Among the patients whose RDW was measured for the second time, the mean delta RDW was 1.8% and in 83% of these patients the change in RDW was more than 0.2 from baseline. Although the changes between the RDW0 and RDW4 did not correlate with SIRS positivity and sepsis, the mean of these changes was significantly higher in patients who died (P = 0.15).

Among the patients whose RDW was measured for the third time, the mean delta RDW was also 1.8%, and in 79.6% of these patients, the change in RDW was more than 0.2

Table 4. The Correlation of Mean RDW at the Time of Admission (RDW0) with Other Variables

	Mean RDW0	**P Value**
Blood culture		
Positive	16	0.2
Negative	15.2	
SIRS		
Positive	15.6	0.000
Negative		
Sepsis	14.5	
Yes	15.8	0.3
No		
Mortality	15.3	
Yes	15.9	0.017
No	14.8	

from the RDW measured on Day 4 of PICU admission. The changes between the RDW4 and RDW8 did not correlate with SIRS positivity, sepsis, and mortality. The changes between the RDW0 and RDW8 did not correlate with SIRS positivity, sepsis, and mortality either.

4. Discussion

SIRS and sepsis are succeeding clinic and pathophysiologic conditions, and by the progression of these conditions, morbidity and mortality rates increase. Sepsis is one of the main causes of ICU admissions and a key reason for morbidity and mortality in ICU worldwide (12, 13). Despite improvements in intensive care and treatments, mortality rate in patients with sepsis remains very high (14).

Inflammatory response resulting from interaction between genetically predisposed host and causative microorganism causes release of biological biomarkers that can affect prognosis. Biomarkers are biological molecules, which are useful for diagnosis, treatment response monitoring, and predicting prognosis, especially in patients whose clinical symptoms are not specific and in conditions in which diagnostic tests have limitations (6). Several studies have evaluated more than 100 biomarkers in sepsis patients; however, most of them are not clinically practical due to methodical difficulty and unavailability (15, 16). Interestingly, a number of studies have documented the relationship between RDW and mortality in ICU admitted patients (11). Wang et al. confirmed that RDW is an independent determinant of mortality in ICU patients (17). Conversely, Arslan et al. did not find a statistically significant

relationship between prognosis of sepsis patients in ICU and RDW (4).

As what we found in our study, Jo et al. categorized RDW levels and they also showed that mortality rate was significantly higher in patients with RDW ≥ 15.8% (18). Although in the mentioned study, there was no difference in the rate of positive blood culture between RDW tertiles, in our study, the frequency of positive blood culture was significantly more in patients with RDW ≥ 15.8%. In an observational study of critically ill patients, the rate of sepsis was higher according to RDW levels, and RDW was associated with a significant risk for blood stream infection (11). However, in our study, SIRS positivity and not sepsis was significantly more common in critically ill pediatric patients who had elevated RDW levels.

In a recent study, an increase in RDW from baseline in patients with sepsis and septic shock during the first 3 days was found to be associated with mortality (19). Nevertheless, we did not find any significant correlations between the rise of RDW from baseline with SIRS positivity, sepsis, and mortality.

As early identification of patients with greater risk of mortality would allow more aggressive interventions that could decrease mortality rates, RDW could facilitate achieving this goal in critically ill pediatric patients.

References

1. Pomerantz WJ, Weiss SL, Kaplan SL, Randolph AG. *Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis.* UpToDate, Waltham; 2015.

2. Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S, et al. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. *Ann Emerg Med.* 2006;**48**(1):28–54. doi: 10.1016/j.annemergmed.2006.02.015. [PubMed: 16781920].

3. Matot I, Sprung CL. Definition of sepsis. *Intensive Care Med.* 2001;**27 Suppl 1**:S3–9. [PubMed: 11307368].

4. Arslan Z, Ozmen O, Karakoc F, Karaca M, Aktas M. *Factors Affecting Prognosis in Sepsis Patients Admitted to Intensive Care Unit.* 2015.

5. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med.* 2002;**28**(2):108–21. doi: 10.1007/s00134-001-1143-z. [PubMed: 11907653].

6. Dupuy AM, Philippart F, Pean Y, Lasocki S, Charles PE, Chalumeau M, et al. Role of biomarkers in the management of antibiotic therapy: an expert panel review: I - currently available biomarkers for clinical use in acute infections. *Ann Intensive Care.* 2013;**3**(1):22. doi: 10.1186/2110-5820-3-22. [PubMed: 23837559].

7. Bozza FA, Bozza PT, Castro Faria Neto HC. Beyond sepsis pathophysiology with cytokines: what is their value as biomarkers for disease severity?. *Mem Inst Oswaldo Cruz.* 2005;**100 Suppl 1**:217–21. [PubMed: 15962126].

8. Chiari MM, Bagnoli R, De Luca PD, Monti M, Rampoldi E, Cunietti E. Influence of acute inflammation on iron and nutritional status indexes in older inpatients. *J Am Geriatr Soc.* 1995;**43**(7):767–71. [PubMed: 7602028].

9. Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. *Perfusion*. 2005;**20**(2):83–90. doi: 10.1191/0267659105pf793oa. [PubMed: 15918445].

10. Al-Najjar Y, Goode KM, Zhang J, Cleland JG, Clark AL. Red cell distribution width: an inexpensive and powerful prognostic marker in heart failure. *Eur J Heart Fail*. 2009;**11**(12):1155–62. doi: 10.1093/eurjhf/hfp147. [PubMed: 19926599].

11. Bazick HS, Chang D, Mahadevappa K, Gibbons FK, Christopher KB. Red cell distribution width and all-cause mortality in critically ill patients. *Crit Care Med*. 2011;**39**(8):1913–21. doi: 10.1097/CCM.0b013e31821b85c6. [PubMed: 21532476].

12. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric S. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;**6**(1):2–8. doi: 10.1097/01.PCC.0000149131.72248.E6. [PubMed: 15636651].

13. Bone RC. Important new findings in sepsis. *JAMA*. 1997;**278**(3):249. [PubMed: 9218676].

14. Raghavan M, Marik PE. Management of sepsis during the early "golden hours". *J Emerg Med*. 2006;**31**(2):185–99. [PubMed: 17044583].

15. Sonmezer MC, Tulek N. Biomarkers in Bacterial Infections and Sepsis. *Klimik J*. 2015;**28**(3):96–102. doi: 10.5152/kd.2015.20.

16. Meisner M. Biomarkers of sepsis: clinically useful?. *Curr Opin Crit Care*. 2005;**11**(5):473–80. [PubMed: 16175035].

17. Wang F, Pan W, Pan S, Ge J, Wang S, Chen M. Red cell distribution width as a novel predictor of mortality in ICU patients. *Ann Med*. 2011;**43**(1):40–6. doi: 10.3109/07853890.2010.521766. [PubMed: 20961272].

18. Jo YH, Kim K, Lee JH, Kang C, Kim T, Park HM, et al. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. *Am J Emerg Med*. 2013;**31**(3):545–8. doi: 10.1016/j.ajem.2012.10.017. [PubMed: 23380094].

19. Kim CH, Park JT, Kim EJ, Han JH, Han JS, Choi JY, et al. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. *Crit Care*. 2013;**17**(6):R282. doi: 10.1186/cc13145. [PubMed: 24321201].