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Correlation of Some RBCs and Platelets Indices with Outcome of Critically Ill Children Admitted to Pediatric Intensive Care Units

Aliaa Mohammed Diab*[1], Reda Sanad Arafa[1], Yasser Mahmoud Ismael[2], Rana Ashraf Elnoury[1], Effat Hussein Assar[1]

Departments of [1]Pediatric and [2]Clinical and Chemical Pathology, Faculty of Medicine, Benha University, Egypt

***Corresponding author:** Aliaa Mohammed Elhady Diab, **Mobile:** (+20) 01008391980, **E-Mail:** aliaadiab@yahoo.com

ABSTRACT

Background: Platelet and Red blood cell indices ratios serve as a simple and convenient stratification tool for illness severity predictors in pediatric intensive care unit (PICU) mortality. The aim of the current study was toevaluate the ability of red cell distribution width (RDW) and platelet indices and ratios to predict mortality.

Patients and methods: A prospective, observational study was conducted on 99 critically ill children of both sexes admitted to PICU of Benha University Hospitals and Benha Children Hospital (BENCH). All children incorporated in this study were subjected to careful history taking, clinical examination, complete blood count (CBC) and scoring by the third-generation pediatric index of mortality (PIM-3).

Results: Our results showed that RDW, platelet counts and platelet indices ratios independently predicted PICU mortality. RDW measured within 24 hours of PICU admission was independently associated with mortality (p=0.001). Although RDW demonstrated high sensitivity (94.8 %) but low specificity (37.1%) as an independent predictor of mortality, it corresponded fairly to sensitivity and specificity of PIM-3 score in the present study. This is an important observation as a low-cost test of RDW performed nearly at par with more complex index of mortality. Regarding platelet indices, our study found that the platelet ratios [Mean platelet volume (MPV)/ plateletcrit (PCT), MPV/ platelet count, platelet differential width (PDW)/PCT, PDW/Platelet count] were better predictors of mortality than platelet indices by themselves. All the ratios of platelet indices were statistically significant (p-value <0.05).

Conclusion: RDW, platelet count, and platelet indices ratios were independent predictors of PICU mortality. The predictive power of these indices was comparable to the PIM-3 score.

Keywords: Red cell distribution width, Platelet indices, Pediatric index of mortality, Critical illness, Mortality, Pediatric intensive care unit.

INTRODUCTION

The total care provided to children has improved as a result of technological improvements. Despite these advancements, many sick children pass away in PICU each year. Predicting the death of kids admitted to PICUs could lead to better future results [(1)]. The pediatric risk of mortality (PRISM) and pediatric index of mortality (PIM) are the primary ratings designed for the pediatric population; the most recent iterations of these scores are PRISM III and PIM-3. Following a multivariate statistical study, these scores were created by identifying variables related to mortality risk and ranking them [(2)]. It is crucial to remember that PIM employs 10 variables recorded at the time of ICU admission, whereas PRISM takes the worst value of physiological variables gathered over the first 12 or 24 hours for deciding whether to adopt PIM or PRISM [(3)].

Elevated RDW has reportedly been a reliable indicator of death in persons with critical illnesses, cardiovascular conditions, pneumonia, and sepsis [(4)]. Similarly, recent restricted investigations discovered that in pediatric critical patients who weren't chosen, a high RDW number was linked to worse outcomes [(5)]. However, the reporters in non-cardiovascular critical disease have ignored the significant relevance of prognosis. There aren't many researches looking at RDW as a crucial marker in the pre- and postoperative period of pediatric congenital heart surgery to predict mortality [(6)]. Studies have shown that RDW and C reactive protein (CRP) levels are closely connected, suggesting that RDW may reflect the degree of inflammation [(7)].

The most significant and vital component of blood are the platelets. The severity of the sickness is thought to be predicted by thrombocytopenia. Both the platelet count and morphology are altered in critically ill patients, and this is reflected in alterations in the platelet indices. Automated blood analyzers frequently measure platelet indices. As they age, platelets get smaller, and a greater mean platelet volume (MPV) suggests that there are more young platelets in circulation. Increased MPV indicates that either platelet production or platelet breakdown is increasing [(8)].

Platelet count (PC) and platelet volume are added together to form plateletocrit (PCT). When there is a difference in the size of the cells in circulation, the platelet distribution width (PDW) increases, indicating that mature and immature cells are present in circulation at the same time. Studies have shown that MPV and PDW rise in the early stages of sepsis whereas PC and PCT fall [(9)].

We propose that, intuitively, as MPV and PDW increase and platelet count and PCT decrease, the ratio of MPV to PCT, MPV to platelet count, PDW to PCT, PDW to platelet count, and the ratio of the product of MPV and PDW to the product of PCT and platelet count may be useful in predicting mortality in sick children. Two recent researches looked into these ratios in children[(1, 9)].

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The aim of the current study is to evaluate the ability of red cell distribution width (RDW) and platelet indices and ratios to predict mortality.

PATIENTS AND METHODS

Study population:

A prospective, observational study was conducted on critically ill children admitted between April 1, 2018, and September 30, 2018 to the pediatric intensive care units (PICUs) at Benha University Hospital and Benha Children Hospital.

If a patient required transferring from the emergency room or the pediatrics department to the PICU, they were all eligible for enrollment.

Exclusion criteria were as follows: 1) Children ages were less than 1 month or more than 216 months; 2) Patients with a primary hematological disorder (congenital or acquired) affecting the RBCs or platelets; 3) Packed RBC transfusion history within 48 hours of PICU admission; 4) Patients who passed away within 48 hours of admission or were transferred to another PICU since data collection on those patients was challenging; 5) Patients discharged within the first 24 hours; and 6) Patients having missing data for the PIM 3 score estimation.

Study Procedures:

Blood samples were collected from the children in the first 24 hours of PICU admission. Capillary or arterial blood was taken for ABG (arterial blood gas) and was done using 9180 Electrolyte Analyzer. The RBCs indices including RDW, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) and platelet indices including platelet count, platletcrit, mean platelet volume (MPV), platelet differential width (PDW) and large platelet cell ratio (L-PCR) were measured by automated hematology analyzer "Sysmex XS-800i (SN: 63387)" as one part of a complete blood cell count. Normal red cell distribution width coefficient variant (RDW_{CV}) was defined as 11.5%-14.5% in the laboratory of our hospital while the normal range of PLT, MPV, PDW, PLCR, and PCT were 140 – 440 x 10^9/L, 8–15 fl, 10–17%, 13–43%, and 0.11–0.28% respectively. Serum CRP levels were examined with Quick Read CRP test kit (Orion Corporation, Orion Diagnostica, Espoo, Finland).

Ethical approval:

The Benha University Faculty of Medicine's Research Ethics Committee approved this study. Guardians of each patient were given written consent after being informed about every aspect of the investigation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, New York, United States). Means, standard deviations, or median and ranges were used to summarize quantitative data that had been gathered. Numbers and percentages served as a summary of categorical data. Prior to comparing survivors to non-survivors, the normality of the numerical data was evaluated using the normality test and direct visualization techniques. For parametric and non-parametric variables, respectively, the Independent student's t-test or Mann Whitney U test was used to compare numerical variables. Chi-square test was used to compare categorical data. Spearman's correlation was used to conduct correlation analysis. It has a range of -1 to +1. Strong negative correlation is indicated by a -1. While 0 implies no association, +1 indicates a high positive correlation. For the purpose of predicting mortality, multivariate logistic regression analysis was performed. Calculated odds ratios included a 95% confidence interval. RBCs indices and PIM III score underwent ROC analysis. Each variable's area under the curve (AUC) and 95% confidence range were determined. Every P value had two sides. P values of 0.05 or less were regarded as significant.

RESULTS

Baseline characteristics of the patient population

Our prospective 6-month observational study was held in two tertiary PICUs in Benha (Benha Children and Benha University hospitals) where a total of 99 cases met the inclusion criteria. The median age of cases admitted were 1.5 years old with a range of 0.1 to 18 years old. About 49.5% of cases were males. Younger children were more susceptible to mortality. Mann Whitney test showed statistical significant difference between survivors and non survivors regarding their age (p-value 0.01), but there was no statistical significant difference regarding their sex (p-value 0.89). The commonest causes of admission in our PICUs during the study period (April 2018 - September 2018) were respiratory diseases (28.2%) followed by neurological insult (23.2%) and the least diagnosis were hepatic diseases and poisoning (2%).

The commonest diagnostic category associated with mortality in our study were cardiac cases 60% followed by hepatic cases 50%, poly-trauma 40%, neurological cases 39.1%, chest cases 35%, renal cases and Steven Johnson Syndrome 33% and gastroenterology cases with 11% mortality. No mortality was recorded in endocrinal and poisoning cases, illustrated in **Figure 1**.

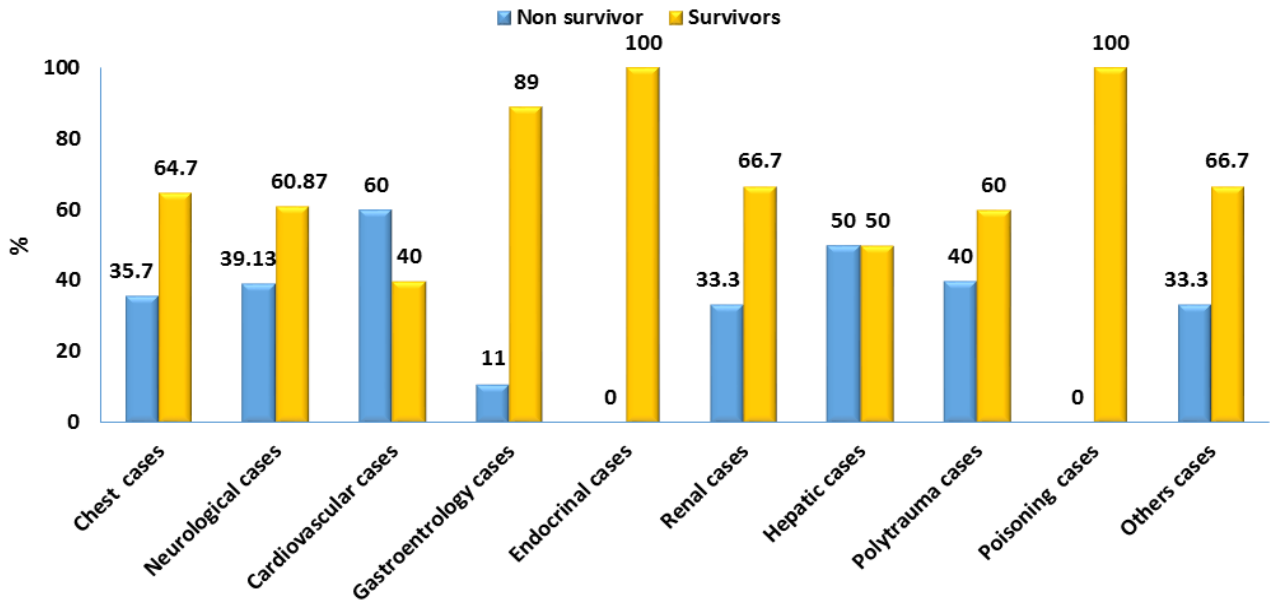


Figure (1): Diagnosis and causes of mortality among study groups.

Predicting PICU mortality:

There was a statistically significant difference between survivors and non survivors regarding mechanical ventilation, use of inotropes and length of stay with p-values <0.001. Non survivors showed longer median length of stay as shown in **table 1**.

Table (1): Mortality in mechanically ventilated cases, on inotropes and with prolonged length of stay.

Variable		Mortality		
		Yes (n = 37)	**No (n = 62)**	**P value**
Mechanical ventilator (MV)	Yes n (%)	35 (94.6)	8 (12.9)	<0.001
Inotropes	Yes n (%)	26 (70.3)	7 (11.3)	<0.001
Length of stay (days)	Median (range)	15 (2 - 82)	8 (2 - 90)	<0.001

There was a statistically significant difference between survivors and non survivors regarding RBCs and platelet indices. RDW (standard deviation/ coefficient variant) was the most significant of RBCs indices with higher values in the non survivors (55.5 ±15.9 fl / 17.9 ±3.7 %), respectively (**Table 2**).

Table (2): Comparison between survivors and non survivors regarding hematological variables.

Variable		Mortality		
		Yes (n = 37)	**No (n = 62)**	**P value**
TLC (*10 ^9/L)	Mean ± SD	11.4 ± 2.63	9.7± 2.1	0.247
RBC (*10^12/L)	Mean ± SD	3.72 ± 0.97	4.32 ± 0.82	0.002
HB (g/dl)	Mean ± SD	9.6 ± 2.6	10.6 ± 2.3	0.056
HCT (%)	Mean ± SD	28.91 ± 7.03	31.73 ± 6.03	0.044
MCV (fl)	Mean ± SD	77.7 ± 8.6	73.6 ± 9.1	0.029
MCH (pg)	Mean ± SD	26 ± 3.2	24.75 ± 4.04	0.112
MCHC (gm/dl)	Mean ± SD	33.67 ± 2.04	33.61 ± 2.56	0.9
RDWcv (%)	Mean ± SD	17.9 ± 3.7	15.6 ± 2.5	0.001
RDWsd (fl)	Mean ± SD	55.5 ± 5.9	44.5 ± 8.1	<0.001
PLT (*10^3 /ml)	Mean ± SD	175 ± 41.31	291 ± 7.82	0.002
PCT (%)	Mean ± SD	0.17 ± 0.031	0.245 ± 0.052	0.005
LPCR (%)	Mean ± SD	21.8 ± 5.11	17.7 ± 4.23	0.039
PDWsd (fl)	Mean ± SD	12.1 ± 2.84	12.7 ± 2.94	0.9
MPV (fl)	Mean ± SD	9.2 ± 1.6	8.8 ± 1.3	0.158

TLC = Total leukocyte count. RBC = Red blood cell count. HB (g/dl) = Hemoglobin (gram /deciliter). HCT = Hematocrit. MCV (fl) = Mean corpuscular volume (femtoliter). MCH (pg) = Mean corpuscular hemoglobin (pictogram). MCHC = Mean corpuscular hemoglobin concentration. RDW $_{CV}$ = Red cell distribution width (co efficient variant). RDW $_{SD}$ = Red cell distribution width (standard deviation). PLT=platelet. PCT = plateletcrit. LPCR = Large platelet cell ratio. PDW $_{SD}$ = Platelet distribution width (standard deviation). MPV = Mean platelet volume.

All ratios of platelet indices were statistically significant between survivors and non survivors (p-value <0.05). MPV/Platelet count ratio showed the highest significance (p-value =0.003) followed by MPV/PCT (p-value =0.006), PDW/Platelet count (p-value =0.006) and PDW/PCT (p-value =0.018).When estimating the ratios of (MPV/Platelet count) and (MPV/PCT), they showed higher values in non survivors. The (PDW/Platelet count) and (PDW/PCT) ratios were also higher in non survivors (**Table 3**).

Table (3): Ratios of platelet indices in survivors and non survivors.

Variable		Mortality		
		Yes (n = 37)	No (n = 62)	P value
MPV/Platelet count	Median (range)	0.06 (0.01 - 0.92)	0.03 (0.01 - 0.18)	0.003
MPV/PCT	Median (range)	50.84 (17.76 – 1500)	35.31 (13.75 – 290)	0.006
PDW/Platelet count	Median (range)	0.08 (0.02 - 2.83)	0.04 (0.01 - 0.23)	0.006
PDW/PCT	Median (range)	76.28 (23.88 - 1213.3)	51.02 (16.04 - 433.33)	0.018

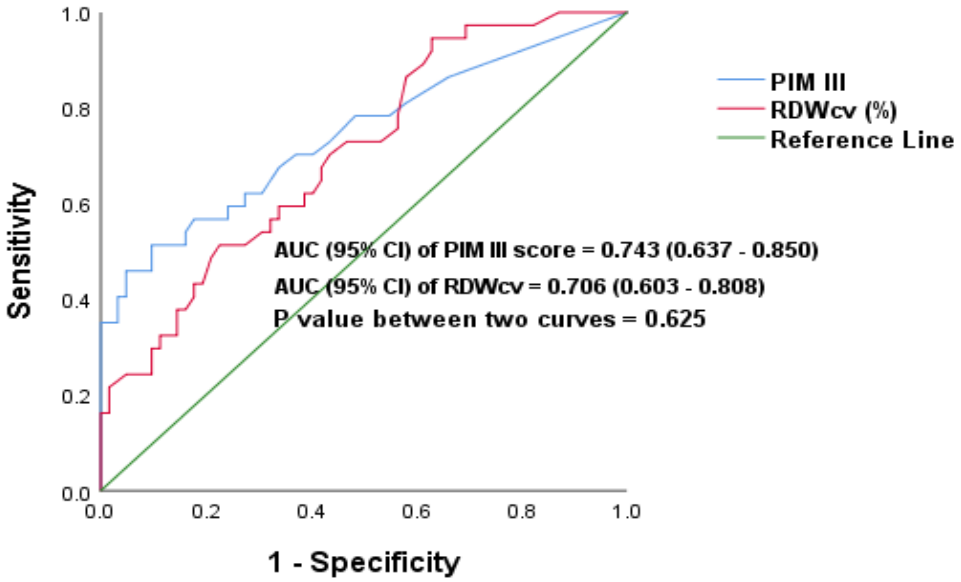
Median (range): for non-parametric data.

Multivariate logistic regression analysis was done. It revealed that predictors of mortality were as follow; decrease in RBC decrease in HCT, increase in RDW_{CV}, decrease in platelet count, increase in PIM 3 score values and finally decrease in systolic blood pressure (**Table 4**).

Table (4): Multivariate logistic regression analysis for prediction of mortality.

Variable	Wald	OR	95% confidence interval	P value
RBC (*10^12/L)	12.254	28.5	4.385 – 200	<0.001
HCT (%)	8.251	1.413	(1.116 - 1.788)	0.004
RDW_{CV} (%)	10.312	1.612	(1.204 - 2.157)	0.001
Platelets (*10^3 /ml)	11.012	1.009	1.004 – 1.014	0.001
PIM III score (%)	6.644	1.139	(1.032 - 1.258)	0.01
Systolic blood pressure	4.967	1.038	1.005 – 1.074	0.026

By spearman correlation, there was a significant negative correlation between PIM III score and age and positive correlations between PIM III score and RDW_{CV} / RDW_{SD}, RDW_{CV} showed area under curve (AUC) of 0.706 with 95% confidence interval ranging from 0.603 to 0.808. Best cut off point was 15% at which sensitivity and specificity were 94.6% and 37.1% respectively (**Figure 2**). C-reactive protein (CRP) showed a significant positive correlation with RDW_{CV} (r = 0.260, p-value = 0.009) (**Figure 3**).



OR = Odds ratio 95% CI = 95% Confidence Interval

Figure (2): ROC analysis of RDW and PIM 3 score for prediction of mortality.

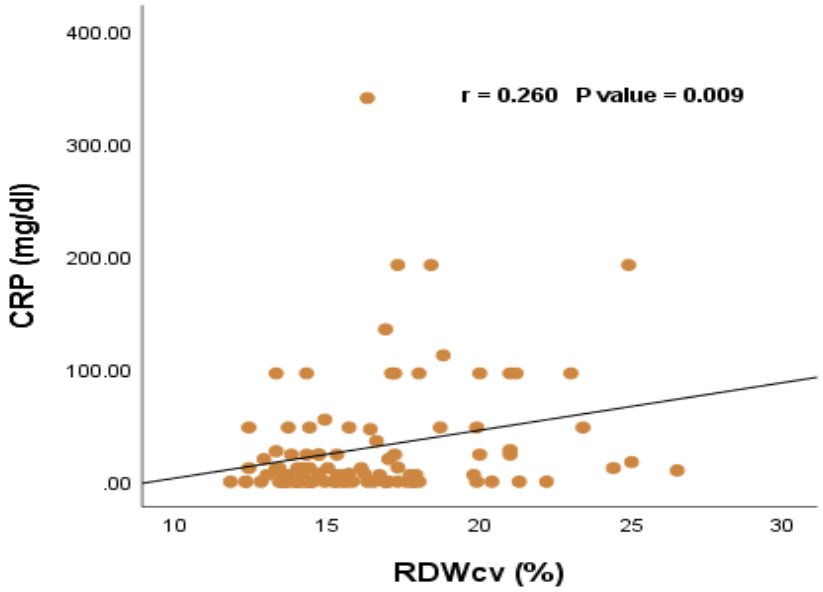


Figure (3): Correlation between RDW_{CV} and CRP

DISCUSSION

This study showed that, the overall mortality rate for children was 37.7%. Regarding study by **Saleem *et al.*** [10] who enrolled 150 children admitted in PICU at Pakistan, they recorded 18% as a mortality rate. **Alsuheel *et al.*** [11] also conducted a study in Saudi Arabia with mortaliy rate was(37.4%) .

Our mortality rates were less than the Indonesian study performed by **Sari *et al.*** [2] where the mortality was (40.58%).

When populations have distinct features in terms of admission pathologies in PICUs, co morbidities, and healthcare systems, death rates in different PICUs around the world can vary widely, sometimes even within the same nation.

In the present study non survivors showed longer median length of stay. Similarly, **Mısırlıoğlu *et al.*** [12] showed long PICU stay among mortality group.

All ratios of platelet indices were statistically significant between survivors and non survivors (p-value <0.05). MPV/Platelet count ratio showed the highest significance (p-value=0.003) followed by MPV/PCT (p-value=0.006), PDW/Platelet count (p-value=0.006) and PDW/PCT (p-value=0.018).When estimating the ratios of (MPV/Platelet count) and (MPV/PCT), they showed higher values in non survivors. The (PDW/Platelet count) and (PDW/PCT) ratios were also higher in non survivors. Multivariate logistic regression analysis was done. It revealed that predictors of mortality were as follow; decrease in RBC, decrease in HCT, increase in RDW_{CV}, decrease in platelet count, increase in PIM 3 score values and finally decrease in systolic blood pressure.

By spearman correlation, there was a significant negative correlation between PIM III score and age and positive correlations between PIM III score and RDW_{CV} / RDW_{SD}

Our research was in line with that of **Purbiya *et al.*** [1], who found that thrombocytopenia affected 9.8% of survivors and 54% of non-survivors. About 5.7% of non-survivors and 23% of survivors both had thrombocytosis. The mean plateletcrit for those who survived was 0.29 (0.13%), while it was 0.16 (0.12%) for those who passed away (p-value 0.0001).

Similar to our study, **Msrlolu *et al.*** [12] research found that there were significant differences between survivors and non-survivors in terms of RDW (p=0.023), platelet count (p=0.037), and haemoglobin (p=0.05), but not in terms of MPV (p=0.66).

According to **Işgüder *et al.*** [13] non survivors showed a considerably lower platelet count than survivors (p-value 0.002). At logistic regression analysis, platelet count (OR 7.3) demonstrated a significant impact on the probability of 28-day mortality risk.

According to all of these investigations, thrombocytopenia is a frequent observation in PICUs. Because any decrease in platelet counts, even without thrombocytopenia, requires an urgent and thorough investigation, serial measures of platelet counts are better predictors of pediatric critical care outcomes than one-time readings [12-14], and this was one of the study's weaknesses in that we didn't track platelet indices over the course of the patient's stay in the PICU.

Platelet count, PCT, and all previously mentioned platelet ratios were substantially different among children who survived compared to those who did not survive in the comparable study conducted by **Golwala *et al.*** [15]. For all of the ratios indicated above, the AUC ROC curve was between 65% and 67%.

When the MPV/PCT was greater than 41.8 (p-value 0.01), the PDW/platelet count was greater than 3.86 (p-value 0.01), and the MPV/Platelet count was greater than 3.45 (p-value 0.01), 65% of the patients died.

In the present study, there was a statistically significant difference between survivors and non survivors regarding RBCs indices . RDW (standard deviation / coefficient variant) was the most significant of RBCs indices with higher values in the non survivors (55.5 ± 15.9 fl / 17.9 ± 3.7 %) respectively. RDW_{CV} showed area under curve (AUC) of 0.706 with 95% confidence interval ranging from 0.603 to 0.808. Best cut off point was 15% at which sensitivity and specificity were 94.6% and 37.1%, respectively.

The findings of our study were consistent with the literature, which indicates that critically sick pediatric patients with significant elevated RDW in the PICU are at an increased risk of dying [16,17].

In an Indian study, **Gadappa and Behera** [18] demonstrated a statistically significant association between mortality and RDW, showing that death was 44% in RDW 16.6 and 84.7% in RDW >22.7 (P = 0.002). 18.45 with Sensitivity 71.0% and Specificity 67.8% is the best RDW cut-off. The cut-off was 18.10 with sensitivity 72.7% and specificity 61.1% after accounting for anemia. Similar to RDW, the PIM-3 score exhibited a sensitivity of 72.7% and a specificity of 62%.

Another group of related studies conducted in critically ill children by **Said *et al.*** [19] and **Ramby *et al.*** [5] showed that admission RDW is related to pediatric ICU mortality and morbidity independent of illness severity and that each 1% increase in RDW was related to a 1.17 (95% CI 1.06, 1.30) increased likelihood of length of stay (LOS) >48 hours. Area under the receiver operating characteristic curve for mortality (AUROC) was comparable to PIM-2 (0.75, 95%CI 0.66, 0.83; p=0.18). Nevertheless the addition of RDW did not significantly increase the PIM-2 score's ability to discriminate on its own,.

In this study CRP showed a significant positive correlation with RDW_{CV}. Non survivors had higher average values of total leucocytic count than in survivor but with no statistical significance.

In our study non survivors showed lower values of hemoglobin, hematocrit and RBCs count than that of survivors that was statistically significant.

Our study supported findings by **Gadappa and Behera** [18] were by which found anemia in 57% of patients. There was a statistically significant relationship between anemia and death (p = 0.009). Similar to this, **Hashemi *et al.*** [20] reported anemia in 52.7% of the patients, with individuals with greater RDW having a higher incidence of anemia (p = 0.048).

This was in contrast to **Sachdev *et al.*** [21] findings that found no discernible variation in the hemoglobin levels between survivors and fatalities.

In conclusion, RDW, platelet counts and platelet indices ratios were independent predictors of PICU mortality. The predictive power of these indices was comparable to the PIM-3 score.

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