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Utility of Red Blood Cell Distribution Width to Albumin Ratio and Hemoglobin to Red Blood Cell Distribution Width Ratio as Biomarkers in Pediatric Sepsis

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Abstract

Objectives – The objective was to compare these parameters in children with severe and non-severe sepsis and to evaluate their utility in predicting mortality. **Material and Methods** – A cross-sectional study conducted in the Pediatric Intensive Care of a district hospital in India. The hematological parameters of 54 children with severe sepsis and 55 with non-severe sepsis were analysed. **Results** – The children with severe sepsis had significantly lower HRR (Hemoglobin-RDW ratio) with higher RDW, plateletcrit and RAR as compared to those with non-severe sepsis. There were no significant differences between the groups with respect to the differential and total white blood cell counts or their ratios and other platelet indices. As compared to the survivors, non-survivors had significantly lower HRR with higher RDW and RAR. At a cut-off value of 3.845, RAR was 79.2% sensitive and 59% specific and at a cut-off value of 0.712 HRR was 77.8% sensitive and 60% specific in prediction of mortality. **Conclusions** – Children with severe sepsis had higher RAR and lower HRR when compared with children with non-severe sepsis. Significantly higher RAR and lower HRR were also noted among non-survivors as compared to survivors. The biomarkers RAR and HRR are readily available and useful in predicting mortality in children with sepsis.

Key Words: Sepsis ▪ Hemoglobin-RDW Ratio ▪ RDW-Albumin Ratio ▪ Biomarker ▪ Pediatric Intensive Care.

Introduction

Globally, 2.9 million deaths among children under 5 years and 0.45 million among those aged 5-19 years are related to sepsis (1). Several biomarkers have been found to be of diagnostic utility in sepsis. Many are readily available with the reports of blood counts or calculated easily without extra financial burden. Red cell distribution width (RDW), RDW-platelet ratio (RPR), RDW-Albumin ratio (RAR), Hemoglobin-RDW ratio (HRR), Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), platelet distribution width (PDW), plateletcrit (PCT) and mean platelet volume (MPV) are some such desirable biomarkers.

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A meta-analysis done in adult sepsis patients concluded that RDW is useful as a biomarker in predicting mortality (2). RPR on the first day of admission into the PICU was found to predict mortality of septic children (3). A study done in adult patients with sepsis concluded that RAR was significantly associated with poor clinical prognosis (4). Another study concluded that low HRR was linked with increased mortality in those affected with Sepsis associated Encephalopathy (5). A study that assessed the diagnostic utility of NLR and PLR found that both had a high predictive value in diagnosis of neonatal sepsis (6). A study done by Qi et al concluded that NLR, PLR, and RDW are useful in prediction of mortality in children with severe pneumonia (7). Platelet count, MPV, PDW, plateletcrit and their ratios at admission have been found to be useful in predicting mortality among critically ill children with severe sepsis (8).

There are no reports on the utility of RDW based indices RAR and HRR in prediction of outcome among critically ill children with sepsis. Besides, there is no study which has compared the utility of red blood cell indices (RDW, RAR, RPR, and HRR), platelet indices (MPV, PDW, plateletcrit) as well as ratios of white blood cell counts (NLR, PLR) in predicting the prognosis of critically ill children with sepsis.

Hence, we planned to compare the utility of all these haematological parameters in identifying children with severe sepsis and in predicting mortality among seriously ill children with sepsis.

Methods

This was a hospital based, cross-sectional study carried out in the Pediatric Intensive Care Unit (PICU) of Regional Advanced Pediatric Care Centre, of a district hospital during July 2021 to February 2022. All patients 1month to 18 years admitted in the PICU with features of sepsis or severe sepsis were involved in the study. Sepsis was defined by evidence or clinical suspicion of invasive infection and two or more systemic inflammatory response syndrome (SIRS) criteria. Severe sepsis was defined as confirmed or suspected invasive infection with two or more SIRS criteria and cardiovascular dysfunction or acute respiratory distress syndrome, or two or more organ dysfunctions (9). The severity of sepsis and the clinical outcome with respect to mortality was noted. Blood investigation reports of these patients at admission were collected from hematology section of department of Pathology. The blood samples were analysed using automated hematology analyzer DXH800 (Beckman Coulter, Miami, USA). HRR was obtained by dividing the hemoglobin (Hb) value (g/dL) by the RDW value (%); RAR was obtained by dividing RDW (%) by serum albumin levels (g/dL); RPR was obtained by dividing RDW (%) by platelet count (10^9/L); NLR was obtained by dividing number of neutrophils by number of lymphocytes and PLR was obtained by dividing number of platelets by the number of lymphocytes.

Ethics Statement

Permission to conduct the study was obtained from the Institutional Ethics Committee and informed consent was obtained from parents.

Statistical Analyses

The data collected from the patient's reports was analysed using SPSS Statistics for Windows, version 16.0 (SPSS Inc., Chicago, Ill., USA). Shapiro-Wilk test used to detect normality of data indicated that the data of hematological parameters were not distributed normally. The continuous variables between the groups were analysed by Mann–Whitney U test. Comparison of the categorical variables between the groups were using the Chi-square test. Receiver Operating Characteristic (ROC) curve was generated for HRR and RAR to obtain cut-offs for prediction of mortality. Statistical significance was tested using two-tailed and $P<0.05$ was taken as significant.

Results

Fifty-four children with severe sepsis and 55 with non-severe sepsis were included. The various demographic and biochemical parameters were compared between the groups as depicted in Table 1.

Table 2 shows the differences among the two groups with respect to various RBC indices and their ratios along with white blood cell counts and ratios. The children with severe sepsis had a significantly lower hemoglobin (P=0.009), MCHC (P=0.014) and hemoglobin-RDW ratio (P=0.001). The RDW (P=0.004) and RDW-Albumin ratio (P=0.001) were higher as compared to those with

Table 1. Demographic and Biochemical Characteristics

Characteristics	Sepsis Median (IQR)	Severe sepsis Median (IQR)	P Value
Age, years	2 (0.9-6)	1 (0.33–5)	0.05*
Sex, male (%)	38 (70.4)	32 (58.2)	0.232
Days of PICU stay (among survivors)	3(2-3)	6 (4.75–8.25)	<0.001*
C reactive protein (mg/L)	6.21 (1.64-32.80)	7.39 (1.09–41.74)	0.898
Serum sodium, (mmol/L)	136 (134-138)	135.5 (133–139)	0.866
Serum Potassium (mmol/L)	4.54 (4.25-5.09)	5.02 (4.34–5.68)	0.035*
Serum bicarbonate (mmol/L)	14.55 (13.27-16.92)	13.8 (8.3–16.9)	0.070
Serum Albumin (g/dL)	4.3 (3.9-4.6)	4.1 (3.4–4.6)	0.150
AST (U/L)	40 (31.7-51)	47.5 (34.2–75.7)	0.090
ALT (U/L)	17(13-23.2)	20(12-43)	0.390

IQR= Interquartile range; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; *P<0.05 statistically significant (Mann-Whitney U test). Reference range: C reactive protein >5 mg/L; Serum sodium 136-149 mmol/L; Serum potassium 3.5-5.3 mmol/L; Serum bicarbonate 23-27 mmol/L; Serum albumin 3.5-5.2 g/dL; AST 0-40 U/L; ALT 0-41 U/L

Table 2. Comparison of Red Blood Cell (RBC) Indices, White Blood Cell Counts and Ratios among the Groups

RBC indices	Sepsis Median (IQR)	Severe sepsis Median (IQR)	P value	White blood cell counts and ratios	Sepsis Median (IQR)	Severe sepsis Median (IQR)	P value
Hb, (gm/dL)	10.9 (9.6-11.9)	10 (8-11.1)	0.009*	Total count (109/L)	12.9 (8.6-16.8)	14.1 (9.7-17.7)	0.221
Hct (%)	35.1 (32.3-38.3)	34.5 (28.5-37.5)	0.099*	Neutrophil(109/L)	6 (3.3-10.6)	7.5 (4.4-12.5)	0.142
MCV (fL)	81.3 (76-85.4)	82.3 (71.9-92.1)	0.343	Lymphocyte (109/L)	4 (2.1-6.6)	4.6 (2.6-6.6)	0.594
MCH (pg)	25.1 (21.7-26.3)	24.1 (21.3-26.9)	0.868	Eosinophil(109/L)	0.09 (0.06-0.3)	0.2 (0-0.27)	0.120
MCHC (gm/dL)	30.1 (29-31.5)	29.3 (27.9-30.5)	0.014*	Basophil (109/L)	0.03 (0.01-0.06)	0.01 (0-0.04)	0.029
RDW (%)	14.7 (13.6-16.6)	17.1 (14.7-19.2)	0.004*	Monocyte (109/L)	0.75 (0.44-1.1)	0.68 (0.36-1.1)	0.386
HRR	0.74 (0.58-0.87)	0.59 (0.43-0.7)	0.001*	NLR	1.4 (0.7-3)	1.5 (0.8-3.6)	0.475
RPR	0.0445 (0.0349-0.0532)	0.0342 (0.0301-0.0658)	0.309	PLR	89 (63.4-131.4)	101.7 (59.1-179.2)	0.452
RAR	3.4939 (3.1227-4.4150)	4.3110 (3.3750-5.1235)	0.008*	ELR	0.02 (0-0.07)	0.01 (0-0.05)	0.059

IQR=Interquartile range; Hb=Hemoglobin, Hct=Hematocrit; MCV=Mean Corpuscular Volume; MCH=Mean Corpuscular Hemoglobin; MCHC=Mean Corpuscular Hemoglobin Concentration; RDW=Red Cell Distribution Width; HRR=Hemoglobin-RDW ratio; RPR=RDW-Platelet Ratio; RAR=RDW-Albumin Ratio; NLR, Neutrophil Lymphocyte Ratio; PLR=Platelet Lymphocyte Ratio; ELR=Eosinophil Lymphocyte Ratio; *P<0.05 statistically significant (Mann-Whitney U test); Reference range: Hb 11.5-15.5 gm/dL; HCT 31-40 %; MCV 77-95 fL; MCH 25-33 pg; MCHC 31-37 gm/dL: RDW 11.6-14%. Table 3 depicts various platelet indices and ratios. There were no significant differences in the groups except for plateletcrit (P=0.031) which was higher in the severe sepsis group.

Table 3. Comparison of Platelet Indices and Ratios

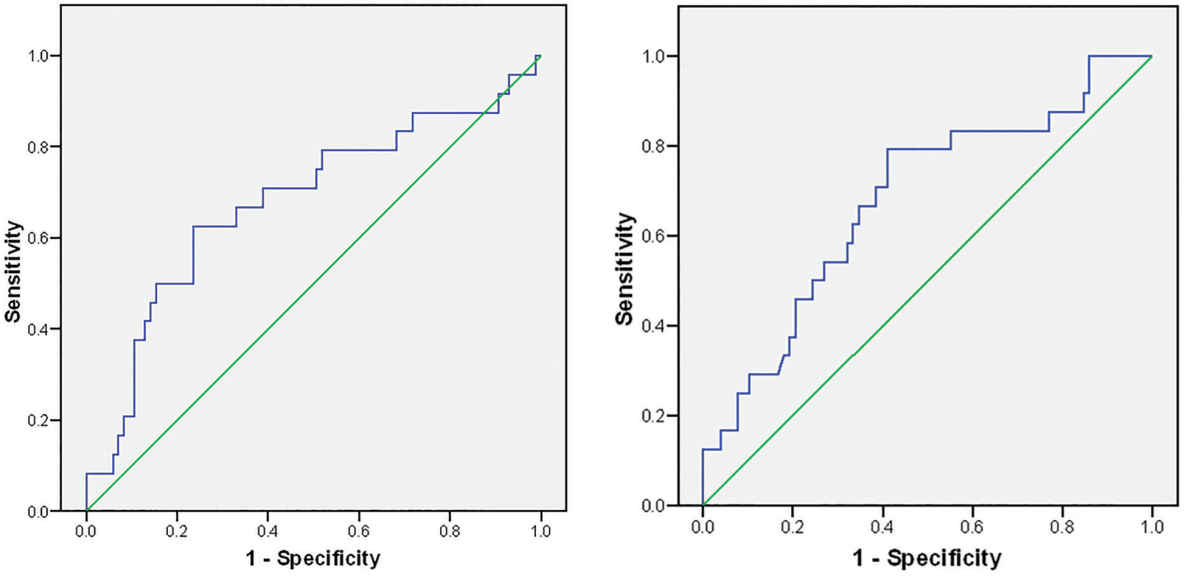
Platelet parameter	Sepsis Median (IQR)	Severe sepsis Median (IQR)	P value*
Platelet count, 109/L	377 (302-472)	425 (303.5-549.5)	0.206
PDW (%)	9.4 (8.6-10.3)	9.500 (8.775-11.075)	0.404
MPV (fL)	9.3 (8.9-9.9)	9.25 (8.98-9.93)	0.655
Plateletcrit (%)	0.32 (0.25-0.42)	0.4 (0.3-0.5)	0.031*
PDW/Platelet count	0.026 (0.019-0.038)	0.024 (0.016-0.032)	0.323
MPV/Platelet count	0.025 (0.019-0.034)	0.023 (0.016-0.033)	0.310

IQR=Interquartile range; PDW=Platelet Distribution Width; MPV=Mean Platelet Volume; *P<0.05 statistically significant (Mann-Whitney U test); Reference range: Platelet count 1.7-4.5 (109 /L); PDW 9-17 %; MPV 7.5-11.5 fL; Plateletcrit 0.22-0.24%.

sepsis. However, there were no significant differences between the two groups with respect to the differential and total white blood cell counts or their ratios (NLR, P=0.475; PLR, P=0.452; ELR, P=0.059).

Among the 54 children with severe sepsis 24 died whereas there was no mortality among the 55 children with non-severe sepsis. As compared to the survivors (N=85), the children who expired (N=24) had a significantly lower albumin {3.8 (3.22-4.37) vs 4.35 (3.8-4.7); P= 0.007}, lower serum bicarbonate {10.95 (7.15-16.17) vs. 14.8 (13.25-17.05); P=0.002}, lower hemoglobin {9 (7.15-11.32) vs. 10.5 (9.4-11.5); P=0.021} and HRR {0.49 (0.37-0.69) vs. 0.67 (0.56-0.83); P=0.008}. The expired children also had a significantly higher RDW {17.4 (15.07-20.22) vs. 15.3(13.9-17.9); P=0.04}, higher PDW {9.6 (9.1-12.8) vs. 9.2(8.5-10.2); P=0.025} and RAR {4.64 (3.85-5.70) vs 3.52 (3.2-4.71) P=0.008}. The other biochemical values and indices were similar among those children who expired as compared to survivors (P>0.05). There were also no differences in total or differential white blood counts and their ratios (NLR, PLR, ELR) (P>0.05).

Fig. 1. (A) depicts the ROC curve generated for RAR in predicting death among critically ill



(A) ROC curve: RDW-Albumin Ratio *(B) ROC curve: Hemoglobin-RDW Ratio*

Fig. 1. *ROC curve generated for RDW Albumin Ratio and Hemoglobin-RDW Ratio in predicting death among critically ill children with sepsis.*

children with sepsis. The Area under the Curve was 0.680. Higher RAR was associated with greater possibility of death. At a cut-off value of 3.845 RAR was 79.2% sensitive and 59% specific in prediction of mortality. Fig. 1. (B) depicts the ROC curve generated for HRR in predicting death among critically ill children with sepsis. The Area under the Curve was 0.682. Lower HRR was associated with greater possibility of death. At a cut-off value of 0.712 HRR was 77.8% sensitive and 60% specific in prediction of mortality.

Discussion

This study reports the differences between children with severe sepsis and non-severe sepsis with respect to various RBC indices and their ratios, white blood cell counts and ratios along with various platelet Indices and ratios. The children admitted with severe sepsis were younger and had a longer stay in PICU. The serum potassium values were higher among children with severe sepsis. The children with severe sepsis had a significantly lower HRR with higher RDW, RAR and plateletcrit as compared to those with non-severe sepsis. However, there were no significant differences between these two groups with respect to the differential and total white blood cell counts or their ratios (NLR, PLR, ELR) and other platelet indices (MPV, PDW, PCT). As compared to the survivors, the children who expired had a significantly lower HRR with higher RDW, RAR and PDW. At a cut-off value of 3.845, RAR was 79.2% sensitive and 59% specific and at a cut-off value of 0.712 HRR was 77.8% sensitive and 60% specific in prediction of mortality.

The current study reports the utility of RAR and HRR in predicting mortality among children with sepsis. A previous study found that higher RAR was linked to increased mortality among patients with heart failure (10). Higher RAR has also been reported to have been linked to higher mortality among adult patients with sepsis (4). These findings are in line with our observation of RAR being linked to higher mortality in children with sepsis. A study done by Ramby et al reported that elevated RDW on the first day of pediatric intensive care unit (PICU) admission was linked to higher PICU mortality (11) like the finding in this study. Lower HRR was linked to higher mortality in critically ill children with sepsis. This agrees with a study by Huang et al which reported that low HRR was linked to increased mortality in patients with sepsis-associated encephalopathy (5). A study that compared the platelet parameters of non-survivors and survivors among children with severe sepsis reported that MPV/PLT, MPV/PCT, PDW/PLT, PDW/PCT ratios were significantly higher in the non-survivors (8). Another study found that MPV/PLT and PDW/PLT were more significantly elevated among non-survivor children with septic shock (12). We found higher PDW in non-survivors compared to survivors though the ratios of indices were not significantly different.

A study by Zhong et al reported that NLR and PCT were significantly elevated among children with severe sepsis compared to non-severe sepsis (13). In the current study, children with severe sepsis had a significantly lower HRR (hemoglobin / RDW ratio) with higher RDW, plateletcrit and RAR as compared to those with non-severe sepsis. However, there were no significant differences in NLR and PCT. A study from Indonesia reported that neutrophil lymphocyte ratio was a predictor of mortality in children with bacterial meningitis (14). In the current study, NLR, PLR and ELR were not significantly different among non-survivors compared to survivors with sepsis.

HRR (hemoglobin/RDW ratio) has not been studied in adult or pediatric sepsis. It has been used as a biomarker in predicting prognosis in different cancer types, with lower values being associated with poor prognosis (15, 16, 17). RDW has been reported previously as a prognostic indicator of pediatric sepsis (11). However, the current study the utility of HRR with a cut-off 0.712 in prediction of mortality in pediatric sepsis with sensitivity 77.8% and specificity 60%. There is a study that has reported the utility of RAR in predicting mortality among adult patients with sepsis. However,

we observed that RA can be used in predicting mortality in children with sepsis with a cut-off of 3.845 (79.2% sensitive and 59% specific).

Limitations of the Study

The limitations this study was that this was a single centre study, and the sample size calculation was not done. A multi-centric study with larger sample size would yield robust results. We measured and analysed the hematological and biochemical parameters only once at admission and dynamic changes in these parameters during the ICU stay were not considered for analysis. There could have been confounding factors which could influence our findings. Hence before the cut-off values of hematological parameters could be used clinically, we need more data in different settings.

Conclusions

In summary, this study has identified that children with severe sepsis had a significantly higher RAR and lower HRR when compared with children with non-severe sepsis. Further, a significantly higher RAR and lower HRR was also noted among non-survivors when compared to children who survived. The biomarkers RAR and HRR are easily obtained and are useful in prediction of mortality in children with sepsis.

Conflict of Interest: The authors report no actual or potential conflicts of interest.

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