



## ASSOCIATION BETWEEN RED CELL DISTRIBUTION WIDTH INCREASE WITH SEVERITY OF DISEASE AND MORTALITY IN PEDIATRIC PATIENT WITH SEPSIS

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### ABSTRACT

An increase in red cell distribution width (RDW) from baseline is significantly associated with adverse clinical outcomes in adult with sepsis. However, the role of RDW changes as severity and mortality predictors in pediatric population remains unclear. Therefore, we investigated the prognostic significance of changes in RDW in pediatric patient with sepsis. This study conducted to evaluate the association between increased RDW level with severity of disease and mortality in pediatric patients with sepsis. We prospectively enrolled 89 patients who were admitted to Pediatric Intensive Care Unit (PICU) with sepsis from December 2013 to June 2014. Red cell distribution width was measured at admission and at 72 hours. Severity of disease was assessed with PELOD score, mechanical ventilator use, and length of stay in PICU. Pediatric Logistic Organ Dysfunction (PELOD) score was measured at 72 hours of admission. We also recorded hemoglobin level, nutritional status, diagnosis on admission, as well as mortality. There were 52 (58.4%) patients with increase in RDW level at 72 hours. There were no significant difference on PELOD score ( $P = 0.327$ ), length of stay in PICU ( $P = 0.713$ ) and mechanical ventilator use ( $P = 0.444$ ) between the increased RDW and no increased RDW group. Mortality in increased and no increased RDW group was 32.2% (29 patients) and 17.9% (16 patients), respectively but the difference was not significant statistically ( $P = 0.224$ ). There was no significant association between RDW increase with severity of disease and mortality in pediatric patient with sepsis.

**KEYWORDS** : Red Cell Distribution Width, Sepsis, Pediatric

### 1. Introduction

Sepsis in children is a global health problem with high morbidity and mortality [1]. The World Health Organization (WHO) recorded 70% of the 8 million deaths of children under 5 years old in developing countries were caused by infectious disease, most of them ended in sepsis [2]. The incidence of sepsis in 502 pediatric patients admitted to intensive care unit in Cipto Mangunkusumo Hospital was about 19% with mortality rate up to 54% [3].

In sepsis, haemodynamic and microcirculation disfunction often occur, which in turn will cause multiorgan failure. Early diagnosis and stratification of the severity of sepsis are very important to prevent the occurrence of those complications [4]. Biomarkers such as procalcitonin [5], are often used for early recognition and determine the severity of sepsis, and also to differentiate various possible causes of sepsis. The availability of sepsis biomarker measurements in some health facilities are still limited [5].

Red cell distribution width (RDW), a part of complete blood count test, are often carried out to evaluate several cause of anemia [6,7]. Recent studies in adults reported the role of RDW values as a prognostic factor in critically ill children, including sepsis [8-14]. In contrast, the role of RDW as prognostic factor in pediatric patients remains unclear. The increasing of RDW level 72 hours after admission has been reported can predict mortality [15]. However, a prospective cohort study had reported that there was no association between an increase in RDW level and the severity of illness and mortality in children with sepsis [16]. Therefore, we need to investigate the association between red cell distribution width increase at 72 hours after admission to PICU with severity of disease, including mortality in patient with sepsis.

### 2. Methods

This prospective study was carried out by assessing the increase in RDW level and mortality in septic children who admitted to PICU in Haji Adam Malik Hospital from December 2013 to June 2014. We

included all patient between the ages of 1 to 18 years who met the criteria for sepsis. Sepsis was defined according to American College of Chest Physicians and The Society of Critical Care Medicine Consensus (2005). Patient with hematological disorder (such as thalassemia, sickle cell disease, leucemia, aplastic anemia, myelodysplasia syndrome), congenital or acquired heart disease, and manifestation of acute bleeding were excluded.

Red cell distribution width (RDW) level drawn after patient was diagnosed with sepsis and 72 hours after admitted to PICU, along with complete blood count test. Age, sex, gender, nutritional status, PELOD score, mechanical ventilator use, length of stay in PICU, and mortality also recorded.

Data were analyzed using statistical software. Chi-square and unpaired t-test are used to compared both of groups, the increased RDW and no increased RDW group. A  $P$  value less than 0.05 was accepted to be statistically significant in all analysis.

### 3. Result

Of the 89 children with sepsis, 52 (58.4%) patient with elevated level of RDW after 72 hours admitted to PICU. Median RDW level at admission was 15% (11.2 – 34.7), with mean hemoglobin level was 10.22 g/dl (2.84). (**Table 1**)

The severity of the disease was assessed using PELOD score, mechanical ventilator use, and length of stay in PICU. There were no significant differences between the increased RDW group and those who did not increase. Higher mechanical ventilator use in increased RDW group (31 patients versus 21 patients), but the difference was not significant statistically ( $P = 0.444$ ).

There was no significant difference in mortality between both group ( $P = 0.224$ ). Mortality in increased RDW and no increased RDW group was 32.2% (29 patients) and 17.9% (16 patients), respectively. (**Table 2**)

**Table 1.** Subject characteristics

Variable	Total
Gender	
Boys	60 (67.4%)
Girls	29 (32.6%)
Nutritional status	
Malnutrition	32 (36.0%)
Normal	52 (58.4%)
Overweight or obese	5 (5.6%)
Comorbidity	
Central nervous system disorder	19 (21.3%)
Respiratory disease	17 (19.1%)
Metabolic disorder	6 (6.7%)
Post surgical	34 (38.2%)
Flame burn	8 (9.0%)
Others	5 (5.6%)
Red cell distribution width (%)	
At admission, median	15 (11.2-34.7)
At 72 hours, median	15.4 (12.3-27.2)
Hemoglobin level (g/dl)	
Mean	10.22 (2.84)

**Table 2.** Severity of disease and mortality

Parameter	Increased RDW group	No increased RDW group	P
PELOD score (n,%)			
<20	40 (44.9)	25 (28.1)	0.327
≥20	12 (13.4)	12 (13.4)	
Mechanical ventilator use (n,%)			
Yes	31 (34.8)	25 (28.1)	0.444
No	21 (23.5)	12 (13.4)	
Length of stay in PICU (mean, days)	10.31	9.84	0.713
Mortality (n,%)			
Yes	29 (32.5)	16 (17.9)	0.244
No	23 (25.8)	21 (23.5)	

#### 4. Discussion

In this prospective study, conducted in Haji Adam Malik Hospital, we reported of the 89 pediatric patient with sepsis, 45 patients (50.4%) were died. Other study in Cipto Mangunkusumo Hospital, Jakarta reported a similar numbers of mortality in pediatric patients with sepsis, which was 53%, but some studies showed lower percentage of mortality in sepsis. Study in Dr. Sardjito, Yogyakarta showed that percentage of mortality in sepsis was about 32% [3,17] and study in Korea reported mortality rate in patients with sepsis ranged from 10% to 29% [14,15]. In developed countries mortality rate due to sepsis was 10.3% or around 4,500 deaths per year [2,18]. The high mortality rate due to sepsis in developing countries is still a big problem.

The RDW value show the volume variation of circulating red blood cells, with normal values in children being 11.5% to 14.5%. An increase in RDW values indicate variability in the size and shape of red blood cells, as well as an increase in reticulocytes release in circulation [6]. Measurement of RDW is often used to evaluate various causes of anemia in the normal population [7], but in critically ill patients an increase of RDW is often associated with a response to inflammation [12]. Red cell distribution width (RDW) level does not always show a strong correlation with condition of anemia in critically ill patients. A retrospective cohort study in septic children found that there was an increase in RDW values in 67% patients but the correlation between RDW values and hemoglobin level was weak (Spearman's correlation,  $r = 0.08$ ,  $P = 0.44$ ) [16]. Based on the result of study in China, an increase in RDW also occurred in 59.79% neonates with sepsis [19]. Study in Italy reported an association between increase of RDW with C-reactive protein (CRP) and blood sedimentation rate, where these parameters have been used widely as marker of inflammation [20]. The similar results was obtain from preliminary study, of the 61 septic children who were hospitalized at PICU of Haji Adam Malik Hospital, 50% subjects

showed an increase of RDW level and had a weak correlation with hemoglobin level ( $r = 0.056$ ,  $P = 0.73$ ) [21].

Study of RDW values in adult has been carried out widely. A study in Boston in adult patient with critically ill condition reported that relative risk of positive blood culture was more prevalent in group with increase of RDW, patients with RDW level 14.7% to 15.8% and above 15.8% have relative risk 1.40 and 1.44, respectively [12]. Study in Mexico, which enrolled adults patients reported that RDW level were higher ( $18.2\% \pm 2.01$ ) in septic patients compared to those without sepsis ( $14.0\% \pm 1.36$ ) and healthy controls ( $12.0\% \pm 0.27$ ), with  $P$  value  $< 0.05$  [13]. Study in Korea, conducted over 3 years, reported that RDW level of 14.1% to 15.7% and above 15.7% were associated with mortality in 28 days of treatment in adult patients with severe sepsis and septic shock, with hazard ratio 1.66 (95% CI 1.00 to 2.76) and 2.57 (95% CI 1.53 to 4.34) [14]. Other study comparing the relationship between an increase in RDW level more than 0.2% of baseline value in 72 hours found that risk of mortality was increase with hazard ratio 3.64 (95% CI 0.77 to 17.14,  $P = 0.102$ ) in 28 days of treatment and 7.44 (95% CI 1.71 to 32.34) in 90 days of treatment [15].

On the other hand, study of RDW in pediatric patients is still limited. Study in neonates with sepsis in China found the incidence of mortality was higher in patients with increased RDW level (91.6%) compared to normal patient (49.32%) [20]. Study in children with severe sepsis and septic shock reported that there was no association between RDW values with disease's severity and mortality, with relative risk 0.59 (95% CI 0.43 to 0.76) [16]. Preliminary study have found a higher proportion of deaths in patients with higher RDW level compared to those with normal RDW level (45% versus 40%), as well as higher risk of mortality although not significant statistically (ratio prevalence 1.12, 95% CI 0.55 to 2.32,  $P = 0.749$ ), this result showed that RDW level was not associated with mortality in children with sepsis [21]. Similar results was found in this study, increasing RDW level at 72 hours after admission was not significantly associated with severity of disease, which was assessed by PELOD score ( $P = 0.327$ ), mechanical ventilator use ( $P = 0.444$ ), and length of stay in PICU ( $P = 0.713$ ), compared to those without increasing level of RDW. Of the 89 patient with sepsis, 29 patients in increased RDW group were died meanwhile in group without increasing level of RDW 16 patients were died. The difference of those numbers between groups were significant clinically, but not statistically.

There was limitation in this study. We included all patient without considering the severity of sepsis. Therefore, further studies with homogenous sample and larger sample size were needed to investigate the role of RDW values in children with sepsis which will lead us to a better management of sepsis.

#### 5. Conclusion

There was no significant difference in severity and mortality in children with sepsis related to increased of RDW at 72 hours of admission, in both groups. Further studies with homogenous sample and larger sample size were needed to investigate the role of RDW value as a prognostic factor in children with sepsis.

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