RESEARCH PAPER

Outcome Prediction Value of Red Cell Distribution Width in Critically-ill Children

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Objective: To study the association between red cell distribution width (RDW) and mortality in critically-ill children admitted in a Pediatric intensive care unit (PICU). **Methods**: 101 participants were recruited consecutively over 3 months. Data collected included demographics, vital parameters, laboratory values, severity and organ failure scores, RDW for the first 5 days of admission, duration of PICU stay and survival outcome. **Results**: 11 patients died during study period. High RDW at admission (RDW D1) correlated significantly with mortality (*P*=0.007). The odds of death increased by 15 to 23 times with rise in RDW D1 from 18% to >21%. The optimal RDW D1 cut-off value for mortality was 18.6%, which yielded sensitivity 90.9%, specificity 70.8%, positive predictive value 27.8%, negative predictive value 98.4%, and area under curve (AUC) 0.83 (95%CI 0.737, 0.925). 29 out of 60 (48.3%) patients with RDW D4 >18% had PICU stay of ≥7 days. **Conclusion**: High (≥18.6%) RDW at admission and its persistent high levels are associated with high mortality and prolonged stay in PICU, respectively.

Keywords: Intensive care unit, Mortality, Predictors, Risk factors

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%. Recently RDW is being evaluated as prognostic marker for mortality in critically-ill patients [1,2]. The association of RDW with mortality and duration of intensive care unit stay has not been studied adequately in children [3]. The objective of our study was to find any association between RDW and mortality in children admitted in a pediatric intensive care unit (PICU).

METHODS

This observational study was conducted in PICU of Sir Ganga Ram Hospital, New Delhi, India. Participants were recruited consecutively over three months. The exclusion criteria included hematological disorders, blood transfusion in last 3 months, and death or transfer-out from PICU within 24 hrs. Data included variables like demographics, vital parameters, complete blood count, serum electrolytes, and microbiological profile. It further included Pediatric Risk of Mortality Score (PRISM) score at 12 and 24 hours, daily Pediatric Logistic Organ Dysfunction (PELOD) score, mechanical ventilation days, inotropes, renal replacement therapy, duration of PICU stay and final outcome (discharge or death). Survival was considered primary outcome, while length of stay in PICU was the secondary outcome [4].

The RDW values were recorded at admission and for the next 5 days. CBC, including RDW estimation was performed by automatic blood analyzer (Beckman Coulter CDXCH 800, California, USA). Institutional Research and Ethics committee approved the study.

Statistical analysis: Quantitative variables were compared using unpaired t-test/Mann-Whitney test. Qualitative variables were compared using Chi-square/ Fisher exact test. A receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value for RDW at admission (RDW D1). The area under curve (AUC) with 95% confidence interval (CI), sensitivity, specificity, positive predictive value and negative predictive value were calculated to analyze the diagnostic accuracy of RDW D1 to predict mortality. A two-sided *P* value of less than 0.05 was considered statistical significant. All analyses were performed with SPSS version 17.0.

RESULTS

One hundred fifteen children admitted in PICU were assessed; 14 patients were excluded (9 stayed in PICU

for <24 hours and 5 had hematological disorders) and 42 patients were under 2 years of age. Twenty-five patients presented with shock at admission; 11 (16.9%) children died during study period.

Table* I** compares the variables between survivors and deaths. 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. High RDW at admission (RDW D1) correlated significantly with mortality (*P*=0.007). The odds of death increased to 15 to 23 times with rise in RDW D1 from 18% to more than 21% (Table* II**). Of the 11 patients who died, 10 had RDW D1 >18.6% (*P*<0.001). The optimal RDW D1 cut-off value for mortality was 18.6% with sensitivity 90.9%, specificity 70.8%, positive predictive value 27.8% and negative predictive value 98.4%. The area (95% CI) under ROC was 0.83 (0.737, 0.925).

TABLE I CHARACTERISTICS OF NON-SURVIVORS AND SURVIVORS IN STUDY POPULATION

Variable	*Deaths* (*n*=11)	*Survivors* (*n*=90)
Age* (mo)	72 (4,196)	36 (1.5,196)
Male, *n* (%)	7 (64)	61(68)
Heart rate (/min)	164.3 (19)	140.4 (21.4)
SBP (mmHg)	86.6 (37.5)	88.9 (22.5)
DBP (mmHg)	56.7 (21)	60 (13.3)
MAP (mmHg)	66 (24)	70.4 (16.7)
$RR (/min)	50.2 (14)	41(12)
$Temp (ºC)	37.9 (0.6)	37.5 (0.5)
RDW		
Day 1	21(6.1)	17.7 (5)
Day 2	22.1(6.5)	17.7 (4.9)
Day 3	21 (4.9)	20.8 (26)
Day 4	20.8 (5.6)	17.9 (4.7)
Day 5	19 (4.2)	17.5 (4.9)
Hb (g/dL)	9.8 (2.4)	9.9 (2.4)
CRP (>6 mg/d), *n* (%)	10 (91)	51 (57)
PRISM 12	22.5 (5.7)	6.8 (5.2)
PRISM 24	23.5 (7.4)	4.3 (4.2)
PELODS		
Day 1	31.2 (12)	7.8 (8.5)
Day 2	32.6 (12.1)	7.3 (8.1)
Day 3	28.7 (13.3)	6.2 (7.4)
Day 4	21 (9.2)	5.3 (8.1)
Day 5	15.2 (12.4)	4 (7.8)
MODS, *n* (%)	9 (82)	10 (11)
MV, *n* (%)	11(100)	40 (44)
#Inotropes, *n* (%)	11(100)	30 (33)
Dialysis, *n* (%)	6 (55)	9 (10)

*Value in mean (SD) or *median (range) SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, RR: respiratory rate, RDW: red cell distribution width, CRP: C-reactive protein, PRISM pediatric risk of mortality score; PELODS: Pediatric logistic organ dysfunction score, MODS: multiorgan dysfunction syndrome, MV: mechanical ventilation; P<0.01 for heart rate, all PELODS Values, MODS, MV, Dialysis, and PRISM values; #P<0.001; $P=0.01; RDW-Day 1, P=0.02 and Day 2, P=0.05.*

The median stay in PICU was 3.4 days. Twenty-nine out of 60 (48.3%) patients on day 4 with RDW >18% had PICU stay of ≥7 days (***Web Table* I**). 45 patients had evidence of infection at admission. The median RDW on day 3 (18 *vs* 15.4; *P*=0.02), day 4 (18.4 *vs* 15.4; *P*=0.02) and day 5 (18.1 *vs* 15.2; *P*=0.02) were significantly higher among chidren with infection as compared to children without infection.

DISCUSSION

In this observational study, we found that high RDW levels at admission can predict mortality in PICU and persistently raised RDW value was associated with prolonged PICU stay. Limitations of present study include a short duration of study and small sample size. Lack of segregated data as per disease profile, and not statistically adjusting other risk factors of mortality were the other limitations.

Elevated RDW has been strongly associated with multiple causes of death and long-term mortality within major demographic and disease sub-populations [5]. Elevated RDW has also been shown to be associated with blood markers of inflammation like interleukin-6, C-reactive protein (CRP) [6], raised erythrocyte sedimentation rate, impaired iron mobilization [7], oxidative stress [8], ineffective red cell production and increased red cell destruction [9]. Pro-inflammatory cytokines suppress erythrocyte maturation, inhibit half-life and deformability of RBC membrane allowing larger reticulocytes to enter the peripheral circulation and increase RDW [10]. RDW may reflect membrane integrity and high RDW may represent membrane instability [11]. Release of immature cells with poor oxygen-binding capacity, implies suboptimal response to oxidative stress. This may explain why the association between RDW and clinical outcome is independent of the severity of acute illness as well as the degree of inflammation [12]. Anemia is known as risk factor for mortality in under–5 age group [13], but hemoglobin levels above 7 g/dL alone does not correlate with mortality [14]. In our study, mortality was associated with high RDW but not with hemoglobin level. There was no

WHAT THIS STUDY ADDS?

- Red cell distribution width is a good predictor of mortality and prolonged stay in pediatric intensive care unit amongst critically-ill children.

TABLE II ADMISSION RED CELL DISTRIBUTION WIDTH (DAY 1) QUANTILES AND ODD RATIO OF DEATH

Day 1 RDW Quantiles	*Survivor, n=90*	*Non-survivor, n=11*	*Odds ratio (95% CI)*	*P value*
15.7-18.04	19 (95)	1 (5)	1.05 (0.95, 1.16)	1.00
18.04-21.5	15 (78.9)	4 (21.1)	1.26 (1.00, 1.59)	0.04
≤21.5	15 (71.4)	6 (28.6)	1.4 (1.06, 1.83)	0.02

RDW: red cell distribution width; values in no.(%); No patient died in RDW quantile ≤ 14.2 (n=21) and 14.2 - 15.7 (n=20).

significant difference in admission RDW between patients with infection and without infection, but persistent high RDW values were found in the former probably reflecting persistent inflammatory response.

High RDW at admission and its persistently high levels seem to be associated with mortality and prolonged stay in PICU. Red cell distribution width may be used as a predictor of outcome in children admitted in PICU in resource-limited settings.

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WEB TABLE I ASSOCIATION OF HIGH RED CELL DISTRIBUTION WIDTH WITH PROLONGED STAY IN PICU

Day	*PICU stay>7days median (IQR)*	*PICU stay ≤7 days median (IQR)*	*P value*
D1	16.9 (14.9, 22.2)	16.3 (14.4, 19.2)	0.14
D2	17.4 (15.3, 23.4)	16.1(14.5, 18.8)	0.05
D3	17.2 (15.2, 23.4)	15.9 (14.3, 19.2)	0.07
D4	18.2 (15.4, 22.1)	15.6 (14.3, 19)	0.03
D5	18.2 (15.3, 21.3)	15.2 (14.2, 18)	0.01

PICU: Pediatric intensive care unit.