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Red Blood Cell Distribution Width (RDW) as a predictor of septic shock in children

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ABSTRACT

Background: Septic shock is a prevalent PICU condition requiring prompt intervention. Using the PELOD II score, which has multiple characteristics to examine, it is challenging to predict prognosis in healthcare-limited settings. A link has recently been shown between red blood cell distribution width (RDW) and mortality risk in critically ill patients, albeit the exact mechanism is unknown.

Methods: This retrospective observational study examined RDW values in pediatric septic or non-septic shock patients. This study examined patient clinical features, RDW hematological markers (RDW-CV, RDW-SD, and RDW/albumin ratio), and the area under the curve to determine the cut-off for the hematological marker, sensitivity, and specificity.

Results: Sixty-one pediatric patients met the inclusion criteria (33 with septic shock and 28 with non-septic shock). The red cell distribution width coefficient variation (RDW-CV) (p=0,058), red cell distribution width standard deviation (RDW-SD) (p=0,05), and RDW Albumin Ratio (RAR) (p=0,014) were shown to be significantly different between the septic shock and non-septic shock groups. The cut-off value for RDW-CV was 15.3% (53.6% sensitivity and 97% specificity), 47.4 fl for RDW-SD (64.3% sensitivity and 84.8% specificity), and 5.65 for RDW/albumin ratio (71.4% sensitivity and 84.8% specificity). RDW-CV odd ratio was 36.9 (95% confidence interval (CI) 4.41-308.96, p 0.001), RDW-SD odd ratio was 10.08 (95% confidence interval (CI) 2.95-34.34, p 0,001), and RDW/albumin ratio was 14.00 (95% confidence interval (CI) 3.98-49.16, p 0,001).

Conclusion: Increased RDW can be one marker in pediatric patients with septic shock. Increased levels of RDW/albumin ratio are significantly associated with the incidence of septic shock. Through the (ROC) area under the curve, the RDW/albumin ratio has better capabilities compared to other predictor markers.

Keywords: red blood distribution width, albumin, RDW/albumin ratio, critical illness, septic shock.
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INTRODUCTION

Septic shock is a potentially fatal illness with substantial morbidity, mortality, and hospitalization expenses.[1] In 2002, the proportion of children with sepsis and septic shock treated in the Pediatric Intensive Care Unit (PICU) in developing countries was roughly 32%, with a 57.3% fatality rate.[2,3] Septic shock is also a leading cause of newborn and child death globally.[1] The leading cause of mortality for 6.3 children per 1000 live births in children aged 5 years. The case fatality rate (CFR) of sepsis in children reached 24.7%, with developing nations having a higher rate (31.7%), particularly on the continents of Africa and Asia, than developed countries (19.3%).[4]

Although blood culture is the gold standard for identifying sepsis, it has several limitations due to its high false negative rate. Because blood cultures barely grew in 30% of samples in individuals with high screening for sepsis, negative results cannot rule out the likelihood of sepsis.[5] Positive blood cultures can sometimes occur as a result of contamination, giving misleading positive results. Another downside of the culture method is that the test results take several days to return, despite patients needing to be treated as quickly as possible. Misdiagnosis, overdiagnosis, and overtreatment are common in this illness, resulting in excessive antibiotic use and rising resistance rates.[6] rapid and dependable laboratory tests to rule out bacterial infection are required for optimal antibiotic therapy. So it can reduce the length of hospital stay and total cost of treatment.

A complete blood count is a basic laboratory test generally available and inexpensive in healthcare institutions. The RDW, which is a variation in the size of the erythrocytes, is one of the parameters in the complete blood count. An increase in RDW has been linked to a septic state caused by inflammation, suppressing red blood cell maturation and lowering red blood cell half-life. In sepsis, oxidative stress can lower the half-life of red blood cells while increasing red blood cell synthesis, increasing RDW.[7] A widely available, low-cost diagnostic tool with clinical efficacy could help clinicians treat it more aggressively.

MATERIALS AND METHODS

Patient and Data Collection

This investigation was carried out retrospectively, utilizing a hospital-based

unmatched case-control series derived from secondary data via a total sampling technique of patient medical records. The study's sample comprised pediatric patients with septic shock, and the control group was non-septic shock patients (hypovolemic shock, cardiogenic shock, anaphylactic shock, and obstructive shock) treated at Dr. Soetomo's PICU from June 2021 to 2022.

Patients aged 0-18 years with complete medical record data and patients with a diagnosis of shock who received at least one inotropic therapy were included in the study. Patients with chronic kidney illness, autoimmune disease, cancer, diagnosis, hematological abnormalities, HIV infection, and a history of blood transfusions were excluded.

Statistical Analysis

Statistical tests were run on the data using MedCalc Software version 20.111. The patient's characteristics (sex, age, nutritional status, test results (procalcitonin, CRP, and patient outcome) were then determined using univariate analysis. The association between independent and dependent variables (RDW-CV, RDW-SD, RDW/albumin ratio, and septic shock) is demonstrated using bivariate analysis.

The Kolmogorov-Smirnov test determined the normality of the Red Cell Distribution Width Coefficient Variation, Red Cell Distribution Width Standard Deviation, and RDW/Albumin Ratio value data. All of the data is regularly distributed (p 0.05). An independent T-test was then used to examine the data. To determine the cut-off values, sensitivity, specificity, and area under the curve (AUC) of the various hematological predictors, the receiver operating characteristic curve (ROC) was utilized. The significance limit was $p < 0.05$ with a 95% confidence interval.

RESULTS

One hundred eighty-eight patients with shock were treated in the PICU between June 2021 and June 2022. The inclusion criteria were met by 61 individuals (33 with septic shock and 28 with non-septic shock). Some medical records were excluded because they had insufficient information and did not meet the study's inclusion criteria.

Table 1 shows the characteristics of the patients. The majority of sepsis patients (57.6%) were male, aged 1-12 months (42.4%), undernourished (66.0%), had the respiratory disease (37%), and died in hospital. Septic shock patients showed greater procalcitonin levels, >5 (96%), but lower CRP levels, 2 (42.4%) as seen in Table 2. The values of RDW-CV, RDW-SD, and RDW/albumin ratio are presented in Table 3. The mean RDW-CV, RDW-SD, and RDW/albumin ratios were 17.4%, 53.5 fl, and 6.0, respectively. It was discovered that the average value of RDW-CV, RDW-SD, and RDW/albumin ratio in septic shock patients was higher than in non-septic shock patients. The independent T-test reveals that there is no significant difference between the two groups in red cell distribution width coefficient variation (RDW-CV) and red cell distribution width standard deviation (RDW-SD) (p 0.05). In comparison, the RDW Albumin ratio differed considerably ($p = 0.014$) between septic shock and non-septic shock. RDW-CV had an odds ratio of 36.9 (95% CI 4.41-308.96), RDW-SD had an odds ratio of 10.08 (95% CI 2.95-34.34), and RDW-SD had an odds ratio of 14.0 (95% CI 3.98-49.16).

The ROC curves were utilized to assess the predictive usefulness of RDW-CV, RDW-SD, and RDW/albumin ratio in patients suffering from septic and non-septic shock. Figure 1-3 depicts the ROC curves for a few single parameters. The area under the receiver operator curve (ROC) analysis (95% CI) for RDW-CV, RDW-SD, and RDW/Albumin ratio was determined to be 0.729 (0.669 to 0.885), 0.780 (0.655 to 0.876), and 0.853 (0.739 to 0.931). The cut-off value for RDW-CV was 15.3% (53.6% sensitivity and 97%

Table 1. Presentation characteristics

Characteristics		Shock Patient	
		Non sepsis n (%)	Sepsis n (%)
Sex	Girl	17 (60.7)	14 (42.4)
	Boy	11 (39.3)	19 (57.6)
Age	1-12 month	12 (42.9)	14 (42.4)
	1-5 year	7 (25.0)	7 (21.2)
	5-18 year	9 (32.1)	12 (36.4)
Nutritional status	Undernutrition	10 (17.2)	22 (66.0)
	Normal	22 (37.9)	7 (22.0)
	Obesity	23 (39.7)	4 (12.0)
Main Diagnosis	Congenital heart disease	6 (22.0)	6 (18.0)
	Neurological infection disease	8 (28.0)	6 (18.0)
	Gastrointestinal disease	3 (11.0)	9 (27.0)
	Respiratory disease	4 (14.0)	12 (37.0)
	Endocrine disease	7 (25.0)	0 (0.0)
Outcome	In-hospital mortality	17 (60.7)	21 (63.6)
	Survived	11 (39.3)	12 (36.4)

P value <0.05 was considered statistically significant for severely wasted children with several comorbidities (neurological and respiratory diseases).

Table 2. Hematological difference between septic shock and non-septic shock patients

Characteristics		Shock Patient	
		Non-septic n (%)	Septic n (%)
Procalcitonin	≤0,5	7 (25.0)	1 (4.0)
	>0,5	21 (75.0)	32 (96.0)
CRP	≤2	12 (42.9)	14 (42.4)
	>2	7 (25.0)	7 (21.2)

Table 3. RDW-CV, RDW-SD, and RAR difference between septic shock and non-septic shock patients

Variable	Non-septic shock (mean)	Septic shock (mean)	*P – value*
Red Cell Distribution Width Coefficient Variation	15.2%	17.4%	0.058
Red Cell Distribution Width Standard Deviation	45.3 fl	53.5 fl	0.05
RDW Albumin ratio	5.01	6.0	0.014

P<0.05 was considered statistically significant for the result RDW Albumin ratio

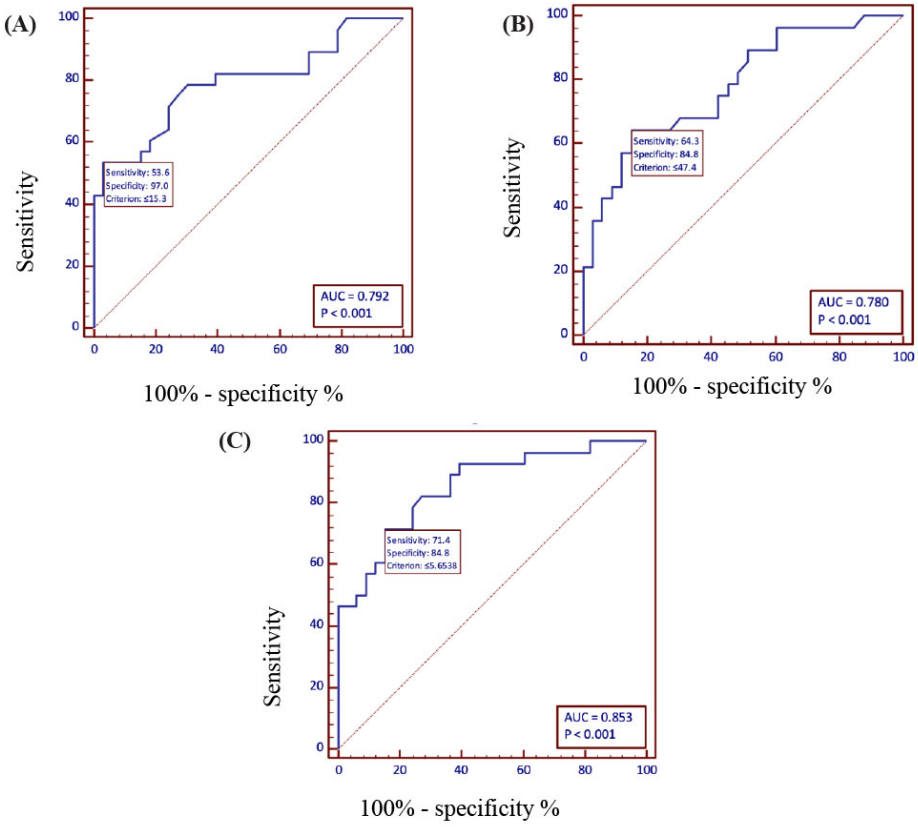

Figure 1. The Receiver Operator Curve (ROC). Red blood cell distribution width Coefficient Variation (RDW-CV) **(A)**, RDW Standard Deviation (RDW-SD) **(B)**, and RDW Albumin Ratio (RAR) **(C)** to diagnose septic shock patients.

specificity), 47.4 fl for RDW-SD (64.3% sensitivity and 84.8% specificity), and 5.65 for RDW/albumin ratio (71.4% sensitivity and 84.8% specificity). The odd ratio of RDW-CV was found to be 36.9 (95% confidence interval (CI) 4.41-308.96, p 0.001), 10.08 for RDW-SD (95% confidence interval (CI) 2.95-34.34, p 0,001), and 14.00 for RDW/albumin ratio (95% confidence interval (CI) 3.98-49.16, p 0,001). The highest ROC area under the curve (AUC) was the RDW/albumin. Based on the rough classifying system, the RDW/albumin ratio has a good interpretation (0.8-0.9), while the RDW-CV and RDW-SD have a fair performance (0.7-0.8).

DISCUSSION

Characteristics of the patient

It was found that septic shock patients were more common in boys (57.6%) compared to girls (42.6%). These findings were also found in the study conducted by Hendra, 54.1% of septic shock male patients, and the research by Watson, 54.8% of septic shock male patients. Age characteristic shows that most patients were one month to 1 year old. Another research by Watson shows most age of children diagnosed with sepsis and septic shock at the age of < 1 year (58.9%), followed by ages 1-5 years (30.8%). This finding is consistent with the theory which states that one of the causes of sepsis and septic shock is an age of less than one year.[8]

Research conducted by Watson found the highest incidence of sepsis was in infants (5.16 cases per 1,000).[9] Meanwhile, Markovitz et al. found a higher mortality rate at an older age (13-17 years).[10] The high incidence at younger ages was because the younger the age, the less the level of maturity of the immune system so that the ability to eradicate pathogens is lower.[1]

The incidence of septic shock is high in children with undernutrition (66%). There is a relationship between nutritional status and sepsis mortality in children. Malnutrition can increase the host's susceptibility to disease, leading to secondary immunodeficiency. Increased metabolism in infectious conditions can also increase the incidence of malnutrition[11]. This research follows the study by Metta.[12]

The most common diagnosis of septic shock patients was respiratory infection (37%), with a predominance of pneumonia and respiratory failure leading to long-term ventilator use. Respiratory failure is the most frequent complication of severe sepsis (85%). Endothelial dysfunction in respiratory infections is caused by a neutrophil infiltration process that causes increased protein and extravasation of fluid into the interstitium and alveolar spaces. Increased interleukin-8 produced by macrophages increases the likelihood of lung injury in septic patients. Disturbances in the respiratory were tachypnea, hypoxemia, decreased ratio of PaO_2/FiO_2, and use of mechanical ventilators due to the increased need for oxygen supplementation.[13]

RDW as a predictor of septic shock patient

RDW measures the complete blood count that indicates erythrocyte size changes (macrocytic, microcytic, and anisocytosis). RDW standard deviation (RDW-SD) or RDW coefficient of variation (RDW-CV)

are the components of RDW in lab data. RDW - CV obtained by dividing RBC by MCV. This test is both inexpensive and readily available.[14-18] Factors affecting RDW include physiological conditions such as pregnancy, aging, gender (women had lower RDW than men), and inadequate physical exercise. In addition, RDW also describes several pathological conditions.[19-20]

This test distinguished between chronic illness anemia, iron deficiency, hemolytic anemia, spherocytosis, vitamin B12 deficiency, folic acid deficit, and anemia. However, it has been discovered that this test can also define a hyperinflammatory state.[15,20] Because it can represent a general inflammatory state, increased RDW is associated with increased mortality in several diseases, including cardiovascular disease, pulmonary disease, hypertension, sepsis, chronic kidney injury (CKD), preeclampsia, rheumatoid arthritis, osteoarthritis, influenza, ARDS, and cancer. Increased RDW values are also associated with increased complications in heart failure, CAD, hepatitis, cancer, diabetes, COPD, stroke, and anemia.[14,16,20,21]

Increased inflammatory processes can interfere with erythropoiesis due to direct disturbances in red blood cell metabolism, such as increased apoptosis[15,22,23], slowed cell turnover (14), myelosuppression/ disruption of the bone marrow cell[17,24], and erythropoietin resistance in the erythroid precursor cell line.[24] Another mechanism that can interfere with RBC formation is the disruption of iron metabolism[23], which causes iron dysregulation and decreased iron bioavailability. High oxidative stress in systemic inflammation can also reduce RBC survival. That causes an increase in immature RBC into circulation and causes an increase in RDW.[24] Micro and macro thrombi due to inflammatory responses can cause pathology of RBC morphology.[25]

Several studies and meta-analyses were undertaken before establishing a link between greater RDW and independent risk of increased mortality risk, hospital stay duration, poor clinical outcomes, and increased requirement for critical care equipment.[14,16,17,21,26] RDW was shown to be within normal limits in the survivor group in research conducted by Bazick et al., whereas RDW increased even on the first day the patient was admitted in the non-survivor group.[27,28] A one-percentage-point rise in the RDW value is related to an increased mortality risk equivalent to a ten-year age increase.[29]

RDW has been contentious in prior investigations due to a lack of specificity. According to some studies, RDW is not a sign of infection but rather a measure of the subsequent inflammatory response caused by infection. As a result, the benefits of RDW as an indication are attributable to its accessibility, rapidity, and ability to identify systemic dysfunction associated with the inflammatory state.[15]

In adults, a high RDW, like creatinine, bilirubin, or platelets, can be a marker of organ dysfunction, as can organ dysfunction scores (SOFA, LODS, APACHE-II, and SAPS-II). When comparing the two scores, RDW and SOFA, the only independent indicators linked with mortality, have greater discriminatory ability because they can thoroughly describe septic dysfunction and create better score performance. However, further studies are needed to confirm and validate these findings.[30]

RDW, like other measures like APACHE II and SOFA, can predict mortality risk. Lorente's research in 2021 found no substantial difference in the ability to predict mortality between RDW, SOFA, and APACHE II(28). Torres et al. discovered that RDW can predict mortality better than other inflammatory markers including lymphocyte count, D-dimer, LDH, or ferritin (15). Increased cytokines and proinflammatory markers (particularly IL-6) can cause an increase in RDW as an inflammatory sign. As a proclivity for inflammation, this scenario can forecast the danger of a cytokine storm and comorbidities.[29,31]

RDW/Albumin ratio as a predictor of septic shock patient

The RDW/albumin ratio was another measure used in this study. The RDW/ albumin ratio distinguished septic shock from non-septic shock (p0.05). Consistent with other research, such as a logistic regression analysis that found RDW-SD and RAR to be independent risk factors for death in COVID-19 patients.[32] Previous research has linked RAR to death in individuals with heart failure[33], aortic aneurysm[34], stroke[35], acute respiratory distress syndrome (ARDS)[36] and malignancy[37]. Another study found RAR to be an independent predictor of sepsis and septic shock in diabetic ketoacidosis patients (HR: 2.9, 95% CI: 2.0, 4.1, p 0.001).[38]

The RDW/albumin ratio increased as albumin decreased. The greater the RAR value, the lower the albumin level. Proinflammatory mediators such as interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor[39] may limit albumin synthesis. Sepsis can cause hypoalbuminemia through various pathophysiological pathways and can also worsen the severity of sepsis.[40,41] Sepsis is linked to increased vascular permeability and capillary leakage, which results in albumin loss from the intravascular compartment. Furthermore, in the setting of severe sepsis, albumin production decreases and catabolism increases.[42,43] Capillary leakage, which increases vascular permeability, is caused by various stimuli, including cytokines such as TNF-alpha and IL-6, chemokines, prostaglandins, complement components, and endotoxins from gram-negative bacteria.[43]

According to the ROC area under the curve (AUC), the RDW/Albumin ratio was more accurate in predicting patient prognosis than RDW-SD and RDW-CV. Higher AUC indicated higher discriminatory ability.[44] RDW/ Albumin ratio is strong (0.80 AUC 0.90), but RDW-CV and RDW-SD have fair discriminatory ability (0.70 AUC 0.80). These findings agreed with those of Xu et al., who discovered that the area under the ROC curve (AUC) (95% CI) of RAR has a higher predictive value than RDW or albumin alone (0.633 vs. 0.604 and 0.602). The area under the ROC curve (AUC) increases when the RAR is paired with the SOFA and SAPS II scores, increasing the predictive power of sepsis mortality. According to Xu, patients with a higher RAR had a worse prognosis, such as a higher mortality rate, a longer ICU stay, illness progression to septic shock, and increased usage of vasopressors and renal replacement therapy (RRT). Higher RAR patients also had higher SOFA and SAPS II

scores.[44-47] This study, however, has several drawbacks. Although the RDW value is only recorded at admission to the isolation PICU, additional confounders such as the patient's iron status, erythropoietin level, and other exact inflammatory cytokines must be corrected. Future research can consider confounding factors and measure the hematological value continuously.

CONCLUSION

Increased RDW can be one marker in pediatric patients with septic shock. Increased levels of RDW/albumin ratio are significantly associated with the incidence of septic shock. Through the (ROC) area under the curve, the RDW/albumin ratio has better capabilities compared to other predictor markers.

AUTHOR CONTRIBUTION

Prima Hari Nastiti: conceptualization, data collection, writing (original draft, final review). Nadiah Raini Khalida**:** writing – data interpretation, original draft, editing. Arina Setyaningtyas: supervision, validation, visualization of work and writing (review and editing). Ira Dharmawati: supervision, validation, visualization of work and writing (review and editing). Neurinda Permata Kusumastuti: conceptualization of research, supervision, visualization of work, and writing (review and editing).

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CONFLICT INTEREST

None.

ETHICAL CLEARANCE

This research has received ethical approval from Dr. Soetomo General Hospital Surabaya (Ref No. 0974/LOE/301.4.2/VII/2022).

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