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Improving Prediction of Severity of Sepsis in Children: A Single Center trial

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Abstract:
Background: Early diagnosis of sepsis and its severity is essential for timely management to improve patient survival.
Aim of the work: define prognostic indicators of mortality in children presenting with sepsis.
Materials and Methods: A prospective observational cohort study included 45 children with sepsis admitted to the Pediatric Intensive Care Unit (PICU), Children Hospital, Cairo university. Studied predictors included clinical assessment, modified Sequential Organ Failure assessment m (SOFA) score calculation, age- adjusted quick Sequential Organ Failure assessment (qSOFA), Pediatric Risk of Mortality (PRISM) score and lab investigations, including reticulocyte distribution width (RDW).
Results: The age of enrolled children with sepsis ranged between 0.16 - 5 years (median= 1 year), 27 (60 %) of them were males. Of them, 14 (31%) patients died. The mortality among them was predicted by the mSOFA above the cutoff point of 12 had 92% sensitivity, 96% specificity, 92% positive predictive value (PPV), and 96% negative predictive value (NPV) with area under the curve (AUC): 0.97, 95 % confidence interval (CI) 0.93 to 1, the PRISM III score above the cutoff point of 15 had 92% sensitivity, 90 %specificity, 81 % PPV, and 96% NPV with AUC: 0.96, 95 % CI 0.9 to 1, and the RDW above the cutoff point of 21 had 92% sensitivity, 66% specificity, 56% PPV, and 95% NPV with AUC: 0.86, 95 % CI 0.754 to 0.973. The age-adjusted qSOFA failed to predict mortality. Combining the RDW with these scores improved the mortality prediction as the combined RDW to the mSOFA above the cutoff point of 34 showed 100% sensitivity, 90 %specificity, 82 % PPV, and 100% NPV with AUC: 0.97, 95 % CI 0.93 to 1 and the combined RDW to the PRISM III score above the cutoff point of 41 had 92% sensitivity, 96 % specificity, 92 %, PPV, and 96% NPV with AUC: 0.98, 95 % CI 0.96 to 1.
Conclusion: RDW combined with mSOFA score above the cutoff point of 34 and PRISM III score above the cutoff point of 41 were sensitive and specific predictors of mortality among children with sepsis. They may be used as indicators for timely referral of children with sepsis from the emergency ward to the PICU.

Level of Evidence of Study: IV (*1*)**.**
Keywords: Pediatric sepsis; red cells distribution width; RDW; Sequential Organ Failure assessment score; SOFA score; mSOFA; Pediatric Risk of Mortality; PRISM III score
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBC: complete blood count; mSOFA: modified Sequential Organ Failure assessment; MDR: multidrug-resistant; NPV: negative predictive value NICU: neonatal intensive care unit; NPV: negative predictive value; PICU: Pediatric Intensive Care Unit; PPV: positive predictive value; PRISM: pediatric risk of mortality score; qSOFA: quick Sequential Organ Failure Assessment; RDW: reticulocyte distribution width

Introduction

Sepsis is a leading cause of child mortality, accounting for 19 % of deaths worldwide. The highest age-specific incidence of sepsis in children is younger than five years of age (*2*). Early diagnosis and categorizing patients according to sepsis severity is crucial for increasing the possibility of initiating timely and specific treatment (*3*). Clinical scores were designed to help assess the severity and prognosis of sepsis, such as the Sequential (sepsis-related) Organ Failure Assessment (SOFA) and Pediatric Risk of Mortality (PRISM) score in which the higher the scores, the more severe the sepsis (*4*). Modified SOFA (mSOFA) was also developed to avoid risks and difficulty of obtaining arterial samples the peripheral oxygen saturation by relying on non-invasive peripheral oxygen saturation assessment. mSOFA was validated against the SOFA

score and proved to have similar prediction ability (*5*). However, these scores include many variables, their calculation requires lengthy time and there is room for improving their sensitivity and specificity of predication of mortality among children with sepsis. There is no specific single test for that purpose; hence, many efforts are made to search for simpler, easy, and quick parameters, especially if it is routinely tested like any of the parameters in the complete blood count (CBC).

The RDW is routinely measured as a part of the CBC and can be used as a simple tool to stratify patients by severity of illness and identify those at risk for poor outcomes to facilitate focused interventions and triage decisions without additional costs. However, previous studies that evaluated the use of the RDW were done on adults (*6*) or neonates (*7*) with insufficient data on toddlers and children (*8*, *9*). In the neonates, the RDW was confirmed to be an independent risk factor for mortality in septic newborns, and the effectiveness of mortality prediction was superior to the SOFA score (*7*). Therefore, this study aimed to define prognostic indicators of mortality in children presenting with sepsis to allow for early referral to the PICUs and timely management of those critically ill children.

Subjects and Methods

This prospective cohort study was conducted at the Pediatric Intensive Care Unit, Children Hospital, Faculty of Medicine, Cairo University Hospitals. The study was approved by the Ethical Committee of the Faculty of Medicine, Cairo University, Egypt, approved the study (MS-484-2020). All the participants' caregivers consented to the study.

Participants

Forty-five children aged two months to 5 years were enrolled once admitted to the PICU. Enrolled patients had sepsis, severe sepsis, or septic shock according to sepsis-3 definitions (*10*). Patients who received blood transfusion 90 days before enrollment in the study, patients with chronic anemia, and patients with cardiac conditions were excluded.

Methods

Clinical assessment at admission by thorough history taking and examination was done. The cohort underwent the necessary diagnostic tests as C-reactive protein (CRP), blood culture, and cultures from other sites were obtained to detect sepsis. For detection of major organ dysfunction, the liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin), the kidney function tests (urea and creatinine), coagulation test (prothrombin, partial thromboplastin time), chemistry (glucose, potassium, blood urea nitrogen) and venous blood gases were tested as dictated by clinical judgment. The following tests were done at baseline and at follow up (at enrollment in the study), after 48 hours, and weekly till discharge:

1) CBC to identify the white cell count, red cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC, as well as the RDW coefficient of variation, using the Sysmex XS 800i, (Sysmex, Japan). 2) Calculation of the mSOFA score scores (*5*), where the peripheral saturation of oxygen (SpO_2) to fraction of inspired oxygen (FiO_2) ratio was used instead of the the partial pressure of oxygen in the arterial blood (PaO_2):FiO_2 ratio to avoid risks and difficulty of obtaining arterial samples from children (*11*, *12*). The cardiovascular status was assessed by the average blood pressure and the need for inotropic support the neurological status was assessed by the Glasgow coma scale (GCS), the platelet count was used as an indicator of the coagulation system, the urinary system was assessed by the urine output and the serum creatinine level. mSOFA assigns 0 (normal function) to 4 points (most abnormal) for each system giving a possible score of 0 to 24. 3) Age-adjusted quick (q) SOFA score taking into account only 3 clinical components: the respiratory rate, the blood pressure, and the altered mental status severity (*13*, *14*). 4) PRISM III score of 17 variables: cardiovascular (Systolic blood pressure, diastolic blood pressure, and heart rate), respiratory (respiratory rate, SP, PaCO2) neurological (GCS, pupillary reaction), hematology variables (white blood cell count, prothrombin time and partial thromboplastin time), acid-base balance and blood gas, chemistry including potassium, calcium, blood glucose, blood urea nitrogen, and creatinine), these variables were subdivided into 26 ranges and maximum total PRISM III score = 75, the higher the score, the higher the likelihood of mortality (*14*).

Patients were classified into two groups: Group (1) included those who survived (n=31), and Group (2) included those who died (n=14). Both groups were compared as regards age, sex,

underlying cause, causative organism, type of organism, type of system failure, complications, number of blood transfusions, the use of mechanical ventilation, the RDW, white blood cell count (WBC), the PRISMIII, the mSOFA and age-adjusted qSOFA scores.

Statistical Analysis

We used Statistical Package for Social Sciences version 24 for Windows (SPSS, IBM, USA). We used frequencies and percentages for the description of qualitative variables. For numerical variables, we used mean and standard deviations for parametric data. We used the Shapiro-Wilk test to test the normality of numerical variables. We used Spearman correlation to test the correlation between numerical variables. We used ANOVA to test the difference between more than two numerical variables for parametric data and the Friedman test for nonparametric data. A p-value less than 0.05 was considered statistically significant.

Results

The median age of the study group was one year (mean ± SD =1.6 ± 1.8; range 0.7-3 years) and 27 (60%) of them were males. The study group weight SDS (mean ± SD= 0 ± 0.9; range= -1.9 to +1.5) and height SDS (mean ± SD= 0.2 ± 0.9; range= -1.8to +1.6) were within accepted SDS norms for age and sex. Forty patients (88.9%) suffered from respiratory distress, which was the most common presenting symptom, followed by disturbed consciousness level in 25 (55.6%). (Table 1) (Figure 1). Positive blood cultures were detected in 29 (64.4%) children. Multidrug-resistant (MDR) *Klebsiella pneumoniae* was the most detected organism in 11(24.4%) of cases; *Staphylococcus aureus* and *Enterobacter* MDR were the least detected (in 1 (2.2 %) case). (Figure 2). After enrollment in the study, 30 (66.7%) received a blood transfusion (after two days to 4 weeks). Patients had a mean ± SD PRISM III score of 16±5; range= 6-30, and a mean ± SD mSOFA score of 10±4; range= 4-24. The RDW level positively correlated with the CRP level (p = 0.01, r = 0.37), PRISM III score (p =0.0003, r = 0.50), and mSOFA score (p=0.0002, r =0.53), but did not correlate with the age-adjusted quick SOFA score (p = 0.3, r = 0.18). For those who did not receive a blood transfusion (n=15), the mean RDW level on admission was 21.7 ± 2.6 versus 22.6 ±3.4 for those who required blood transfusion (p-value 0.3). The RDW level was higher at admission than in the 2nd, 3rd, and 4th weeks, with p values of 0.012, 0.032, and 0.020, respectively. Also, the RDW was higher at 48 hours compared to the second week, (p= 0.043).

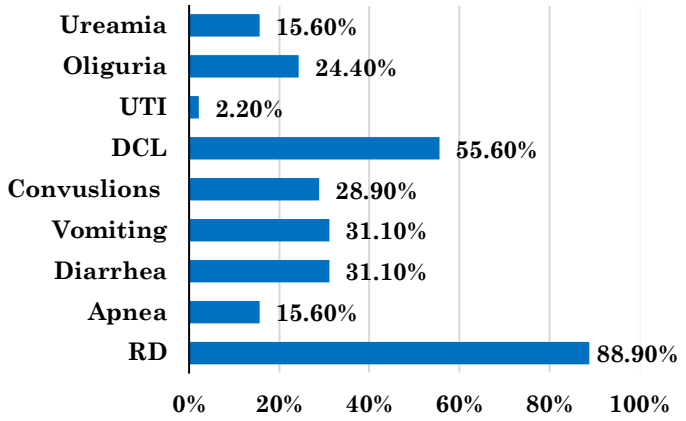


Figure 1. Clinical presentation of the included patients at admission (n=45)
RD: Respiratory distress; DCL: disturbed consciousness level; UTI: urinary tract infection

Fourteen (31%) patients died. The mean time of death was (26.6± 4.8) days, ranging between (17 and 30 days) after admission. The patients who died had higher mean RDW levels at admission of 25± 2.8 versus 21 ± 2.3 for those who survived (p=0.019), higher mean PRISM III score of 23 ± 4 versus 13 ± 3 (p=0.00), higher mean mSOFA of 15 ± 4 versus 7.8 ±2 (p= 0.00) and incomparable mean age-adjusted qSOFA score 2.1 ± 0.7 versus 1.8 ± 0.8 (P= 0.22).

Table 1. Comparison between survivors and children who Died from sepsis

	Survivors (N=31)		Died (N=14)		P-value
Age (years)	1.9 ± 1.9		1.8 ± 1.5		0.9
	Number	%	Number	%	
Sex					
Males	19	61	8	57	0.14
Females	12	39	6	43	
Cause of sepsis					
Respiratory	20	64	7	50	0.39
GIT	3	10	4	28	
CNS	8	25	2	14	
UTI	0	0	1	7	
Received blood transfusion	17	54	13	92	0.3
Mechanical ventilation	28	90	14	100	0.58
Causative organism					
No growth	10	32	6	42	0.13
Klebsiella pneumoniae	7	23	4	29	
Staphylococcus aureus	7	23	3	18	
Pseudomonas Aeruginosa	3	10	0	0	
Candida albicans	3	10	1	7	
Enterobacter MDR	1	3	0	0	
Type of system failure					
Respiratory	29	93	14	100	0.6
Circulatory	14	45	14	100	
CNS	9	29	13	92	
GIT	9	29	5	35	
Renal	3	10	2	14	
Hematology	11	35	13	92	
Liver	4	13	5	35	
WBC'S count (1000/mm3)	14 +/- 6		17 +/- 8		0.32
RDW % (Range)	19 (18–20)		26 (23.5–28)		0.019
PRISM III	13 +/- 3		23 +/- 4		0.00
m(SOFA)	7.8 +/- 2		15 +/- 4		0.00
Age-adjusted qSOFA	1.8 +/- 0.8		2.1 +/- 0.7		0.22

CNS: Central Nervous System; GIT: Gastro-Intestinal Tract; MDR: multidrug resistant; mSOFA; Modified Sequential organ failure assessment score; PRISM III: Pediatric Risk of Mortality Score; qSOFA; Quick Sequential organ failure assessment score; RDW: Red Cell Distribution Width: UTI: Urinary Tract Infection; WBCs: White Blood Cells.

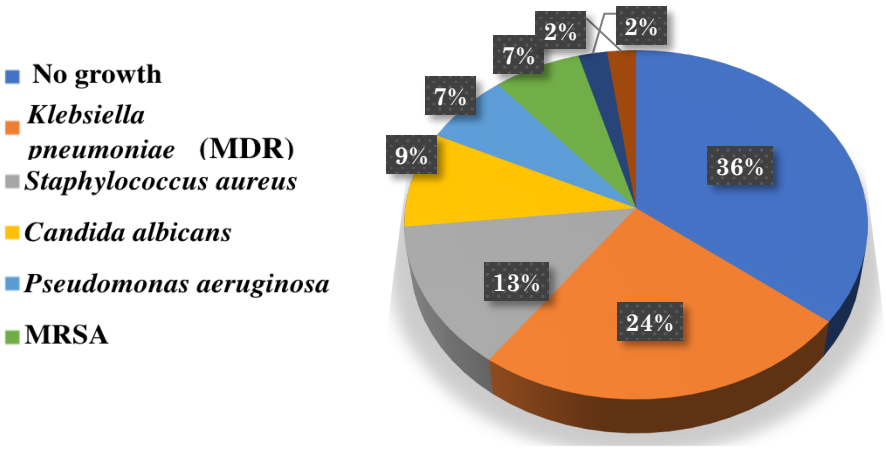
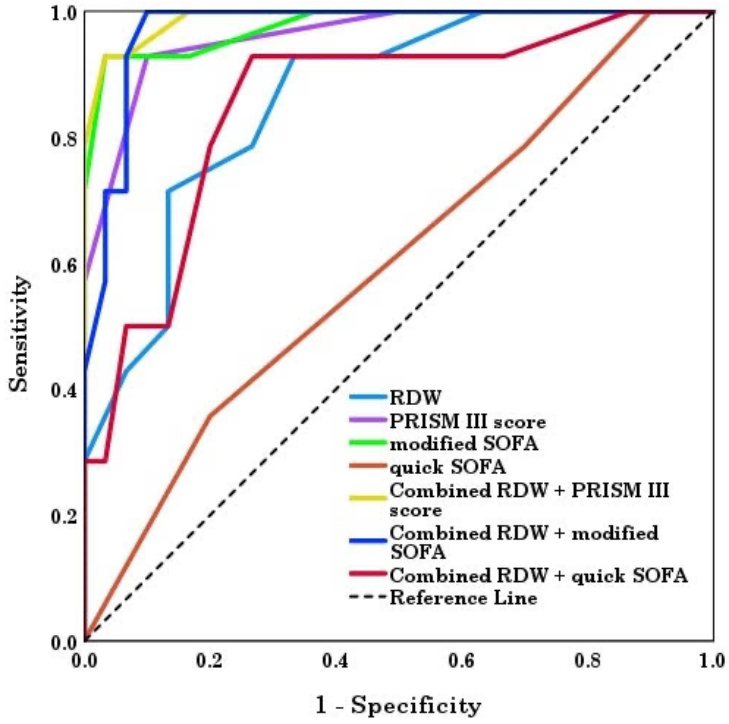


Figure 2. The blood culture results of patients during admission (n=45)
MDR: multi-drug resistant; MRSA: Methicillin-resistant *Staphylococcus aureus*



Test Result Variable(s)	AUC	SE	95% CI of AUC			P value
RDW	0.863	0.056	0.754	-	0.973	0.000
PRISM III	0.961	0.028	0.906	-	1.000	0.000
mSOFA	0.977	0.021	0.936	-	1.000	0.000
qSOFA	0.600	0.092	0.420	-	0.780	0.290
Combined RDW + PRISM III	0.989	0.011	0.968	-	1.000	0.000
Combined RDW + mSOFA	0.973	0.021	0.931	-	1.000	0.000
Combined RDW + qSOFA	0.854	0.063	0.729	-	0.978	0.000

Figure 3. ROC curve analysis for comparing the RDW, PRISM **III** score, mSOFA score, age-adjusted qSOFA, combined the RDW with PRISM **III** score, combined the RDW with the mSOFA score, combined the RDW with the age - adjusted qSOFA score for predicting sepsis mortality.

Table 2. Comparison of the scores for prediction of sepsis mortality

Test variables	Cutoff point	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI
RDW	>21	92.9 %	66.1 - 99.8	66.7 %	47.2 - 82.7	56.5	43.4 - 68.8	95.2	74.8 - 99.3
PRISM III	>15	92.9 %	66.1 - 99.8	90.0 %	73.5 - 97.9	81.2	59.5 - 92.8	96.4	80.3 - 99.4
modified SOFA	>12	92.9 %	66.1 - 99.8	96.7 %	82.8 - 99.9	92.9	65.3 - 98.9	96.7	81.4 - 99.5
qSOFA	>2	35.7 %	12.8 - 64.9	80.0 %	61.4 - 92.3	45.5	23.4 - 69.4	72.7	63.4 - 80.4
Combined RDW + PRISM III	>41	92.9 %	66.1 - 99.8	96.7 %	82.8 - 99.9	92.9	65.3 - 98.9	96.7	81.4 - 99.5
Combined RDW + mSOFA	>34	100.0 %	76.8 - 100.0	90.0 %	73.5 - 97.9	82.4	61.5 - 93.2	100.0	.....
Combined RDW + qSOFA	>23	92.9 %	66.1 - 99.8	73.3 %	54.1 - 87.7	61.9	46.9 - 75.0	95.7	76.7 - 99.3

CI: confidence interval; mSOFA; Modified Sequential organ failure assessment score; NPV: negative predictive value; PPV: positive predictive value; PRISM III: Pediatric Risk of Mortality Score; RDW: Red Cell Distribution Width; qSOFA: quick Sequential Organ Failure Assessment.

The mortality among them predicted by the mSOFA above the cutoff point of 12 had 92% sensitivity, 96% specificity, 92% positive predictive value (PPV), and 96% negative predictive value (NPV) with area under the curve (AUC): 0.97, 95 % confidence interval (CI) 0.93 to 1, the PRISM III score above the cutoff point of 15 had 92% sensitivity, 90 %specificity, 81 % PPV, and 96% NPV with AUC: 0.96, 95 % CI 0.9 to 1, and the RDW above the cutoff point of 21 had 92% sensitivity, 66% specificity, 56% PPV, and 95% NPV with AUC: 0.86, 95 % CI: 0.754 to 0.973. The age-adjusted quick SOFA failed to predict mortality. Combining the RDW with these scores improved the mortality prediction as the combined RDW to the modified SOFA above the cutoff point of 34 had 100% sensitivity, 90 %specificity, 82 % PPV, and 100% NPV with AUC: 0.97, 95 % CI 0.93 to 1 and the combined RDW to the PRISM III score above the cutoff point of 41 showed 92% sensitivity, 96 %specificity, 92 %, PPV, and 96% NPV with AUC: 0.98, 95 % CI 0.96 to 1. (Table 2). (Figure 3).

Discussion

One of the most important issues in the situation of emergency is to stratify critically ill children according to the severity of illness and the urgency to be transferred to intensive care units, especially in limited-resources countries with few available ICU beds. In our tertiary care hospital, we receive hundreds of patients every day, and sepsis is a serious disease that should be promptly recognised and not missed. There is a need for selection criteria that would help identify the patients to be treated at the ward and those who should be transferred urgently and timely to the PICU to implement appropriate management. Many scores depend on different clinical and biochemical factors have been proposed to help categorize the patients in need of PICU care, including the PRISM and the SOFA. Furthermore, many studies have been done to modify these score either to make them simpler, more rapid and less invasive. One of the commonly used modifications is the modified SOFA score where we use the SpO_2: FiO_2, (SF) ratio, instead of the PaO_2: FiO_2 (PF) ratio as in the clinical setting sometimes it is difficult to obtain an arterial blood gas (*5*). The mSOFA was validated and proved to be as accurate for assessment of the respiratory components (*11*). Another modification was the quick SOFA score that takes into consideration only 3 components; respiratory rate, altered mental status, and hypotension, however, the age-adjusted quick SOFA was more accurate among children (*13*).

While the RDW is known to predict 28-and 30 day mortality rate among patients with sepsis the accuracy was reported to be 75%- 83% (*7*, *15*). The RDW prediction of mortality was also confounded by many factors including blood transfusion, underlying disease, nutritional status, etc. (*16*). No single test was found to be reliably predictive of mortality in sepsis. RDW above the cutoff point of 21 prediction of morality in our study was 92% sensitivity, 66% specificity, 56% PPV, and 95% NPV, hence the low specificity would overpredict morality. In the present work, we studied combining the RDW to other scoring systems to improve the prediction of mortality among children with sepsis. The initial presentation RDW above 21 if combined with a modified SOFA score above the cutoff point of 34 predicted mortality with 100% sensitivity, 90% specificity, 82 % PPV, and 100% NPV. Hence, RDW when combined with other scores, especially the modified SOFA score above the cutoff point of 34 and the PRISM III score above the cutoff point of 41, can be used as selection criteria at the emergency room for early referral of to the PICUs, while the rest of the patients can be stabilized and managed at the general wards.

The combined RDW mSOFA can easily be assessed by the pediatrician at emergency room promptly. RDW automated reading would not affect the timely calculation of the mSOFA. The paediatrician promptly calculates the mSOFA while clinical assessing the cardiovascular hypotension, Glasgow coma scale, looking for jaundice, non-invasive measurement of oxygen saturation and collects blood sample for the assessment of creatinine level (*5*). The RDW being an automated reading would not delay or add to the lab burden. The high sensitivity (100%) of the RDW-mSOFA prediction of mortality allows the practitioner not to miss cases with sepsis, or delay their referral and dismiss them as cold to be managed at general ward. Yet, it has to be stressed that the collection of the blood sample for RDW should be done before receiving blood if any.

The combination of RDW and PRISM III score above the cutoff point of 41 showed 92% sensitivity, 96% specificity, which was less than the RDW-mSOFA combination. Moreover PRISM III is a more elaborate scoring system (*17*).

The high RDW among children with sepsis may be attributed to the response to systemic inflammatory processes through downregulation of the expression of erythropoietin receptors (*10*), and the presence of inflammatory cytokines which dysregulates erythropoiesis (*18*). Also, high oxidative stress leads to reduced RBC survival (*19*). Hypoxemia also leads to pulsed erythropoietin (EPO) release, which will induce immature reticulocyte release into the circulation, leading to anisocytosis (*20*).

Limitations to the study include the small sample size, and does not address confounders that affect RDW, as we did not study as serum iron, ferritin, and transferrin binding capacity to study impact of iron deficiency anaemia on march of sepsis. The study scope did not include the effect of the late presentation of cases or late referral to the PICUs on the mortality rate.

Further multicentre, prospective longitudinal validation studies with large sample sizes are needed to determine the optimum utility of RDW combined with the mSOFA score as an initial prompt scoring system to be used in the emergency departments to determine the outcome of sepsis among children and the related factors.

Conclusion

RDW combined with the modified SOFA score above the cutoff point of 34 and PRISM III score above the cutoff point of 41 predicted mortality among our studied cohort with sensitivity

of 100 % and 92 % respectively and specificity of 90% and 92 % respectively. RDW combined with modified SOFA and PRISM III scores may be used as indicators for timely referral of children with sepsis from the emergency ward to the PICU.

Author Contributions

Dr Youssry was the principal investigator in designing the protocol of the study, analysis of the data and writing the manuscript. Dr Zarea shared in data collection and writing the results and discussion. Dr Rady shared in designing the protocol of the study and helped also in data collection. Dr Khedr shared in data collection, analysis of the data and writing the manuscript.

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Authors declare that there was no extramural funding of the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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