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Original article

Prognostic Value of Red Blood Cells Distribution Width in Acute Kidney Injury in PICU

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Abstract:

Background: RDW predicts short-term outcome in critically ill AKI patients. RDW's long-term all-cause mortality prognostic value in children is unknown. **Methods**: one hundred PICU patients were studied. Clinical Pathology Department undertook laboratory tests. Scoring system used in this study are SOFA score which is a straightforward and objective measure to calculate organ dysfunction in six organ systems, APSIII score, RIFLE score and KDIGO classification. **Results:** RDW > 15.45 had 81.5% sensitivity and 60.3% specificity for predicting mortality. Statistically significant (p 0.001) Septic shock, high GCS, high SOFA score, high APS III, high initial blood creatinine, and high initial RDW are death risk factors. The higher initial serum creatinine wasn't an independent risk factor in multivariate regression analysis. RDW, KDIGO and RIFLE criteria had no correlation. **Conclusion:** Higher RDW was associated with increased mortality in critically ill AKI patients. Large prospective trials with longer follow-Up must corroborate our findings.

Keywords: PICU, Red Blood Cells Distribution Width, Acute Kidney Injury

Introduction:

Acute kidney Injury (AKI) refers to an abrupt decrease in kidney function and it is common, harmful and potentially treatable condition. Early detection and treatment of AKI may improve outcomes (1)

The definition of AKI is any of the following: An increase in serum creatinine by 0.3mg/dl or more within 48 hours or increase in serum creatinine to 1.5 times baseline or more within the last 7 days or urine output less than 0.5ml/kg/hr for 6 hours (1).

AKI is one of the most common complications in critically ill children which results in poor prognosis and high risk of mortality. Up to 50% of children admitted to PICU were complicated with AKI and up to 27%

died consequently during hospitalization. When AKI occurs concomitantly with other sever organ dysfunction like myocardial infarction or sepsis, the mortality rate increases up to 60%. (2).

Red blood cell distribution width (RDW) reflects the size variation of circulating red blood cells and is calculated in automated complete blood counts. Previously, the clinical use of RDW was limited to the differential diagnosis of anemia. An increased RDW was considered significantly associated with risk of adverse outcomes in critically ill children (3).

RDW has been proved useful as a predictor of short-term prognosis in critically ill patient with AKI. However, it remains unknown whether RDW has a prognostic value of long-term all-cause mortality in these children (4).

Evidence that RDW could be an additive predictor for mortality in AKI patients undergoing continuous renal replacement therapy (CRRT) (5).

Aim of the study:

The aim of this work was to evaluate the impact of Red Blood Cells Distribution Width (RDW) on prognosis of critically ill children with Acute Kidney Injury

Patients and methods:

The Study was prospective study and was conducted on 100 patients admitted to PICU Benha University from 1/8/2021 to 1/3/2022. The patient was divided to survivors group and non survivors group. Laboratory work was conducted in Clinical Pathology Department Benha University.

Informed written consent was taken from parents [ethical committee approval (MoHP No: 0018122017/certificate No: 1017)]. The database includes a Children with AKI who were hospitalized in PICU at first admission for more than two days (6).

Inclusion criteria:

All children that were diagnosed suffering from Acute kidney Injury less than 18 years, Children admitted to PICU due to critical illness as burn, trauma, sepsis, dehydration, circulatory shock, nephrotoxic drugs, poisoning, cardiac surgeries, anemia, chronic diseases (lung, heart, liver), Both sexes will be included, Age less than 18 years .

Exclusion criteria:

Leukemia, Children with no RDW measured during PICU stay, Missing > 5% of individual data.

Methods:

Children were subjected to history taking to fulfill the needed data: (1) History taking: Full history taking, the Drugs which were used and their doses, History suggestive of acute kidney injury as (oliguria , arrhythmia , hematuria , edema) **,** History suggestive of acute metabolic complications, as (sweating, headache, blurring of vision, tremors, convulsions, and coma). (2) Clinical examination with special emphasis on anthropometric measures as: Weight and its centile, Height and its centile, Body Mass Index (BMI), Vital signs SBP , DBP , Respiratory rate , Temperature , Local examination : heart and chest auscultation , abdominal palpation & neurological examination , Urine output. (3) Scoring

system: Sequential organ failure assessment (SOFA)**:** It is a simple and objective score that allows for calculation of both the number and severity of organ dysfunction in six organ system (respiratory, coagulation, liver , cardiovascular , renal , neurologic). Patients with a SOFA score of 2 or more had an overall mortality risk of approximately 10% in a general hospital population with presumed infection. Depending on a patient's baseline level of risk, a SOFA score of 2 or greater identified a 2 to 25-fold increased risk of dying compared with patients with a SOFA score less than 2 (7). Acute physiology scores III (APS III): It is a severity of disease classification system for predicting mortality in PICU. (8). Kidney disease improving global outcomes (KDIGO) criteria: It is criteria defines acute kidney injury in Pediatrics as "increased *creatinine level greater than or equal to 1.5 times the baseline (historical or measured), which is known or presumed to have occurred within the prior seven days."* Pediatric modified Risk Injury Failure Loss End-stage renal disease (pRIFLE) classification.: It is a doubling of serum creatinine or a reduction of urinary output below 0.5 ml/kg per hr. during at least 12 hrs**.** [4). Laboratory investigations: CBC (RDW, HCT, Hemoglobin), Blood Urea Nitrogen (BUN), Serum creatinine, Bilirubin , Random blood glucose , Serum electrolytes (sodium, potassium, calcium, chloride), Abdominal U/S .

Statistical Analysis:

Results were organized, tabulated and statistically analysed using statistical package for social sciences (SPSS 27.0, IBM/SPSS Inc., Chicago, IL) software statistically computer package version 11. Two types of statistical analysis were conducted: Descriptive statistics for quantitative data, the mean and standard deviation were calculated. Analytical statistics for the difference between two means were statistically analysed using the student (t) test, for qualitative data the number and percent distribution were calculated. Chi square was used as a test of significance and when found inappropriate fisher exact test was used significance was adapted to $P \leq 0.05$ for interpretation of results of tests significance. (9)

Results :

The study included 100 patients admitted to PICU for different causes such as (septic shock, chest infection, urinary tract infection, acute gastroenteritis, postoperative sepsis, drug induced nephrotoxicity). The median age of the non survivors cases was 17 months and the median age in the survivors group was 12 months with no statistically significant difference between the two groups (p=0.453).

There were 44.4% boys and 55.6% girls in the non survivors group as compared to 57.5% boys and 42.5% girls in the survivors group with no statistically significant difference between the two groups, with higher girls' prevalence in the survivors group.

There was no statistically significant difference between the two groups regarding the mean weight, height and BMI.

Table (1) shows that the mean Glasgow Coma Scale was statistically significantly lower in the non-survivors' group as compared to the survivors group (6.81 ± 0.88 and 11.33 ± 1.76 respectively) (p< 0.001). The mean SOFA score was statistically significantly higher in the non-survivors' group as compared to the survivors group (16.56 ± 1.45 and 9.25 ± 2.35 respectively) (p< 0.001). The mean APS III score was statistically significantly higher in the non-survivors' group as compared to the survivors group (16.56 ± 1.45 and 9.25 ± 2.35 respectively) (p< 0.001).

Table (2) shows that as regard RIFLE criteria, there were 7.4%, 70.4% and 22.2% of cases with risk, injury, and failure respectively in the non survivors group, while in the survivors group, there were 12.3%, 75.3% and 12.3% cases with risk, injury and failure respectively. There was insignificant difference between both groups as regard RIFLE criteria.

Table (3) shows that as regard KDIGO classification, there were 29.6%, 40.7% and 29.6% of cases with Stage 1, Stage 2 and Stage 3 respectively in the non-survivors' group, while in the survivors group, there were 63%, 23.3% and 13.7% of cases with Stage 1, Stage 2 and Stage 3 respectively. There was a statistically significant difference between both groups with high prevalence of stage 3 in the non survivors group (p=0.011).

Table (1): Analysis of the neurological scores in the two study groups.

	Groups		Test of significance	P value
	Non survivors (N=27)	**Survivors (N=73)**		
Glasgow Coma Scale score	6.81 ± 0.88	11.33 ± 1.76	t = - 12.696	< 0.001*
SOFA score	16.56 ± 1.45	9.25 ± 2.35	t = 15.105	< 0.001*
APS III	16.56 ± 1.45	9.25 ± 2.35	t = 13.741	< 0.001*

Table (2): Analysis of the RIFLE criteria in the two study groups.

	Groups		**Test of significance**	**P value**
	Non survivors (N=27)	**Survivors (N=73)**		
R	2 (7.4%)	9 (12.3%)		
I	19 (70.4%)	55 (75.3%)	MC = 1.786	0.409
F	6 (22.2%)	9 (12.3%)		

Table (3): Analysis of the KDIGO classification in the two study groups.

	Groups		Test of significance	P value
	Non survivors (N=27)	**Survivors (N=73)**		
Stage 1	8 (29.6%)	46 (63%)		
Stage 2	11 (40.7%)	17 (23.3%)	$\chi 2$= 8.991	0.011*
Stage 3	8 (29.6%)	10 (13.7%)		

Table (4) shows that the initial serum creatinine was statistically significantly higher in the non survivors group as compared to the survivors group (1.4 and 1.1 mg/dl respectively) (p= 0.020). The final serum creatinine was statistically significantly higher in the survivors group as compared to the survivors group (2.3 and 1.3 mg/dl respectively) (p< 0.001). The mean percent of change in the serum creatinine was statistically significantly higher in the non survivors group as compared to the survivors group (95.61 ± 143.65 and 63.11 ± 149.99 respectively) (p= 0.001).

Table (5) shows that there was a statistically significant difference regarding the duration of hospital stay between the cases in the two study groups (p=0.001). The duration of hospital stay was longer in the non survivors group.

Table (6**)** shows the mean initial RDW was statistically significantly higher in the survivors group as compared to the Survivors group (17.46 ± 2.09 and 15.17 ± 2.29 respectively) (p< 0.001). The mean highest RDW was statistically significantly higher in the non survivors group as compared to the survivors group (19.04 ± 1.40 and 15.60 ± 2.55 respectively) (p< 0.001). The mean percent of change in the RDW was statistically significantly higher in the non survivors group as compared to the survivors group (10.14 ± 12.22 and 2.95 ± 8.22 respectively) (p= 0.001).

Table (7) shows that the best cutoff point of RDW to identify mortality was > 15.45 with 81.5% sensitivity and 60.3% specificity. This value showed a statistically significant value (p < 0.001).

Table (8) shows that with univariate regression analysis, septic shock, increased GCS, increased SOFA score, increased APS III, elevated initial serum creatinine and elevated initial RDW were shown as risk predictors for mortality. However, with multivariate regression analysis, the elevated initial serum creatinine wasn't shown as independent risk factor.

Table (9) shows that there was insignificant Correlation between RDW and KDIGO classification and RIFLE criteria.

Table (4): Analysis of the initial and final serum creatinine level in the two study groups.

	Groups		Test of significance	P value
	Non survivors (N=27)	**Survivors (N=73)**		
Initial serum creatinine (mg/dl)	1.4 (0.4-4.1)	1.1 (0.3-6.8)	z = -2.331	0.020*
Final serum creatinine (mg/dl)	2.3 (1.3-7)	1.3 (0.9-13)	z = -4.475	< 0.001*
Percent of change	95.61 ± 143.65	63.11 ± 149.99	z = -3.018	0.001*

Table (5): Analysis of the length of hospital stay in the two study groups.

	Groups		Test of significance	P value
	Non survivors (N=27)	Survivors (N=73)		
Length of hospital stay (Days)	3 (2-147)	7 (2-30)	z= - 3.250	0.001*

Table (6): Analysis of the initial and highest RDW in the two study groups.

	Groups		Test of significance	P value
	Non survivors (N=27)	Survivors (N=73)		
Initial RDW	17.46 ± 2.09	15.17 ± 2.29	t = 4.552	< 0.001*
Highest RDW	19.04 ± 1.40	15.60 ± 2.55	t = 6.647	< 0.001*
Percent of change	10.14 ± 12.22	2.95 ± 8.22	Z= -3.486	0.001*

Table (7): Predictive value of initial RDW in detection for the mortality.

Diagnostic criteria	Initial RDW
AUC	0.788
Cut off point	15.45
P	< 0.001*
Sensitivity	81.5 %
Specificity	60.3 %
PPV	72.7 %
NPV	78.1 %
Accuracy	76.9 %

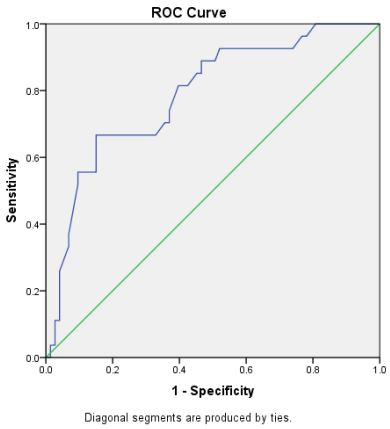

Fig (1): ROC Curve

Table (8): Univariate and multivariate regression analysis of mortality (n=27).

Variables	Univariate analysis	Multivariate analysis		
		OR	95% CI for OR	P value
Age	0.432			
Female gender	0.194			
BMI	0.306			
Septic shock	< 0.001*	3.422	1.940-3.869	< 0.001*
GCS	< 0.001*	2.162	1.457- 2.632	0.001*
SOFA	< 0.001*	2.801	1.970-3.008	< 0.001*
APS III	< 0.001*	3.523	2.546-4.198	< 0.001*
Initial serum creatinine	0.002*	1.648	0.825-1.810	0.136
Initial RDW	< 0.001*	2.416	1.639- 2.874	0.001*

Table (9): Correlation between RDW and KDIGO classification and RIFLE criteria.

Pearson Correlation	RDW	
	R	**P**
KDIGO classification	0.077	0.57
RIFLE criteria	0.095	0.489

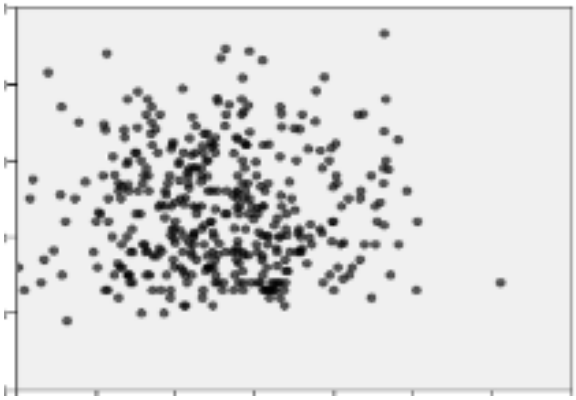

Fig (2): Correlation between RDW and KDIGO classification and RIFLE criteria.

Abbreviations:
P: probability.
Continuous data are expressed as median (range)
Continuous data are expressed as mean ± SD.
t: Independent samples t-test
z: Mann-Whitney U-test
*: Statistically significant (p< 0.05)
OR: Odd's ratio
CI: confidence interval
P1: Comparison between Initial levels and at the end of the study
RDW: Red cell distribution width
SOFA: Sequential organ failure assessment
APSIII: Acute Physiology Score

Discussion

Acute kidney injury (AKI) is a severe decrease in glomerular filtration rate with an increase in serum creatinine (SCr) or a decrease in urine output. AKI is an independent risk factor for 36.4% to 50% mortality, especially in critically ill patients (10). AKI was only tracked by SCr, which rises hours to days after 50% renal functions loss. RDW measures the size variability of circulating erythrocytes, with higher values indicating more heterogeneity. RDW is part of a hospitalized patient's total blood cell count because it is simple and available (11). RDW is primarily used to separate anemia sources, but studies have shown it can also be used to predict cardiovascular illness, malignant tumors, and severe pancreatitis (10). This study evaluates the impact of RDW on the prognosis of critically unwell children with AKI (Table 7). This study found no statistically significant difference between the median ages of the non survivors and the survivors. 44.4% boys and 55.6% girls were in the non survivors' group, compared to 57.5% boys and 42.5% girls in the survivors group, with more girls in the dead group. The two groups had similar average weight, height, and BMI. In agreement with our study, another study (12), proved no significant differences between the two groups in age, sex, MAP, SOFA score, creatinine and eGFR (Table 6). Some researchers in 2020 (12), found that 495 boys and 465 girls with median ages of 15.5 (IQR, 4.8–54.5) months and 8.5 (IQR, 5.0–16.0) kg., mean initial RDW was higher in the non survivors group than in the survivors group (17.46 ± 2.09 vs. 15.17± 2.29). The non survivors group had a much greater mean RDW than the survivors (19.04 ±1.40 vs. 15.60 ±2.55). The RDW changed much more in the non survivors group than in the survivors group (10.14±12.22 vs. 2.95 ±8.22) respectively and this is

matching with our study. In another study done also in 2020 (13), similar disparities between survivors and non-survivors, were found. Non-survivors needed additional inotropic medications and MV. RDW in non-survivors outnumbered survivors and this agrees with our study. Patients were categorized based on fatalities within 28 days and in the study done in 2011, it was proved that that 62.8% of patients died by Day 28 (12). In the survivors' group, RDW was substantially higher, the same as our study (16.02, 5% vs. 15.31%, P 0.01). AKI patients have significantly higher RDW values than non-AKI patients (WMD=1.127, 95% CI=0.426-1.827; P= 0.002) (15). In subgroup analysis, CI-AKI (WMD=0.582, 95% CI=0.314-0.849; P=0.000) and CSA-AKI (WMD=1.297, 95% CI=1.174-1.420; P=0.000) showed a significant correlation, with no heterogeneity. Ethnicity, mean age, and sample size in AKI cases were also significant and this is matching with our study. Although the mechanism of RDW values in AKI patients is unclear, various possible explanations exist. Anemia is an independent risk factor for AKI. It was discovered that the high RDW group in AKI had reduced red blood cells (RBC), which may aggravate AKI (15). RDW levels are connected with inflammation and serum antioxidants, which mediate effects on RDW through IL-6 (16), and serum IL-6 levels may predict AKI patient death (17). RDW levels also affected remaining renal function (18). This study found a statistically significant difference between the two groups' hospital stays (p=0.001). The non survivors had longer hospital stays. While in a very recent study done in 2022 (19), it was found that sepsis patients' (n=849) ICU outcomes were: 165 patients (19.4%) required mechanical breathing in 3.9±2.4 days; 151 (17.8%) required red cell transfusion in 8.1±6.4 days; 148 (17.4%) required vasopressor medication in 5.1±2.9 days; 73 (8.6%) died in 14.2±5.4 days; and 34 (4%) required RRT in 9.6±6.9 days after ICU admission. RRT [OR 1.023, 95%CI: 1.016-1.030; p0.001] and RDW [OR 1.180, 95%CI: 1.018-1.368; p=0.03] requirements were also associated with ICU admission. 18 RRT patients required continuous venovenous hemodiafiltration. The study also showed that death within 28 days of ICU admission was associated with high RDW [OR 1.368, 95%CI: 1.221-1.533; p0.001] and urea levels. In contrary to our study, no statistical difference between the two study groups' hospital stays was found (13), and this disagrees with our study (Table 5). Two study groups had statistically different PICU stays. This study found that RDW > 15.45 best predicts death with 81.5% sensitivity and 60.3% specificity (Table 7), was statistically significant (p 0.001). In a study done in 2019, it was found that RDW is a predictive for AKI, specifically, contrast induced AKI and cardiac surgery associated AKI (14). In our study RDW produced ROC curves, RDW's AUC was 0.788 (P 0.001) (Fig 1). In another study it was found that (20), the stated factors produce ROC curves (SOFA scores, RDW plus SOFA scores and APS III scores, and RDW plus APS III scores). SOFA's AUC was 0.648, while RDW+SOFAs were 0.669 (P 0.0001). APS III and RDW plus APS III AUCs were 0.702 and 0.708 (P = 0.0028). In the study done in 2011(12), changing ROC curves (RDW value, SOFA score and SOFA score plus graded RDW score), were found. The 28-day RDW and SOFA AUCs were 0.586 and 0.694 (P 0.01). AUC, SOFA, and graded RDW

totaled 0.746. The PELOD-2's AUROC was 0.803 (95% CI 0.751–0.855) for predicting PICU mortality (13). RDW enhanced performance (AUROC 0.821, 95% CI 0.773–0.868). RDW added model performed better (cNRI 0.357, 95% CI 0.153–0.562, P=.001). IDI failed to reduce discrimination. Septic shock, high GCS, high SOFA score, high APS III, high initial serum creatinine, and high initial RDW were risk indicators for mortality in this study (Table 1,4). The higher initial serum creatinine was not an independent risk factor in multivariate regression analysis (Table 8). Higher RDW was related with increased hospital mortality and 30-day all-cause mortality in critically ill AKI patients (Table 6). Adjusted for age and gender, the ORs (95% CIs) for RDW levels 13.5-14.3%, 14.4-15.6%, and 15.7-21.2% were 1.22 (1.05-1.43), 1.56 (1.35-1.81), and 2.66 (2.31-3.06), respectively. High RDW was linked with increased mortality after controlling for age, gender, albumin, hemoglobin, liver disease, renal disease, malignancy, bilirubin, WBC, BUN, APS III, SOFA, SIRS, RRT, and temperature. 30-day all-cause mortality also declined. The greater RDW, high CRP, high SOFA score and low MAP enhanced mortality risk (12). Even after adjusting for age, gender, CRP, Hb, MAP, and SOFA score, RDW remained a strong predictor of 28-day death. High RDW, SOFA and lowered MAP were independent risk factors for 28-day all-cause death in a multivariate Cox regression analysis utilizing RDW as a continuous variable. The same as our study, the study done in 2020 (13), found that MV support, vasoactive-inotropic medication use, Hg, white blood cell count, platelets count, RDW, and severity of illness and organ failure scores, including PRISM-III, SOFA, PELOD-2, pMODS scores, were linked with PICU mortality. PELOD-2 score, Hb, and increased RDW (>14.5%) were independent PICU mortality risk factors after adjusting for age, sex, and CRP. This study found no correlation between RDW, KDIGO, and RIFLE (Table 2,3,9) & (Fig 2). Favorable relationships between baseline RDW and SOFA score (r = 0.12, P 0.05) was found (12). Baseline RDW levels were adversely linked with Hb (r = 0.20, P 0.01). No relationships were found between RDW level and age, CRP or eGFR and this agrees with our study.

Limitations

This study contains flaws. The single-center retrospective design may have been biased. Insufficient disease information may skew multivariate analyses. We didn't know the patient's serum iron levels or if erythropoietin altered RDW results. Mortality follow-up varied. This may alter prognosis because we only utilize hospital and 30-day all-cause mortality.

Conclusions

Higher Red blood cell distribution width was associated with increased mortality in critically ill Acute Kidney Injury patients.

Conflict of interest

None of the contributors declared any conflict of interest.

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