Original Research Article

A study on the predictive value of red blood cell distribution width as a biomarker of outcome in paediatric critical illness

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ABSTRACT

Background: Red blood cell distribution width (RDW) is a simple, low cost measure, which is routinely reported as a standard component of complete hemogram. Several recent studies have found a positive association between RDW and risk of both morbidity and mortality in several diseases, particularly in critically ill adults. But, data regarding the outcome predictive utility of RDW in critically ill paediatric population is limited. The objective of the study was to determine the association between RDW and mortality and morbidity in paediatric critical illness.

Methods: A cross sectional observational study was conducted from February 2019-May 2019 at Cheluvamba Hospital, Mysuru. 97 subjects admitted to Paediatric intensive care unit (PICU) were included in the study. Data regarding subject demographics, hospitalization characteristics, laboratory values and outcomes were collected.

Results: A significant positive correlation was found between mortality among critically ill children and RDW measured within 24 hours of PICU admission (p=0.01) and peak RDW during the first 7 days of PICU stay (p=0.01). The relative change in RDW correlated significantly (p=0.01) with the number of intensive care unit (ICU) free days. Our subjects were divided into quartiles based on the admission RDW, subjects in the fourth quartile were found to have the highest mean Paediatric risk of mortality (PRISM III) score, Paediatric index of mortality (PIM 2) score and the least number of ICU free days. Area under the receiver operator curve (AUROC) for incidence of death was 0.706 for admission RDW, 0.71 for peak RDW and 0.882 for PIM 2 score.

Conclusions: Our data demonstrates that RDW at the time of PICU admission could serve as a cost-effective marker for early identification of critically ill paediatric population who are at risk for adverse outcomes.

Keywords: Red blood cell distribution width, Critically ill, Paediatric, PIM 2 score, PRISM III score

INTRODUCTION

Red blood cell distribution width (RDW) measures the variability in red blood cell size and is calculated as proportional variation in Mean corpuscular volume (MCV), with a normal range of 11.5-14.5%.[1] RDW is a simple, low cost measure and is routinely reported as a standard component of complete blood count (CBC).

Increased RDW values reflect greater variability in RBC size, which generally indicates dysfunctional erythropoiesis, shortened RBC lifespan, or premature release of reticulocytes from the marrow into the peripheral circulation.[2] In critical illness, the ongoing acute systemic inflammatory response resulting from multiple underlying aetiologies can alter both erythropoiesis and erythrocyte maturation and function.[3,4] The resulting changes in RDW observed in the critically ill subjects may therefore reflect the degree of underlying inflammation and provide useful prognostic information.[5-7]

Several recent studies have found a positive association between RDW and risk of both morbidity and mortality in

several diseases, particularly in critically ill adults.[8-11] But, data regarding the outcome predictive utility of RDW in critically ill paediatric population is limited. Therefore, we would like to study the association of RDW at admission to Paediatric intensive care unit (PICU) with length of PICU stay and mortality to determine its potential use as a pragmatic biomarker in critically ill paediatric population.

Objectives

The objectives of the study were to determine the association between RDW and mortality in critically ill children admitted to PICU and to determine the association between RDW and duration of PICU stay.

METHODS

Study population

Children (in the age group of 2 months to 18 years) admitted to PICU at Cheluvamba Hospital, a tertiary care hospital in Mysuru.

Study period

February 2019 to May 2019 (4 months).

Study design

Cross sectional observational study.

Sample size

Sample size was calculated to be 105, considering the total pediatric admissions in the age group of 2 months to 18 years to Cheluvamba Hospital and the total number of PICU admissions (7.5%) at Cheluvamba hospital over a period of 1 year.

Applying the formula:

$$n = Z^2 pq \div d^2$$

where,

Z is the standard normal variate, at 5% type 1 error (p<0.05), it is 1.96

p=0.075, q=1-p=(1-0.075)=0.925
d=absolute error=5% (0.05)

Sampling method

Purposive sampling.

Inclusion criteria

All patients in the age group of 2 months to 18 years, admitted to PICU from February 2019 to May 2019 were included in the study after applying the exclusion criteria.

Exclusion criteria

Death within 1 hour of PICU admission, lack of Complete blood count (CBC) report within 24 hours of PICU admission, elective admission to ICU (includes admissions after elective surgery or admission for an elective procedure, example- insertion of a central line. An admission or operation was considered elective if it could be postponed for more than 6 hours without adverse effect) and recurrent admission to PICU during the course of hospital stay.

Methodology

After obtaining the Institutional ethical committee clearance and obtaining informed consent from the parents of the selected study subjects, 105 subjects were included in the study after applying the inclusion and exclusion criteria.

We obtained the following data: (1) demographics: age, sex, weight, admission diagnoses, and (2) hospitalization characteristics, like: initial vital signs within 1 hour of PICU admission, subjects' Complete blood counts (CBC) at admission and during the first 7 days of admission to the PICU, admission RDW (determined from the first CBC collected within the first 24 hours in PICU), relative change in RDW (to evaluate the change in RDW, we calculated the difference between the admission RDW and the highest RDW in the first 7 days after admission to PICU. We divided that difference by the admission RDW to calculate the relative change in RDW). Admission severity of illness was determined using the Paediatric Index of Mortality 2 (PIM2) score (a validated score used to estimate mortality risk on PICU admission using physiologic and laboratory variables collected within 1 hour after admission),[12] and highest PRISM III score (Paediatric risk of mortality score) in the first 24 hours of admission to PICU was determined, the number of ICU free days was calculated, (ICU free days were defined as the number of days between transfer to a regular ward and 28 days after PICU admission. Subjects were assigned zero ICU-free days if they died in the PICU or had a PICU length of stay (LOS) more than 28 days). Final outcome was taken as discharge or death. Survival was considered the primary outcome, while the number of ICU free days was considered as the secondary outcome.

RESULTS

105 subjects' in the age group of 2 months to 18 years, admitted to PICU, at Cheluvamba Hospital, Mysuru, from February 2019 to May 2019 were screened, of these 97 subjects (59 males and 38 females) who met the study criteria were included in the study and the data collected from them was analysed. Table 1 shows the baseline characteristics of the study subjects. Independent sample t test was used to compare the means between the subjects who died during the course of PICU stay and those who survived. The mean values of RDW on day 1 of admission

to PICU (p=0.001), peak RDW during first 7 days of PICU stay (p=0.001), PRISM III score during the initial 24 hours of PICU admission (p=0.001), PIM 2 score (p=0.001) and PIM 2 risk of mortality (p=0.001) was significantly higher for those subjects who died during the course of PICU stay compared to those who survived (p<0.05). Although the mean haemoglobin values were lower among those subjects who died during the course of PICU stay, it was not statistically significant.
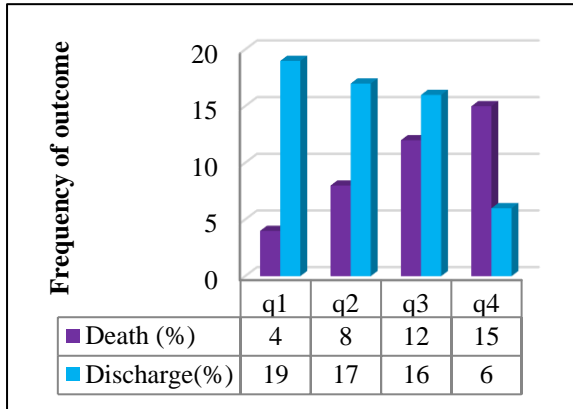

Figure 1: The distribution of the number of deaths and the number of survivors during the course of PICU stay between the subjects grouped into different quartiles based on admission RDW.
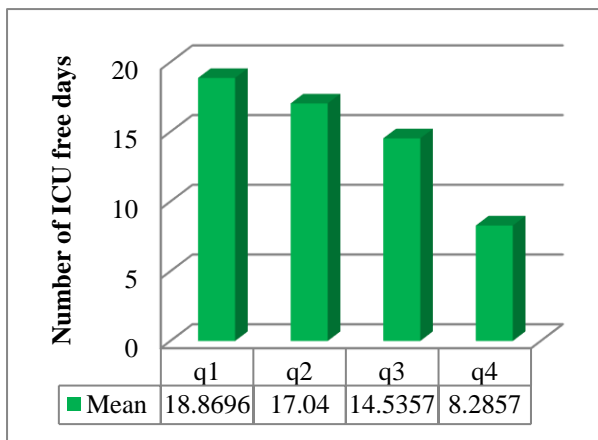

Figure 2: The distribution of the number of ICU free days between the subjects grouped into different quartiles based on admission RDW.

We divided our subjects into quartiles based on admission RDW (RDW measured within 24 hours of admission to PICU) as follows: first quartile (q1), <14.09%; second quartile (q2), 14.10 to 15.99%; third quartile (q3), 16.00-18.90%; fourth quartile (q4), >18.91%. On comparison of subjects between the first and fourth admission RDW quartiles, subjects in the fourth quartile had a statistically significant higher mortality (p=0.03).
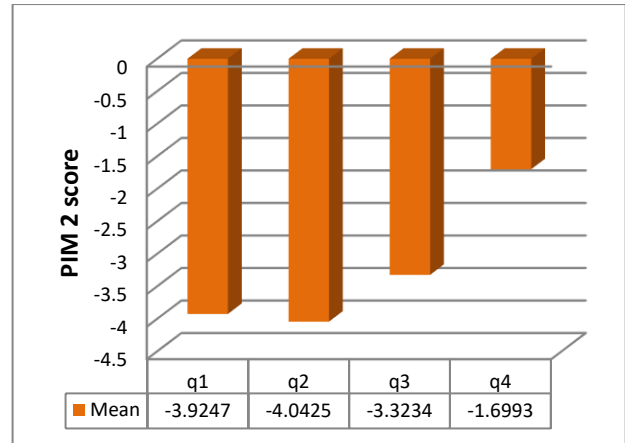

Figure 3: Distribution of the PIM 2 score in the first 24 hours of PICU admission among the subjects grouped into different quartiles based on admission RDW.
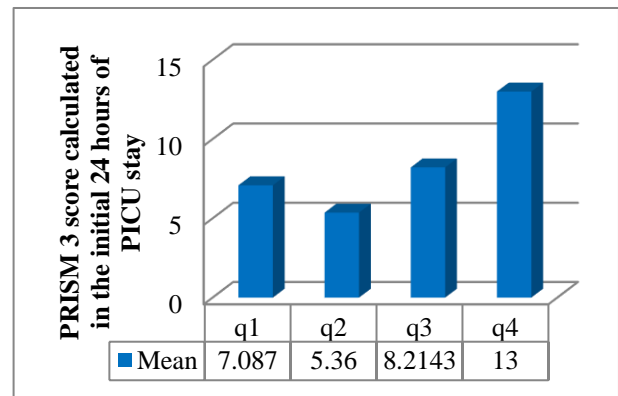

Figure 4: Distribution of the PRISM III score in the first 24 hours of PICU admission among the subjects grouped into different quartiles based on admission RDW.

The PRISM III score during the initial 24 hours of PICU admission, the PIM 2 score and the number of ICU free days varied significantly between the quartiles. The mean PRISM III score (mean±SD, 13.0±8.67) and also the mean PIM-2 score (mean±SD, -1.69±2.30) being the highest for subjects grouped under the fourth admission RDW quartile. The mean number of ICU free days being the highest (mean±SD, 18.86±9.49) for the subjects in the first quartile and the least (mean±SD, 8.28±11.43) for the subjects in the fourth quartile.

Figure 1 depicts the distribution of the number of deaths and the number of survivors during the course of PICU stay between the subjects grouped into different quartiles based on admission RDW. The mean number of deaths being the highest (71.4%) for the subjects in the fourth quartile and the least (17.4%) for the subjects in the first quartile, with a statistically significant (p=0.003) difference.
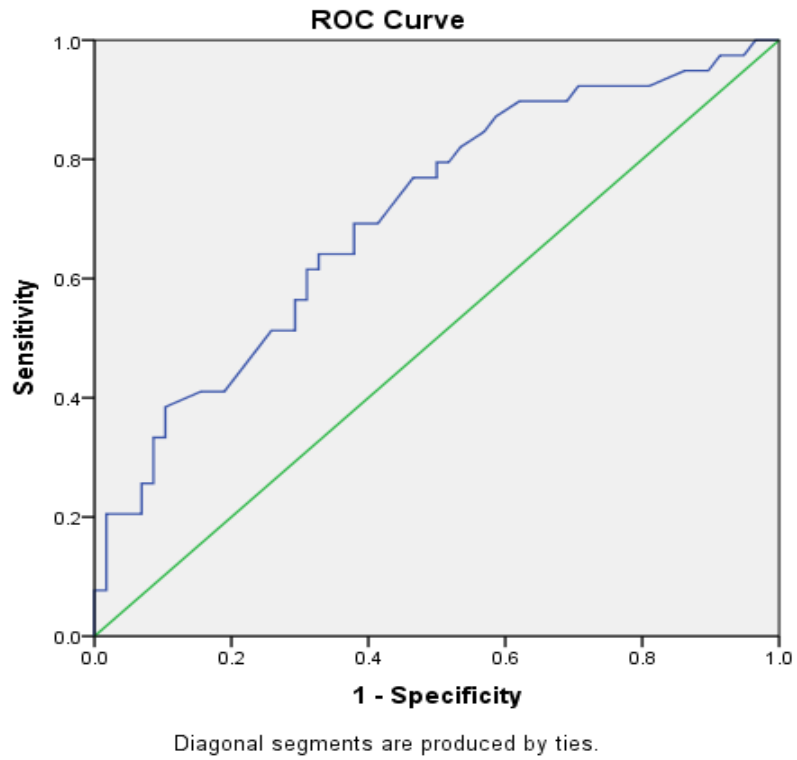
Figure 5: ROC curve for admission RDW and the outcome (incidence of death).
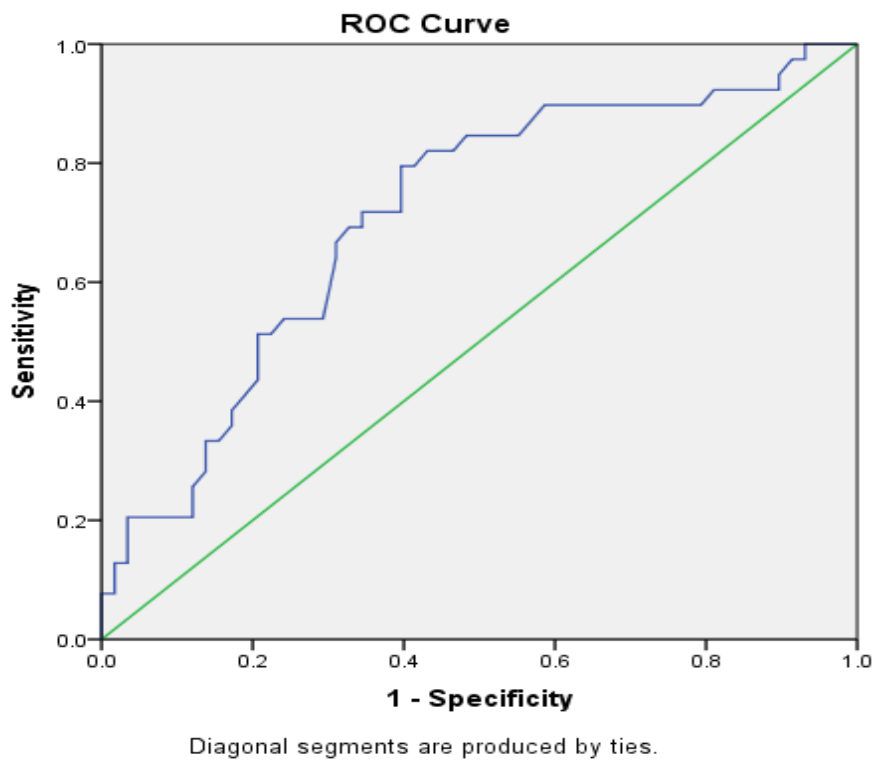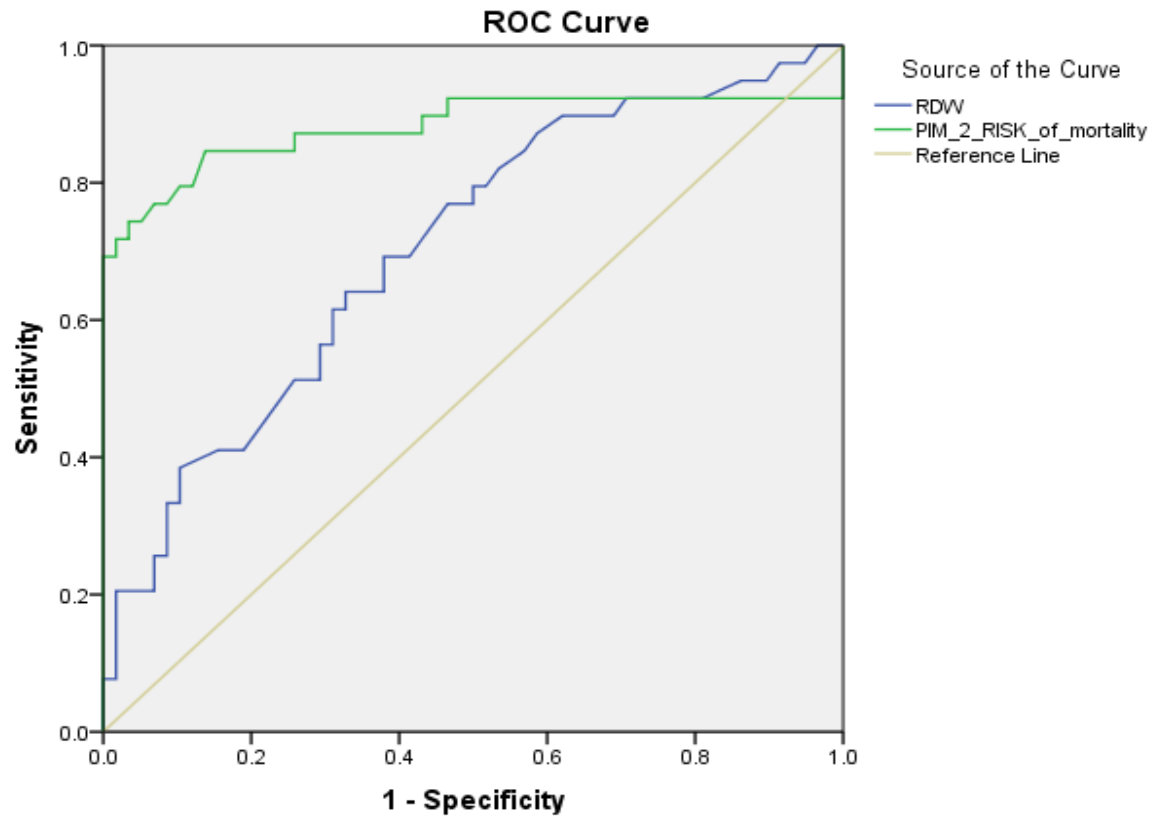

Figure 6: ROC curve for the Peak RDW during the first 7 days of PICU admission and the outcome (incidence of death).

Figure 7: Comparison of AUROC for PIM 2 risk of mortality and admission RDW.

Figure 2 depicts the distribution of the number of ICU free days between the subjects grouped into different quartiles based on admission RDW. The mean number of ICU free days being the highest (mean±SD, 18.86±9.49) for the subjects in the first quartile and the least (mean±SD, 8.28±11.43) for the subjects in the fourth quartile, with a statistically significant (p=0.012) difference.

Figure 3 depicts the distribution of the PIM 2 score in the first 24 hours of PICU admission among the subjects grouped into different quartiles based on admission RDW. The mean PIM 2 score being the highest (mean±SD, -1.69±2.30) for the subjects in the fourth quartile, with a statistically significant (p=0.001) difference.

Figure 4 depicts the distribution of the PRISM III score in the first 24 hours of PICU admission among the subjects grouped into different quartiles based on admission RDW. The mean PRISM III score being the highest (mean±SD, 13.0±8.67) for the subjects in the fourth quartile, with a statistically significant (p=0.007) difference.

On univariate analysis, using Pearsons product movement correlation, we found a statistically significant positive correlation between Relative change in RDW during the first 7 days after PICU admission (p<0.01) and the duration of PICU stay and a statistically significant negative correlation between Relative change in RDW during the first 7 days after PICU admission and the number of ICU free days (p<0.01).

A receiver operator characteristics (ROC) curve for the incidence of death was calculated for admission RDW. As depicted in Figure 5, Area under the ROC (AUROC) was 0.706 for admission RDW.

AUROC for the incidence of death was calculated for Peak RDW during the first 7 days of PICU admission. As depicted in Figure 6, Area under the curve (AUC) was 0.71.

Similarly, the AUROC for the incidence of death was calculated for PIM 2 risk of mortality and admission RDW. AUC was 0.882 (95%CI, 0.793-0.970) for PIM 2 risk of mortality and 0.706 (95% CI, 0.6-0.811) for admission RDW, as depicted in Figure 7.

Table 1: Patient characteristics.

Group characteristics	Death	Mean	Standard deviation	P value
Age (months)	Yes [a]	47.1795	53.62731	0.402
	No [b]	57.2069	59.92005	
PIM 2 score [c]	Yes	-1.4782	2.16532	0.001
	No	-4.5245	1.03602	
PRISM III score [d]	Yes	15.1538	7.8188	0.001
	No	3.6034	2.67503	
Hemoglobin (g/dL)	Yes	9.9	2.49758	0.071
	No	10.7448	2.04237	
WBC count (10^3/mL)[e]	Yes	18.4928	20.34742	0.163
	No	14.3826	7.46959	
Platelet (10^3/mL)	Yes	318.1795	188.77038	0.242
	No	362.5	177.14255	
RBC (10^6/ml)[f]	Yes	4.2056	1.11601	0.377
	No	4.3748	0.76153	
HCT (%)[g]	Yes	37.9462	40.94686	0.304
	No	32.3138	5.94175	
MCV (fl)[h]	Yes	301.6667	1318.6051	0.192
	No	74.6017	8.82736	
MCH (pg)[i]	Yes	24.1692	4.02572	0.296
	No	27.8828	21.78148	
MCHC (g/dl)[j]	Yes	31.5103	2.81311	0.002
	No	33.2902	2.62021	
Admission RDW (%)	Yes	18.5872	4.3016	0.001
	No	15.8741	2.92134	
Peak RDW (%)	Yes	18.9231	4.10644	0.001
	No	16.3138	3.20802	
Relative change in RDW (%)	Yes	3.3367	6.75274	0.825
	No	3.061	5.47732	
PIM 2 risk of mortality	Yes	24.6638	29.34807	0.000
	No	1.7017	1.57541	
Duration of PICU stay (days)	Yes	4.4359	4.7395	0.869
	No	4.569	3.19601	
Number of ICU free days (days)	Yes	16.4	9.01665	0.001
	No	23.431	3.19601	

[a]subjects who died during the course of PICU stay, [b]subjects who survived, [c]Pediatric index of mortality 2 score, [d]Pediatric risk of mortality score during first 24 hours of PICU admission, [e]white blood cell count, [f]Red blood cell count, [g]Hematocrit, [h]Mean corpuscular volume, [i]Mean corpuscular hemoglobin, [j]Mean Corpuscular Hemoglobin Concentration,[k]

DISCUSSION

RDW has shown its predictive ability as a biomarker associated with mortality in adult patients with both chronic illness (congestive heart failure, cancer, pulmonary hypertension, arteriosclerosis) as well as in acute illness (pneumonia, sepsis, blood stream infections, stroke).[14-20] But, we have very limited data regarding the utility of RDW in critically ill children. Our study shows that RDW measured within 24 hours of PICU admission and peak RDW during the first 7 days of PICU stay is independently associated with mortality among critically ill children, and, relative change in RDW correlated significantly with the number of ICU free days. In ROC analysis of relationship between admission RDW and mortality, AUC for admission RDW was 0.706 (95%

CI,0.6-0.811), whereas the AUC for PIM 2 risk of mortality was 0.882 (95% CI,0.793-0.970).

Our findings are consistent with other similar studies which evaluated the relationship between RDW and the outcome in critically ill pediatric subjects. Sachdev et al, reported that high RDW at admission correlated significantly with mortality (p=0.007).[21] The odds of death increased by 15-23 times with rise in RDW from 18% to more than 21%. In ROC analysis of admission RDW the area under ROC curve was 0.83 (95% CI, 0.737-0.925). Other studies with a much larger sample size also had findings similar to our study. Said et al, reported that both admission RBC distribution width and relative change in RBC distribution width correlated with mortality, fewer ICU-free days and ventilator-free days.[22] In ROC analyses

of the relationship between RDW and mortality, the AUC for Admission RDW was 0.611 (95% CI, 0.076–0.218), whereas the AUC for PIM-2 score was 0.901 (95% CI, 0.908–1.166). Rambly et al, which did not exclude subjects who had received prior transfusions, reported that in all critically ill pediatric patients, RDW was independently associated with PICU mortality.[23] AUC for RDW achieved similar discriminative power for mortality (AUROC 0.64, 95% CI, 0.50-0.77)

Other studies have demonstrated that RDW remains an independent predictor of mortality even in the presence of recent blood transfusions.[5,10,18,20] Although some prior studies of RDW have excluded patients who received recent (between one week to three months) transfusions.[11,18,24] Purtle et al determined that a RBC transfusion given even 48 hours before RDW measurement did not confound the association of RDW with mortality.[25] In our study, we chose not to exclude subjects who had received blood or blood product transfusions prior to sample collection for measuring RDW, as our objective was to determine if RDW, regardless of underlying cause for its elevation, was predictive of outcome. Furthermore, the inclusion of patients regardless of recent transfusion improves the generalizability of our findings.

RDW is elevated in states of ineffective red cell production and increased red cell destruction, which is a common feature of many infectious and inflammatory conditions.[2,3,4] An association between increasing RDW and elevated levels of acute phase reactants including erythrocyte sedimentation rate, high sensitivity C-reactive protein, and interleukin-6 has been demonstrated in adults, suggesting that RDW may be elevated in the setting of acute inflammatory states secondary to rapid red blood cell destruction or blunted erythropoiesis.[8] Pro-inflammatory cytokines suppress red blood cell maturation, decrease half-life and deformability of RBC membrane allowing larger reticulocytes to enter the peripheral circulation and increase RDW.[2]

Although this implies a causative role for inflammation to increase RDW, we lacked specific measures to determine the extent to which inflammation modified the association of RDW with the number of ICU free days or mortality. However, prior studies have shown that increased RDW remains predictive of outcomes independently, indicating that inflammation alone cannot entirely explain the pathophysiologic processes leading to RDW elevation in critical illness.[2,3,4] Release of immature cells with poor oxygen-binding capacity, is a 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.[2,4]

An important note, however, is that RDW is most likely to be a marker of an underlying pathophysiological process (i.e., inflammation, impaired erythropoiesis, or bone marrow dysfunction) rather than itself being a cause of adverse clinical outcomes.

CONCLUSION

In conclusion, objective prognostic scores that are based on routine clinical and laboratory data, such as PIM-2 or PRISM III scores, may be useful to guide communication, triage, and management decisions for critically ill patients but these scores are complex to calculate and experts have cautioned against using these, to predict outcomes for individual patients. Our data demonstrate that RDW at the time of PICU admission is independently associated with PICU mortality and morbidity and may help to alert PICU clinicians to a subgroup of patients within the general, critically ill paediatric population who are at risk for adverse outcomes. It's low cost and near universal availability may help in early identification of these at-risk patients, providing an opportunity to intervene early and thereby improve outcomes and optimize resource utilization.

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