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Original Research Article

Assessment of the association between RDW and mortality in children admitted in pediatric intensive care unit (PICU)

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Abstract

Aim: The aim of the present study was to assess the association between RDW and mortality in children admitted in pediatric intensive care unit (PICU).
Methods: The study was conducted in the department of Pediatric medicine, Sir Padampat mother and child health institute (SPMCHI) and advanced hematology laboratory, SMS medical College, Jaipur from October 2018 to April 2019. 170 patients were included in the study. All the patients who were admitted in PICU of SPMCHI hospital, SMS medical college consecutively in the above said time period were taken as subjects in this study, after screening for inclusion and exclusion criteria.
Results: Total 170 children admitted in ICU ranged from 1month to 17 years, Majority of subjects belonged to age group 1month-5 years (36.4%), followed by 5-10 year and rest was age group of 10-18 years (30.7%). Out of 170 children, total number of males was 109(64.2%) and number of females was 61(35.8%). Among age group 1m-5y total 49(79%) were having haemoglobin in range of 9-11g/dl, 11 (17.7%) were having haemoglobin in range of 11-13g/dl, 2(3.3%) were having haemoglobin more than 13g/dl. In age group 5-10y total 39(69.6%) were having haemoglobin in range of 9-11g/dl, 13 (23.2%) were having haemoglobin in range of 11-13g/dl, 4 (7.1%) were having haemoglobin more than 13g/dl. Among age group 10-18y total 36 (69.2%) were having haemoglobin in range of 9-11g/dl, 13 (25%) were having haemoglobin in range of 11- 13g/dl, 3 (5.8%) were having haemoglobin more than 13g/dl.
Conclusion: CRP in our study did not correlate with mortality, hence to conclude in resource poor setting where parameter for predicting mortality in critical care are not readily available, RDW which can be measured easily by coulter counter can be used as a predictor of mortality.

Keywords: Red cell distribution width, Mortality, Pediatric patients, Pediatric intensive care unit, Prognostic factor

Introduction

Pediatric intensive care units (PICU) with growing life sustaining technologies have resulted in advanced care for children and adolescents. Moreover, characterizing the disease severity at admission and assessing risk factors correlating with mortality can help improve the quality of patient care. By means of simple laboratory values this goal seems to be attainable. Red

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cell distribution width (RDW) is a laboratory parameter which expresses the variability in red blood cell size and is calculated as the standard deviation in red blood cell (RBC) size divided by the mean corpuscular volume (MCV). Clinically, it is a widely available and low-cost test. Its normal range is between 11.5–14.5%. Reference ranges may vary depending on the individual laboratory and patient's age. Elevated RDW on complete blood count reflects marked anisocytosis on peripheral blood smear review, which can be caused by any disease involving red blood cell (RBC) destruction or production [1].

Studies have revealed that RDW could be used as a predictor of mortality in critically ill patients [2, 3]. Although the mechanism of this relationship is not fully apparent, it seems that in critical illnesses, the acute systemic inflammatory response can alter both erythropoiesis and erythrocyte maturation [4-7]. Red blood cell distribution width is a measure of the range of variation of Red blood cell (RBC) volume that is reported as part of a standard complete blood count. Red cell distribution width (RDW) is the standard deviation (SD) in red blood cell size divided by the mean corpuscular volume. It is included in the complete blood count panel with normal range of 11.5% to 14.5% [8, 9].

Elevated RDW has been strongly associated with multiple causes of death and long-term mortality within major demographic and disease sub–populations [10]. Elevated RDW has also been shown to be associated with blood markers of inflammation like interleukin-6, C reactive protein (CRP) [11], raised erythrocyte sedimentation rate, impaired iron mobilization [12], oxidative stress [13], ineffective red cell production and increased red cell destruction [14]. Higher levels of inflammation were associated with higher erythropoietin concentration among non-anemic older adults, while an inverse association was observed in anemic persons [15]. This suggests that in a pro-inflammatory state the increase in erythropoietin is a compensatory mechanism for maintaining normal hemoglobin concentration and that anemia occurs when the compensatory increment in erythropoietin production is unsustainable. Indeed, a number of studies have shown that pro inflammatory cytokines suppress erythropoietin gene expression, inhibit proliferation of erythroid progenitor cells, down-regulate erythropoietin receptor expression, and reduce erythrocyte life-span with aging, which again suggests that increased erythropoietin production is a compensatory mechanism for decreasing bone marrow response and/or red cell survival [16].

The aim of the present study was to assess the association between RDW and mortality in children admitted in pediatric intensive care unit (PICU).

Materials and Methods

The study was conducted in the department of Pediatric medicine, Sir Padampat mother and child health institute (SPMCHI) and Advanced hematology laboratory, SMS medical college, Jaipur from October 2018 to April 2019. 170 patients were included in the study. All the patients who were admitted in PICU of SPMCHI hospital, SMS medical college consecutively in the above said time period were taken as subjects in this study, after screening for inclusion and exclusion criteria. Later on subjects were divided into two groups spontaneously based on their outcome of PICU stay. Survivors acted as controls and non survivors acted as cases.

Inclusion criteria

Critically ill children admitted in PICU

Exclusion criteria

- Blood transfusion in last 3 months
- Death or transfer out from PICU within 24 hrs
- Refusal for consent
- Haematological disorders.

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- Anemia (Hb<9gm/dl)

Methodology

All the patients who were admitted to PICU during the study period were assessed for the eligibility, all the critically ill patients who were admitted to PICU were taken as study subjects. All those patients who received blood transfusion in last 3 months, patients who were admitted for less than 24 hours or died within 24 hours, patients who refused to give consent, patients with haematological disorders, patients with anemia with haemoglobin less than 9 gm/dl were excluded from study.

After getting written consent from guardians on the very first day of their admission, 2ml of venous blood was collected in EDTA vacutainers under aseptic precautions and it was sent to laboratory as early as possible. The samples were run in automated hematology analyzer SYSMEX XN-1000 in this RDW was analysed. RDW for consecutive 3 days were recorded for each patients along with CRP. Patients were followed until discharged or death and were classified according to the outcome as controls (survivors) and cases (non-survivors) respectively.

Data collecting sheet was checked for completeness and stored securely. Data from collecting sheet was entered into a computer using Microsoft Excel 2014 package. It was then exported into statistical programme Epi info version 7.2.1.0 statistical software. For analysis with the help of statistician. Continuous variables of platelet indices were summarized as mean, median standard deviation. A table of baseline characteristics was generated, and receiver operator curve (ROC) curve was plotted for each platelet index then area under the curve (AUC) was computed for each index and optimum cut-off values for each platelet index was calculated. Then sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy was computed for each cut-off value.

Results

Table 1: Distribution of patients

Age Group (years)	No.	Percentage
1m-5yr	62	36.4
5-10yr	56	32.9
10-17yr	52	30.7
Gender		
Male	109	64.2
Female	61	35.8

Total 170 children admitted in ICU ranged from 1month to 17 years, Majority of subjects belonged to age group 1month-5 years (36.4%), followed by 5-10 year and rest was age group of 10-18 years (30.7%). Out of 170 children, total number of males was 109(64.2%) and number of females was 61(35.8%).

Table 2: Hemoglobin levels in study population

Age Group (years)	Hb 9-11 g/dl		Hb 11-13 g/dl		Hb>13g/dl	
	N	%	N	%	N	%
1m-5y	49	79	11	17.7	2	3.3
5--10y	39	69.6	13	23.2	4	7.1
10--18y	36	69.2	13	25	3	5.8
Total	124	72.9	37	21.8	9	5.3

Among age group 1m-5y total 49(79%) were having haemoglobin in range of 9-11g/dl, 11 (17.7%) were having haemoglobin in range of 11-13g/dl, 2(3.3%) were having haemoglobin

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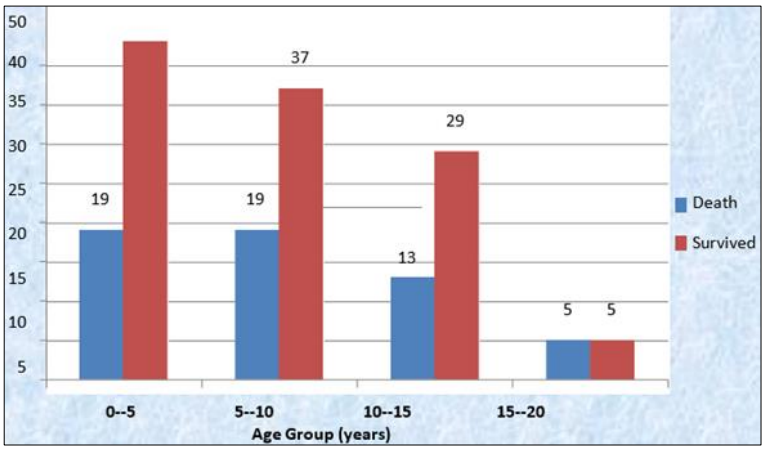
more than 13g/dl. In age group 5-10y total 39(69.6%) were having haemoglobin in range of 9-11g/dl, 13 (23.2%) were having haemoglobin in range of 11-13g/dl, 4 (7.1%) were having haemoglobin more than 13g/dl. Among age group 10-18y total 36 (69.2%) were having haemoglobin in range of 9-11g/dl, 13 (25%) were having haemoglobin in range of 11- 13g/dl, 3 (5.8%) were having haemoglobin more than 13g/dl.



Graph 1: Age distribution of study subjects in relation to mortality

Out of 62 patients in 1m-5 year age group 19 (30.6%) patients died, among 56 patients in 5-10 years age group 19 (33.9%) patients died, among 52 patients in 10-18 year age group 18 (34.6%) patients died. Maximum mortality (34.6%) was observed among 10-18 year age group. Overall mortality was 32.9% Relation of age with mortality with age was statistically insignificant (p=0.667).

Table 3: Organ system affected among study subjects in relation to mortality

Affected System	Death		Survived		Total
	N	%	N	%	N
CNS	32	41.6	45	58.4	77
CVS	3	23.1	10	76.9	13
Respiratory	10	21.3	37	78.7	47
GIT	3	25.0	9	75.0	12
Genito Urinary	3	50.0	3	50.0	6
Others	5	33.3	10	66.7	15
Total	56	32.9	114	67.1	170

Majority of patients were admitted because of CNS ailments n=77 (45.3%), respiratory ailments contributed n=47 (27.6%), CVS n=13 (7.6%), GIT n=12 (7.1%), other n=15(8.8%), genitourinary system n=6 (2.3%). Mortality rate was highest among genitourinary system (75%) CNS ailments (41.6%), respiratory (21.3%), CVS (23.1%), GIT (25%) The relation between mortality and system involved was insignificant (P value 0.102), although highest number of mortality was observed among CNS affected patients.

Table 4: Haemoglobin level of study subjects in relation to mortality

Hemoglobin (mg/dl)	Death		Survived		Total
	N	%	N	%	N
9-11	42	33.9	82	66.1	124
11-13	12	32.4	25	67.6	37
>13	2	22.2	7	77.8	9
Total	56	32.9	114	67.1	170

124 patients were having hemoglobin in range of 9-11 mg/dl, out of which 42 (33.9%) died and 82 survived (66.1%), 37 patients were having hemoglobin in range of 11-13 mg/dl out of

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which 12 (32.4%) expired and 25 (67.6%) survived, 9 patients were having hemoglobin more then 13mg/dl out of which 2 expired (22.2%) and 7 survived (77.8%). maximum mortality was observed in patients having hemoglobin in range of 9-11mg/dl. Relation between hemoglobin and mortality was insignificant (p=0.770).

Table 5: Mean RDW among survivor and children who died

Day of ICU admission	Mean RDW (%)		P Value (t test)
	Death(n=56)	Survived(n=114)	
Day 1	19.63 ± 1.11	15.78 ± 1.22	<0.001 (S)
Day2	19.53 ± 0.89	15.69 ± 1.18	<0.001 (S)
Day3	19.31 ± 2.79	15.71 ± 1.23	<0.001 (S)

Mean RDW on day 1among non survivor was 19.63 ± 1.11 and among survivor was 15.78 ± 1.22.Mean RDW on day 2 among non-survivor was 19.53 ± 0.89 and among survivor was 15.69 ± 1.18.Mean RDW on day 3 among non-survivor was 19.31 ± 2.79 and among survivor was 15.71 ± 1.23.Mean RDW on all three days was statistically significant. Mean RDW was high in non-survivor on all three days in comparison to survivors.

Table 6: Mortality in relation to RDW on day 1, 2 and 3

Cut off value of RDW on day 1	Death		Survived		Total
	N	%	N	%	N
≥ 17.7%	56	86.2	9	13.8	65
<17.7%	0	0.0	105	100.0	105
Cut off value of RDW on day 2					
≥ 17.9%	56	91.8	5	8.2	61
<17.9%	0	0.0	109	100.0	109
Cutoff values of RDW on day 3					
≥ 18.5%	54	98.2	1	1.8	55
<18.5%	2	1.7	113	98.3	115

Sensitivity of RDW on day 1 in predicting mortality was 100 percent and specificity was 92.1%, positive predictive value was 86.2% and negative predictive value was 100%.Area under the curve was 0.990. Sensitivity of RDW on day 2 in predicting mortality was 100 percent and specificity was 95.6%, positive predictive value was 91.8% and negative predictive value was 100%. Area under the curve was 0.996. Sensitivity of RDW on day 2 in predicting mortality was 94.6 percent and specificity was 99% positive predictive value was 98.2% and negative predictive value was 98.3%. Area under the curve was 0.978.

Discussion

The present study was a hospital based prospective observational study done in pediatric intensive care unit, department of paediatrics, SMS medical college, Jaipur conducted from October 2019 to April 2020. A total of 170 patients admitted in PICU were enrolled after applying inclusion and exclusion criteria out of them 114 patients survived who were considered as controls and 56 patients died who considered as cases.

In our study 170 children admitted in ICU were included, ranged from 1month to 17 years. Majority of subjects belonged to age group 1month-5 years (36.4%), followed by 5-10(32.9%) year and rest was age group of 10-18 years (30.7%). Said Ahmed *et al.* [17] studied over 3913 patients admitted in PICU, all the patients admitted to PICU were taken as study population. Mean age of cohort was 7.45 ± 6.67years. El-Hamed *et al.* [18] studied on 100 critically ill patients admitted to PICU aged from 1 month to 13 years. Mean age of population was 2.2 ± 2.4 years.

Out of total 170 patients under study, total number of males was 109 (64.2%) and total number of females was 61(35.8%). Sachdeva *et al.* [19] studied on 101 patients, out of total

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101 patients 68 (67%) were males and 33(33%) were females. Among age group 1m-5y total 49(79%) were having haemoglobin in range of 9-11g/dl, 11(17.7%) were having haemoglobin in range of 11-13g/dl, 2(3.3%) were having haemoglobin more than 13g/dl. Among age group 5-10y total 39(69.6%) were having haemoglobin in range of 9-11g/dl, 13(23.2%) were having haemoglobin in range of 11-13g/dl, 4(7.1%) were having haemoglobin more than 13g/dl. Among age group 10-18y total 36(69.2%) were having haemoglobin in range of 9-11g/dl, 13(25%) were having haemoglobin in range of 11-13g/dl, 3(5.8%) were having haemoglobin more than 13g/dl. El-hamed *et al.* [18] studied on100 patients, Range of haemoglobin in study population was 5.6-14.8mg/ dl, and mean haemoglobin was 10.7±2 mg/dl.

Majority of study subjects in our study group belonged to age group 1m-5 years, out of 62 patients in 0–5-year age group 19 (30.6%) patients died, among 56 patients in 5-10 years age group 19 (33.9%) patients died, among 52 patients in 10-18-year age group 18 (34.6%) patients died. maximum mortality (34.6%) was observed among 10-18-year age group. Overall mortality was 32.9% and Relation of age with mortality was statistically insignificant (p=0.667). El-hamed et.al[18] studied on 100 patients, mean age among non- survivor population was 2±2.2 years. Overall mortality was 43%, Relation of mortality with age was insignificant (P=0.981).

In our study, 35(32.1%) out of 109 male patients died, whereas 21 (34.4%) out of 61 females patients died. Relation of mortality with gender was not statistically significant (p=0.757). Sachdeva *et al.* [19] studied on 101 patients, 7 (10.2%) out 68 males patients died and 4(12.1%) out of 33 females patients died. Relation of mortality with gender was not statistically significant (p=0.50). 124 patients in our study group were having hemoglobin in range of 9-11 mg/dl, out of which 42(33.9%) died and 82 survived(66.1%), 37 patients were having hemoglobin in range of 11-13 mg/dl out of which 12 (32.4%) expired and 25 (67.6%) survived, 9 patients were having hemoglobin more than 13mg/dl out of which 2 expired (22.2%) and 7 survived (77.8%) maximum mortality was observed in patients having hemoglobin in range of 9-11mg/dl. Relation between hemoglobin and mortality was insignificant (p=0.770). Sachdeva *et al.* [19] studied on 101 patients and concluded that Admission hemoglobin was inversely related to RDW D1 (r=–0.3, p=0.02) but there was no significant difference in the hemoglobin levels between survivors and deaths. Mean hemoglobin among non survivors populations was 9.8 mg /dl and among survivors it was 9.9mg/dl. El-Hamed *et al.* [18] studied on 100 patients hemoglobin ranges from 7.3-14.8 among survivors (n=57) hemoglobin ranges from studied on total 100 patients, among survivors (57%) 5.6-12.8 there was a significant association between hemoglobin and mortality (<0.001).

Out of 56 non survivors, Mortality rate was highest among genitourinary system 75%(3/6) CNS ailments 41.6% (32/77), respiratory 21%(10/47), CVS23.1%(3/13), GIT 25% (3/12) The relation between mortality and system involved was insignificant (P value 0.102), although highest number of mortality was observed among CNS affected patients (n=32) followed by respiratory system (n=10), CVS (n=3), GIT (n=3) and genitourinary (n=3). Ramby *et al.* [20] studied on total 596 patients out of which maximum patients were admitted with CVS ailments 161(27%), followed by sepsis104(17.4) followed by respiratory ailments 97(16.3%). mortality was highest among study group having sepsis 51% followed by CVS 25%, this relation of system involvement with outcome was insignificant.

At Cut off value of RDW >17.7% on day one, 56(86.2%) out of 65 patients died and rest survived. At value <17.7% none of the patient died. At this cut off value the mortality was significantly high (p<0.001). Sensitivity of RDW on day 1 in predicting mortality was 100 percent and specificity was 92.1%, positive predictive value was 86.2% and negative predictive value was 100%. Area under the curve was 0.990. Zhang *et al.* [21] studied on 1,539 patients, including 1,084 survivors and 455 non survivors. The primary endpoint was hospital mortality. Cutoff RDW on day 1 was 14.8. Median RDW among survivor population was13.8 (13, 14.8) and among non-survivor it was 14.5(13.4, 15.8) Two- sided P<0.05 was considered to be statistically significant. RDW remained significantly associated with mortality after

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adjustment for sex, age, Charlson index albumin and CRP, with an odds ratio of 1.1 (95% CI: 1.03-1.16). Diagnostic performance of RDW in predicting mortality appeared to be suboptimal (AU-ROC: 0.62). Sensitivity of RDW was 63% and specificity was 69%. Sensitivity of RDW on day 2 in predicting mortality was 100 percent and specificity was 95.6%, positive predictive value was 91.8% and negative predictive value was 100%. Zhang *et al*. 2013 [21] studied on 1,539 patients. Repeated measurements of RDW were arbitrarily selected on day 3, 6, 10, 13, 17 and 20 during ICU stay. The results showed that none of these changes in RDWs was associated with in-hospital mortality, indicating that repeated measurements of RDW are of limited value in critical care settings. At Cut off value of RDW on day three>18.5%, 54(98.2%) out of 55 patient died. At this cut off value the mortality was significantly high (p<0.001). Sensitivity of RDW on day 3 in predicting mortality was 94.6 percent and specificity was 99% positive predictive value was 98.2% and negative predictive value was 98.3%. Sachdeva *et al*. [19] day 3 median RDW among non survivors was 21(4.9) and among survivors it was 20.8(26), they find in their study median RDW on day 3 (18 vs 15.4; P=0.02) were significantly higher among patients with infection as compared to children without infection.

Conclusion

The value of RDW on day 3 on admission above 18.5 percent can be considered as independent predictor of mortality with sensitivity of 94.6percent and specificity of 99.1 percent, positive predictive value was 98.2% and negative predictive value was 98.3%. CRP in our study did not correlate with mortality, hence to conclude in resource poor setting where parameter for predicting mortality in critical care are not readily available, RDW which can be measured easily by coulter counter can be used as a predictor of mortality.

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