Original Research Paper

Internal Medicine

CORRELATION VALUE OF RED BLOOD CELL DISTRIBUTION WIDTH (RDW) WITH SEPSIS SEVERITY

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ABSTRACT

Introduction: Sepsis is defined as the presence of infection (probable or documented) along with systemic manifestations of infection. Sepsis is a pro-inflammatory condition caused by systemic infections. The release of proinflamatory cytokines is believed to cause anemia through several mechanisms including (1) inhibiting the induction of erythrocytes for maturation and proliferation of erythrocytes, (2) inhibiting erythrocytes and (3) reducing the survival of erythrocytes. This condition causes the release of erythrocyte imatur with a variation in size and shape. Red blood cell Distribution Width (RDW) is an expression of the variation in the size of red blood cells. RDW increases with increased red blood cell destruction, nutritional deficiency and blood transfusion, which is a common condition in sepsis. The severity of sepsis is most often calculated using an APACHE II score, which predicts the severity and end of multi organ failure. In this study, we wanted to find out the difference in RDW scores between infectious patients without sepsis and sepsis, sepsis and severe sepsis patients. Also to find out rdw's relationship with APACHE II score.

Method: Cross-sectional research was conducted on 41 sepsis patients (27 men and 14 women) who entered the Adam Malik Hospital ER from February 2016 to September 2016. Patients are grouped into 3 infections without sepsis, sepsis and severe sepsis based on clinical physical examinations and laboratory examinations. Grouping sepsis criteria in accordance with the National Guidelines for Medical Services, Ministry of Health RI 2014. To see the difference in average variables between infection groups without sepsis, sepsis and severe sepsis used independent T tests, chi square and Mann-Whitney. To see the correlation between RDW values and sepsis severity, spearman correlation test was used. Analysis using SPSS v.17.

Results: There was a significant rdw average difference between the sepsis group and non-sepsis infections (14.69 SB 2.31 and 13.39 SB 1.6 respectively) while for the sepsis and severe sepsis groups there was no significant RDW average difference. As well as the APACHE II score, there was no significant difference between the two groups.

Conclusion: RDW differed significantly between the sepsis group and non sepsis infections, but did not differ significantly between the sepsis group and severe sepsis.

INTRODUCTION

Sepsis is one of the most common reasons for admission to intensive care units (ICU) around the world. Over the past two decades, the incidence of sepsis in America has tripled and is now the top ten leading cause of death. In the United States alone, about 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal. Sepsis patients are generally hospitalized for a long time, rarely leaving the ICU before 2-3 weeks. Despite the use of antimicrobial agents and advanced life support, mortality rates for sepsis patients have remained between 20% and 30% over the past 2 decades.[1]

Worsening of sepsis is associated with increased mortality based on the number of organ malfunctions. The severity is most often calculated using an APACHE II score, which predicts the severity and end of multi organ2 failure. Some studies have concluded that apache II scores greater than 15 are significantly associated with mortality of [3-5]. However, calculating the APACHE II score was also impractical compared to identifying biomarkers associated with the severity of sepsis patients.[2]

In the ward of diseases in H. Adam Malik Hospital Medan (2010), the death rate due to sepsis is quite high at 520 per year [6]. But whether the mortality rate is correctly caused by sepsis or by other causes must be proven by a culture that turns out the results are not always positive, so that other examinations such as prokalcitonin (PCT) are needed to be used as a sign of sepsis and know the relationship with the severity of sepsis so

that the diagnosis and management of sepsis can be faster and more precise which causes a decrease in mortality rates. Prokalsitonin has better accuracy values than previous sepsis maps, such as leukocyte/white blood cell (WBC), neutrophil count and C-reactive protein (CRP), but is limited by relatively expensive prices and not all health facilities are able to provide it. Therefore it is still necessary to look for markers that can predict sepsis well, simple, inexpensive and also easy to use in everyday practice at no additional cost.[7,8]

Red blood cell Distribution Width (RDW) is an expression of the variation in the size of red blood cells. RDW is calculated as standard red blood cell size deviation (RBC) divided by mean corpuscular volume (MCV) multiplied by 100 and the result is expressed in percentage. Individual RBC size is determined automatically by flowcytometry. RDWs are widely available, inexpensive and included in the full blood count panel. The normal range ofRDW is 11.5-14.5%.[9,10] RDW increases with increased red blood cell destruction, nutrient deficiency and blood transfusion. It has been reported that the increase in RDW is associated with inflammatory markers that lower half-life red blood cells, in turn increasing RDW.[9,11]

Inflammatory responses are important in sepsis pathophysiology, but there is little research on RDW and sepsis. Previous research by Bazic HS in 2011[9] on higher sepsis patients was observed in groups with higher RDW, and increased RDW was associated with bloodstream infections. Therefore, researchers are interested in conducting a study to

assess whether RDW has a relationship with sepsis / severity. Similar research has never been done in Indonesia.

METHOD
This type of research is cross-sectional and analytically descriptive. The research was conducted from February 2016 to September 2016. The research was conducted at IGD RSUP H. Adam Malik Medan, with inclusion criteria: Patients with infection and sepsis aged ≥ 18 who entered the IGD of RSUP HAM who gave approval to participate in the research voluntarily and in writing.

Anamnesis and physical examination of the subject are carried out to find the focal of the infection and get rid of exclusion criteria if any. Blood samples were taken from fossa cubiti for a complete blood test (including RDW), electrolytes, creatinine and procalcitonin. AGDA examination, blood taken from the femoral artery.

To see an overview of rdw characteristics and values in the sepsis group and non sepsis infection group was presented in the form of tabulation and described normality test using Shapiro-Wilk. To see the difference in variable averages between infection groups without sepsis, sepsis and severe sepsis used independent T, chi square and Mann-Whitney tests.to see a correlation between RDW values and the severity of sepsis used spearman correlation tests. The data is processed and analyzed using SPSS program with α < 0.05 stated significant.

RESULTS
This study was followed by 25 subjects with sepsis and 16 patients with infection without sepsis. Demographic characteristics, clinical examinations and laboratory between sepsis patients and infections without sepsis are shown in table 1.

Table 1. Demographic Characteristics, Clinical Examinations, and Laboratories among Patients Sepsis and infection without sepsis.

	Sepsis	Infection without Sepsis	P
	(n = 25)	(n = 16)	
Demographics			
Gender, n (%)			0.717[a]
Male	17 (68)	10 (62,5)	
Women	8 (32)	6 (37.5)	
Age, Average (SB), year	54.8 (16.88)	42.25 (17.8)	0.029[b]
Clinical Examination			
Sensorium, n (%)			<0.001[a]
Apathy	3 (12)	0	
Cm	9 (36)	16 (100)	
Somnolen	13 (52)	0	
Pulse Rate, average (SB), x/min	99.76 (10.87)	86.81 (7.41)	<0.001[c]
Breath Rate, average (SB), x/min	26.88 (3.7)	22.5 (3.14)	0.001[c]
Temperature, average (SB), °C	37.57 (1.35)	37.16 (0.57)	0.058[c]
TDS, average (SB), mmHg	106.8 (11.45)	112.5 (9.31)	0.051[c]
TDD, average (SB), mmHg	68.8 (6.66)	73.13 (4.79)	0.034[c]
Hb, average (SB), g/dl	13.25 (2.11)	13.22 (1.48)	0.956[b]
Leukocytes, average (SB), /mm3	22,652 (11,698.24)	13,465 (8,781.79)	0.01[b]
RDW, average (SB)	14.69 (2.31)	13.39 (1.6)	0.03[c]

[a] Chi square, [b] T Independent, [c] Mann Whitney

The average RDW in the group of subjects with sepsis was 14.69 with a standard deviation of 2.31 while in the infection group without sepsis the average RDW was 13.39 with a standard deviation of 1.6. The results of the analysis using the Mann Whitney test proved that there was a significant rdw average difference between the two study groups (p = 0.03).

Demographic Characteristics, Clinical and Laboratory Examinations of sepsis and severe sepsis patients presented in table 2.

Table 2. Demographic and Laboratory Characteristics between Sepsis and Severe Sepsis Patients

	Severe Sepsis	Sepsis	p
	(n = 14)	(n = 11)	
Demographics			
Gender, n (%)			
Male	11 (78.6)	6 (54.5)	0.389[a]
Women	3 (21.4)	5 (45.5)	
Age, Average (SB), year	52.86 (15.68)	57.27 (18.77)	0.386[b]
Clinical Examination			
Sensorium, n (%)			0.587[c]
Apathy	1 (7.1)	2 (18.2)	
Cm	6 (42.9)	3 (27.3)	
Somnolen	7 (50)	6 (54.5)	
Pulse Rate, average (SB), x/min	103 (10.86)	95.64 (9.83)	0.07[d]
Breath Rate, average (SB), x/min	28.43 (3.16)	24.91 (3.51)	0.013[d]
Temperature, average (SB), °	38.02 (0.87)	37 (1.65)	0.058[d]
TDS, average (SB), mmHg	107.14 (13.83)	106.36 (8.09)	0.560[d]
TDD, average (SB), mmHg	67.86 (6.99)	70 (6.33)	0.409[d]
Laboratory			
Hb, average (SB), g/dl	13.33 (2.48)	13.16 (1.63)	0.150[b]
Leukocytes, average (SB), thousand/mm3	21,118.57 (13961.4)	24,603.64 (8219.39)	0.412[d]
Platelet, average (SB), thousand/mm3	240,071.43 (232,721.84)	325,818.18 (116,087.74)	0.046[d]
Procalcitonin, average (SB)	58.62 (73.44)	10.12 (13.4)	0.029[d]
APACHE II, average (SB)	17 (4.47)	14.27 (5.26)	0.174[b]
RDW, average (SB), fl	14.63 (2.24)	14.77 (2.5)	0.763[d]

[a] Fisher' Exact, [b] T Independent, [c] Chi square, [d] Mann Whitney

The average RDW in the subject group with severe sepsis was 14.63 with a standard deviation of 2.24 while in the average sepsis group RDW was 14.77 with a standard deviation of 2.5. The results of the analysis using the Mann Whitney test proved that there was no meaningful RDW average difference between the two study groups (p=0.763).

RDW and APACHE II Correlation
Correlation of RDW and APACHE II score of 25 sepsis subjects presented in table 3.

Table 3 Correlation Rdw And Apache II

	APACHE II	
	r	p
RDW	-0.191	0.360

Spearman's correlation analysis showed that there was no meaningful correlation between RDW and APACHE II (p=0.360).

DISCUSSION

Inflammatory response is important in sepsis pathophysiology. Pro-inflammatory cytokines found in patients with SIRS including TNF-α, IL-6 and IL-1β can suppress erythrocyte maturation, allowing larger reticulocytes to enter peripheral circulation and increase RDW. Furthermore pro-inflammatory cytokines have an effect that can be inhibited directly at the half-life circulation of red blood cells, and a balance of deformability of the red blood cell membrane which in turn can manifest as an increase in RDW.[9]

The study was conducted by Razek AA et al (2015)[13] in 90 patients divided into 45 sepsis patients and 45 controls. It was found that the average RDW in sepsis patients was 16.81 with a standard deviation of 2.0 different from the average control RDW value of 15.14 standard deviation of 0.86 (p <0.001). In our study, the average RDW in the group of subjects with sepsis was 14.69 with a standard deviation of 2.31 while in the non sepsis infection group the average RDW was 13.39 with a standard deviation of 1.6. The results of the analysis using the Mann Whitney test proved that there was a significant rdw average difference between the two study groups (p = 0.03).

Similarly, a previous study by Bazick et al (2011)[9] in 51,413 patients, found significant differences in RDW values among sepsis patients, namely 27.1% of sepsis patients with RDW 13.3-17.5% and 45% of sepsis patients with RDW 14.7 - >15.8%. The higher the RDW, the higher the number of sepsis patients.

Previous studies have not directly compared RDW levels in the sepsis and severe sepsis groups. Some studies instead divided the severity of sepsis based on APACHE II scores and SOFA scores, or by survival and non survival groups. As in the Esper RC et al (2008) study of 184 patients divided into sepsis groups, without sepsis and control. The RDW average in the sepsis group was 18.23 ± 2.01. The group without sepsis14.03 ±1.36 and the control group 12.72 ± 0.27. Another study by Lorente et al (2014) on 297 patients divided into survival and non survival groups. RDW was found in non-survival groups to be more meaningful than the survival group.

In our study the average RDW in the group of subjects with severe sepsis was 14.63 with a standard deviation of 2.24 while in the average sepsis group RDW was 14.77 with a standard deviation of 2.5. The results of the analysis using the Mann Whitney test proved that there was no meaningful RDW average difference between the two study groups (p=0.763). The cause of the discrepancy in RDW in this study is likely due to the number of patients included in this study which only 41 people divided into 2 groups. Research may be needed with a larger number of patients.

Worsening of sepsis is associated with increased mortality based on the number of organ malfunctions. The severity is most often calculated using an APACHE II score, which predicts the severity and end of multi organ failure.[2] Apache II scores were measured during the first 24 hours of ICU entry; maximum score is 71. A score of 25 is an estimated mortality rate of 50% and a >35 is an estimated mortality rate of 80%[14]. APACHE II has some limitations that can provide dubious value. For example, in the case of young patients with severe sepsis but without chronic organ failure, the APACHE II score may be relatively low despite the risk of poor outcomes. In contrast, older sepsis patients with chronic organ failure can provide a high APACHE II score even when the risk of death from sepsis is low[15].

Research by Cattermole et al (2009)[16] on 330 patients in the ER. Apache II score calculation is also meaningful in groups with good outcomes compared to poor outcomes, 12.3 standard deviations of 6.8 and 18.8 standard deviations of 7.9,

respectively. In our study the average APACHE II score in the severe sepsis group was 17 with a standard deviation of 4.47 and in the sepsis group was 14.27 with a standard deviation of 5.26. No significant difference in average APACHE II scores were found for both study groups (p=0.174).

Previous studies have identified RDW's relationship with worsening disease severity in sepsis patients. Where sepsis is an inflammatory condition with a noticeable increase in oxidative stress. APACHE II is a measure of increased severity of the disease and worsening severity due to increased inflammation. The negative impact on morphology of erythrocyte cells and erythroroid cells can be assessed by measuring RDW[11].

A study conducted by Mahmood et al (2014) on 349 sepsis patients, found that RDW correlated weakly but meaningfully with APACHE II. Correlation of RDW with mortality, found that in RDW 14.5% is not different meaningful, but in RDW 16% is an independent predictor of mortality increase. RDW may be useful for distinguishing the severity of sepsis patient [17]. In our study, of the 25 sepsis patients studied, the RDW average was 14.69 standard deviations of 2.31 and the average apache II score was 15.8 standard deviations of 4.92. Spearman's correlation analysis showed that there was no meaningful correlation between RDW and APACHE II (r = -1.91 p=0.360).

This research has limitations, among others; First, RDW measurement in this study was only done once at the time of initial entry. So we cannot assess the potential impact of changes in RDW values that could possibly be linked to mortality and survival of sepsis patients. second, researchers did not examine blood B12 and folic acid levels, where B12 deficiency and folic acid can also increase RDW values. Nonetheless, our study exclusivity of all anemia patients so that the effects of B12 deficiency and folic acid can be heeded.

CONCLUSION

There were significant rdw average differences between the infection study group without sepsis and sepsis. There were no significant differences in average RDW, APACHE II scores and correlations between RDW and APACHE II scores for the study group of sepsis and severe sepsis.

Conflict of interest

There was no conflict of interest in this study

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