

## Red cell distribution width and mortality in pediatric sepsis

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### Abstract

**Background** Red cell distribution width (RDW) is a hematological parameter routinely obtained as part of the complete blood count. Recently, RDW has emerged as a potential independent predictor of clinical outcomes in adults with sepsis. However, RDW as a mortality predictor in pediatric populations has not been well established.

**Objective** To determine the relationship between RDW value and mortality outcomes in pediatric sepsis patients.

**Methods** We performed a cross-sectional study of 40 consecutive pediatric patients with sepsis admitted to the PICU from December 2013 to March 2014. All patients' RDW were collected within 24 hours of sepsis diagnosis. We determined the association between RDW and hemoglobin (Hb) using Spearman's correlation. The RDW values of 11.5-14.5% were considered to be normal while those >14.5% were considered to be elevated. We compared mortality and PICU length of stay (LoS) between the normal and elevated RDW groups using Chi-square and Mann-Whitney tests.

**Results** The median age of patients was 34 months (range 2 months to 17 years). There were 28 (70%) male subjects. Subjects' median RDW was 14.8% (range 11.2-27.8%) and was not correlated with Hb ( $r=0.056$ ;  $P=0.73$ ). Mortality rates in the normal and elevated RDW groups were 40% and 45%, respectively. There were no significant associations between RDW group and mortality ( $P=0.749$ ) or PICU LoS ( $P=0.350$ ).

**Conclusion** Unlike in adults, RDW values are not correlated with mortality in pediatric sepsis patients. [Paediatr Indones. 2016;56:320-4. doi: 10.14238/pi56.6.2016.320-4].

**Keywords:** red cell distribution width; pediatric; sepsis; mortality

Sepsis in children remains a major global health problem with high morbidity and mortality.<sup>1</sup> The United States incidence was reported to be 0.56 cases per 1,000 children per year, with deaths occurring in 4,500 cases per year.<sup>2,3</sup> The *World Health Organization* (WHO) reported that 70% of the 8 million deaths in children under 5 years of age in developing countries were due to infectious diseases, most of which ended with sepsis.<sup>3</sup> Therefore, early diagnosis and stratification of severity in sepsis are very important to prevent fatalities.<sup>4</sup>

Biomarkers, such as interleukin (IL) and procalcitonin (PCT), are often used to detect the state of sepsis, determine the degree of severity, and distinguish between the possible causes of sepsis.<sup>4</sup> Unfortunately, the availability of these examinations, especially in rural areas, is limited.<sup>5</sup>

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Red cell distribution width (RDW) has emerged as prognostic factor in adult sepsis.<sup>6-8</sup> Red cell distribution width refers to the coefficient of variation in cell size of the circulating red blood cells (RBCs), and is often evaluated together with other complete blood count parameters.<sup>7,9</sup> However, using RDW to predict mortality in pediatric sepsis has not been well established.<sup>10</sup> The aim of the study was to determine the relationship between RDW value and mortality in pediatric sepsis.

## Methods

We performed a cross-sectional study to assess for a relationship between RDW value and mortality in sepsis patients admitted to the PICU at Haji Adam Malik General Hospital from December 2013 to March 2014. Inclusion criteria were septic children aged 1 month to 18 years. The diagnosis of sepsis was made according to The American College of Chest Physicians and The Society of Critical Care Medicine (2005) consensus criteria, which was the manifestation of systemic inflammatory response syndrome (SIRS) with evidence of probable or documented infection.<sup>11,12</sup> Subjects were considered to have SIRS if they showed at least two of the four criteria: body temperature  $>38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) or  $<36^{\circ}\text{C}$  ( $96.8^{\circ}\text{F}$ ), heart rate  $>90$  beats per minute or  $>2$  standard deviations (SD) for age, respiratory rate  $>30$  times per minute or  $>2$  SD for age or partial pressure of carbon dioxide in the arterial blood ( $\text{PaCO}_2$ ) less than 32 mmHg, and abnormal white blood cell count (more than  $15,000/\mu\text{L}$  or less than  $5,000/\mu\text{L}$  or more than 10% immature [band] forms).<sup>11</sup> Exclusion criteria were children with hematological disorders (such as thalassemia, sickle cell disease, leukemia, aplastic anemia, or myelodysplasia syndrome), cardiovascular disease (congenital or acquired), or acute hemorrhagic manifestations. Subjects' parents provided informed consent. This study was approved by the Research Ethics Committee of the University of Sumatera Utara Medical School.

Characteristic data, including sex, age, primary disease, body weight, body height, and nutritional status, as well as laboratory data for sepsis diagnosis (complete blood counts, PCT, and blood cultures), were obtained from medical records. We also reviewed

family and past medical histories from parents or guardians. We collected subjects' RDW within 24 hours of sepsis diagnosis by taking approximately 2 mL of venous blood using a sterile disposable syringe and transferred it into an ethylenediaminetetraacetic acid (EDTA) vial. Specimens were processed within one hour using a Sysmec 4000i in the Department of Clinical Pathology. Subjects were divided into two groups based on their RDW values, the normal group (RDW value 11.5 - 14.5%) and the elevated group (RDW value  $> 14.5\%$ ). All subjects were followed to evaluate outcomes, which were either death or moved to the inpatient ward care. We also recorded subjects' PICU LoS. Data were analyzed with SPSS for Windows version 19.0. The association between RDW value and hemoglobin (Hb) level was analyzed using Spearman's correlation. Comparisons of mortality and PICU LoS between the RDW groups were analyzed using Chi-square and Mann-Whitney tests, with a significance level of  $P < 0.05$ .

## Results

During the study period, 61 septic children were treated in the PICU. Twenty-one children were excluded due to hematological disorders, congenital

**Table 1.** Characteristics of subjects

Variables	(n=40)
Median age, months (range)	34 (2-203)
Gender, n	
Male	28
Female	12
Nutritional status, n	15
Underweight	21
Normoweight	4
Overweight	
Underlying disease, n	
Central nervous system	6
Respiratory	7
Metabolic	2
Post-operative	18
Burn	3
Other	4
Mean hemoglobin level, g/dL (SD)	11.2 (2.33)
Median RDW value, % (range)	14.8 (11.2-27.8)
Elevated group, n	20
Normal group, n	20
Died, n	17
Median PICU LoS, days (range)	6.1 (1.1-37.5)

or rheumatic heart disease, or acute hemorrhagic manifestations. The median RDW was 14.8% (range 11.2 - 27.8%). Spearman's correlation revealed a weak correlation between RDW value and Hb ( $r=0.056$ ;  $P=0.73$ ). Characteristics of study subjects are shown in **Table 1**.

Mortality rate in the normal and elevated RDW groups were 40% and 45%, respectively. There was no significant association between RDW and mortality ( $P=0.749$ ). Elevated RDW increased the risk of mortality with a prevalence ratio (PR) of 1.12 (95%CI 0.55 to 2.32) (**Table 2**). The median PICU LoS was 144 hours in the elevated group and 157.7 hours in the normal group, but Mann-Whitney test, revealed no significant difference between groups ( $P=0.35$ ).

consecutive pediatric patients with severe sepsis and septic shock revealed elevated RDW values in 67% septic patients, but Spearman's analysis showed a weak correlation between RDW value and Hb level ( $r = 0.08$ ;  $P = 0.44$ ).<sup>10</sup> A retrospective study in China also found elevated RDW in 58/97 (59.79%) septic neonates.<sup>17</sup> Similar to previous studies, our findings showed that RDW was elevated in 50% of subjects, but there was weak correlation between RDW value and Hb level ( $r = 0.056$ ) suggesting the involvement of inflammatory processes in the rise of RDW values in septic patients.

Using RDW as a prognostic factor in critically ill adults has been well established. According to a prospective, longitudinal study of patients who

**Table 2.** Correlation between RDW and mortality

RDW value	Outcomes		Prevalence ratio (95% CI)	P value
	Died, n	Survived, n		
Elevated, n	9	11	1.12 (0.55 to 2.32)	0.749
Normal, n	8	12		

## Discussion

The overall mortality rate from pediatric sepsis in our study was 17/40 subjects (42.5%), similar to other Indonesian referral hospitals, such as Cipto Mangunkusumo Hospital, Jakarta (53%) and Dr. Sardjito General Hospital, Yogyakarta (32%).<sup>13,14</sup> As a comparison of sepsis outcomes in another Asian country, lower sepsis mortality rates were reported in two Korean studies, 10% to 29%.<sup>7,8</sup> In the United States, another developed country, the sepsis mortality rate was reported to be 10.3%.<sup>2</sup> Therefore, sepsis remains to be one of the major global health problems with high a risk of mortality.

In critically ill patients, RDW is usually elevated in response to systemic inflammatory processes, and not solely due to anemic conditions following some diseases.<sup>15</sup> A 3-year retrospective study with a large cohort of unselected adult outpatients in Italy reported significant relationships between elevated RDW and C-reactive protein (CRP), as well as erythrocyte sedimentation rate, both of which are widely known to be inflammatory markers.<sup>16</sup> In Philadelphia, a retrospective cohort study in 90

underwent chronic dialysis in Croatia, an RDW elevation of 1% was found to raise the risk of mortality by 54%, with hazard ratio 5.15 (95%CI 2.33 to 11.36;  $P<0.001$ ).<sup>18</sup> Elevated RDW in 162 patients with pulmonary hypertension was found to increase the mortality risk by 2.4 times (95%CI 1.02 to 5.84;  $P=0.045$ ) compared to normal RDW patients.<sup>19</sup> Subjects known to have had a stroke with elevated RDW had a 2.38 times greater risk of mortality (95%CI 1.41 to 4.01), as reported by a retrospective study using national representative data from the *National Health and Nutrition Examination Survey* (NHANES), United States.<sup>20</sup> Another Korean study in post-cardiac arrest patients reported that elevated RDW values increased the risk of mortality 1.95 times (95%CI 1.05 to 3.60;  $P=0.034$ ) during a 30-day post-resuscitation period.<sup>21</sup>

A Korean study reported that the increment of RDW value in sepsis and septic shock was significantly correlated with 28-day mortality, with hazard ratios of 1.66 (95%CI 1.00 to 2.76) in subjects with RDW values ranging from 14.1% to 15.7% and 2.57 (95%CI 1.53 to 4.34) in subjects with RDW values >15.7%.<sup>7</sup> Another prospective cohort study of 329 severe sepsis

and septic shock patients held in the same country, found that the elevation of RDW values from baseline levels after 72 hours raised the risk of 28-day and 90-day mortality, with hazard ratios of 3.64 (95%CI 0.77 to 17.14; P=0.102) and 7.44 (95%CI 1.71 to 32.34), respectively.<sup>8</sup>

Unlike adults, studies of RDW in pediatric sepsis are limited and with less conclusive results. In China, higher mortality rate was reported in septic neonates with elevated RDW compared to those with normal RDW (91.76% vs. 49.32%).<sup>16</sup> In contrast, a prospective study of children with severe sepsis and septic shock reported no significant relationship between RDW value and mortality, with relative risk 0.59 (95%CI 0.43 to 0.76).<sup>10</sup> Our findings in this study showed that the elevated RDW group had a higher mortality rate compared to the normal RDW group (45% vs. 40%, respectively), but this difference was not significant (RR 1.12; 95%CI 0.55 to 2.32; P=0.749).

Our study had several limitations. First, our subjects had a wide variety of diseases and ranges of severity, so our subject population was not homogenous. Second, we analyzed the relationship between RDW value and mortality after dividing subjects into elevated and normal groups, not including the real value of RDW.

In conclusion, RDW value is not correlated with mortality in pediatric sepsis patients in the PICU. Further studies are needed with more homogenous subjects and including the real value of RDW in statistical analysis.

## Conflict of Interest

None declared.

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