Analysis of the D-dimer/Platelets Ratio in Sepsis Patients at Dr. Wahidin Sudirohusodo Hospital Makassar

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ABSTRACT

Sepsis is a condition with a life-threatening organ dysfunction. This condition is caused by a dysregulated host response to infection. This study aimed to determine the ratio and cut-off value of D-dimer/platelets in sepsis patients. This study was a cross-sectional observational study. This study took secondary data from the medical records of 142 patients at Dr. Wahidin Sudirohusodo Hospital (RSWS) from January 2018 to December 2021. The results of this study showed that the D-dimer/platelet ratio was significantly higher in those who died (mean 0.151) compared to those who survived (mean 0.028) ($p < 0.015$) with a cut-off value of 0.020.

Keywords: Sepsis, mortality, D-dimer, platelets

INTRODUCTION

Sepsis is a multifaceted host response to an infection pathogen that may be significantly amplified by endogenous factors. A change in the total SOFA score of ≥ 2 points can be used to identify organ dysfunction in sepsis patients.[1] In 2017, there were approximately 48.9 million cases of sepsis and 11 million deaths caused by sepsis worldwide. It was reported that 19.7% of global sepsis cases had caused death worldwide. The incidence of sepsis varies in each region. Sub-Saharan Africa, Oceania, South Asia, East Asia, and Southeast Asia were reported to have the highest incidence of sepsis.[2]

Coagulopathy is a condition that is frequently found in sepsis. Coagulopathy in sepsis can be found as hypercoagulopathy, which plays a role in the formation of venous thromboembolism or as Disseminated Intravascular Coagulation (DIC).[3]

D-dimer is a marker of fibrinolysis indicating hemostatic abnormalities.[4] A study by Han *et al.* in China concluded that D-dimer value can be a prognostic factor in mortality in septic patients. This prognostic factor is influenced by vasopressor therapy and leukocyte count. Both low and very high D-dimer values are associated with a higher risk of death.[5]

Platelets play an important role in infection by promoting immune response and activating the coagulation cascade. Thrombocytopenia is a condition that is commonly found in septic patients.

Thrombocytopenia is also associated with a poor prognosis in septic patients.[6] There are several etiologies of thrombocytopenia in septic conditions, such as decreased production, hemodilution, increased consumption of platelets, and breaking down of platelets mediated by the immune system.[6-8] Thrombocytopenia has a role in the pathogenesis of multi-organ failure in septic patients. Lung damage, Acute Kidney Injury (AKI), septic cardiomyopathy, and DIC are several examples of platelet-mediated organ damage.[9]

Among all types of biological dysregulation, hemostasis derangement is very frequent in septic patients. Disseminated intravascular coagulation is a form of systemic blood clotting, mostly characterized by widespread activation of both platelets and coagulation cascade, leading to massive thrombin generation. Prevalence of acute DIC in patients with sepsis may be comprised between 25-50% and its onset enormously magnifies the risk of death.[5] Hematological failure is common in patients with septic shock. Thrombocytopenia below <50,000/uL is a strong negative prognostic marker in patients with sepsis and is thought to result from platelet activation and consumption.[9]

An elevated D-dimer/platelet ratio can be regarded as an increased D-dimer and a low platelet count status. Increased D-dimer values have been associated with worse clinical outcomes in some studies. Elevated D-dimer and thrombocytopenia have been observed to be associated with poor

prognosis of sepsis.[5,9] To the best of our knowledge, no study has been done to explore the value of the D-dimer/platelet ratio in sepsis patients. However, a study of the D-dimer/platelet ratio in patients with acute pulmonary embolism by Li *et al.* in China concluded that the D-dimer/platelet ratio could be a novel marker for risk stratification in patients with acute pulmonary embolism. This parameter can be used to identify patients who are at high risk of a poor prognosis in acute pulmonary embolism.[10] Therefore this study aimed to determine the D-dimer/platelet ratio in the group of deceased and non-deceased patients with sepsis.

METHODS

This study was conducted with the cross-sectional observational method. Secondary data was taken from the medical records of patients treated at Dr. Wahidin Sudirohusodo Hospital, Makassar starting from January 2018 to December 2021.

The study population was all patients with a clinical diagnosis of sepsis in medical records who were treated at Dr. Wahidin Sudirohusodo Hospital. All patients with a diagnosis of sepsis and had D-dimer and platelet count results were involved as research subjects. Platelet count using Sysmex XN-1000 with hydrodynamic focussing DC detection and D-dimer using Sysmex CS-2500 with turbidimetry.

Inclusion criteria were patients with a diagnosis of sepsis who had performed D-dimer and platelet count at the age of 18-65 years. Patients with solid and non-solid malignancy including hematological disease were excluded.

The research permission has been approved by the Health Research Ethics Commission of the Faculty of Medicine, Hasanuddin University, and Dr. Wahidin Sudirohusodo Hospital with number 426/UN4.6.4.5.31/PP36/2022.

The research data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 25. Descriptive statistic tests, frequency distribution tests, and Mann-Whitney tests were used for data analysis. In addition, a ROC curve was used to determine the AUC and the cut-off value. The p-value <0.05 was reported as significant.

RESULTS AND DISCUSSIONS

A total of 142 patients were involved as research subjects. Table 1 describes the descriptive statistics for the value of D-dimer, platelets, and the D-dimer/platelet ratio (n=142). The D-dimer/platelet ratio varied between 0.001 and 5.139 with a mean of 0.112±0.462.

The distribution of age, gender, and mortality can be seen in Table 2. The 47-year-old category was used based on the mean age.

The D-dimer/platelet ratio was significantly higher in those who died (mean 0.151) compared to those who survived (mean 0.028) (p<0.015) (Table 3, Figure 1).

Table 2. Distribution of variable category

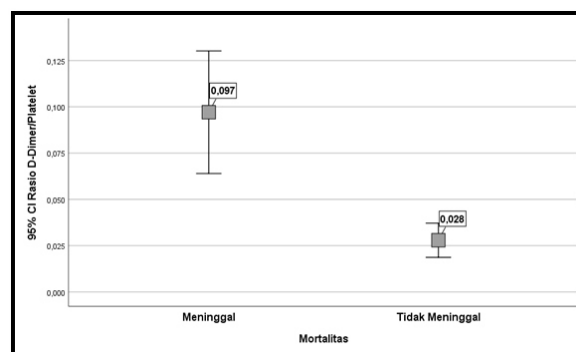|		Frequency	Percentage
Age	<=47 years	57	40.1
	>47 years	85	59.9
Gender	Female	58	40.8
	Male	84	59.2
Mortality	Death	97	68.3
	Survived	45	31.7

Figure 1. Difference in D-dimer/platelet ratio according to mortality

Table 1. Descriptive statistic of D-dimer, platelet, and D-dimer/platelet ratio

Variable	Min	Max	Mean	SD
D-dimer (ug/mL)	0.10	500.00	9.734	42.277
Platelet (10^3/uL)	4	938	209.162	164.940
D-dimer/platelet ratio	0.001	5.319	0.112	0.462

Table 3. Difference in D-dimer/platelet ratio according to mortality

	D-dimer/Platelet Ratio					p
	n	Min	Max	Mean	SD	
Death	97	0.001	5.319	0.151	0.555	0.015
Survived	45	0.001	0.153	0.028	0.031	

Table 4. The AUC of D-dimer/platelet ratio

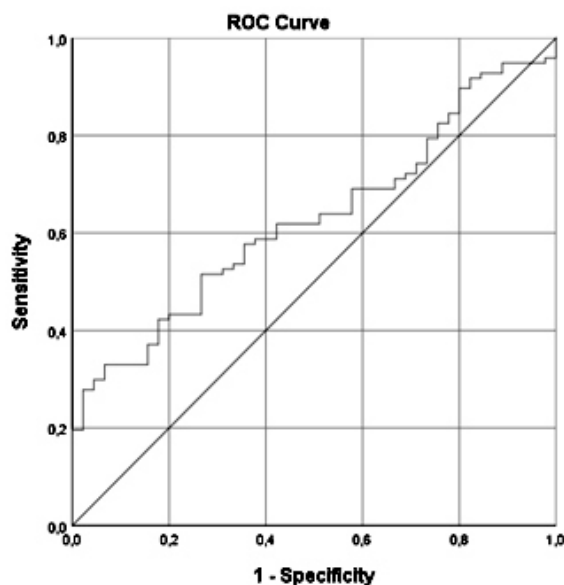| Area	Std. Error	p	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.628	0.047	0.015	0.536	0.719

Figure 2. ROC curve of D-dimer/platelet ratio

Table 4 and Figure 2 show a significant AUC value of 0.628 (p 0.015) and a cut-off value of 0.020.

The results of this study were also obtained as follows: sensitivity=61.9%, specificity=55.6%, PPV=75.0%, NPV=40.3%, and accuracy=60.0%.

D-dimer as a degradation product of fibrin, can reflect the state of coagulation and fibrinolysis.[10] A study by Puspitasari *et al.* concluded that high D-dimer levels could determine the severity of sepsis. Non-survivor patients showed that the mean D-dimer was higher compared to survivors.[11] D-dimer value in sepsis patients has been demonstrated that D-dimer value within the normal reference range had a nearly 4-fold higher risk of dying than those with D-dimer concentrations markedly increased.[5] Both elevated D-dimer and thrombocytopenia are associated with a poor prognosis in septic patients. Therefore, a greater D-dimer/platelet ratio will indicate a poor outcomes according to the results of this study with a cut-off value of 0.020. However, this study has a large standard deviation of platelets. This could be caused by different etiologies of thrombocytopenia during sepsis. The main etiologies of thrombocytopenia during sepsis such as decreased platelet production (viral infection and bone marrow suppressions due to medication), hemodilution (massive vascular infusion fluids), increased platelet consumption, and also immune-mediated destruction.[6] These factors have not been investigated in this study and may have biased the result.

The results of this study also obtained a sensitivity of 61.9%, specificity of 55.6%, PPV of 75.0%, NPV of 40.3%, and accuracy of 60.0%. Note that the accuracy of the D-dimer/platelet ratio of 60% means that this test is likely to provide true prediction at 60% and wrong prediction at 40% due to many risk factors for mortality.

This study has some limitations including it was carried out in a single center and a relatively small sample size. Also, there are many risk factors for mortality from sepsis that may have biased the mortality rate in this study. A study by Velez *et al.* investigated risk factors for mortality from sepsis and showed that patients who died in the ICU received a greater volume of fluid resuscitation in the first 6 hours. However, successful early resuscitation was more frequent in patients who survived. Nutritional support in sepsis patients also showed that a higher proportion of patients who died in the ICU received no nutritional support during their ICU stay compared with those who survived. Antimicrobial therapy also showed successful empirical antibiotic treatment was more frequent in patients who survived and they also had a longer duration of antibiotic therapy than patients who died.[12]

CONCLUSIONS AND SUGGESTIONS

The results of this study showed that the D-dimer/platelet ratio was significantly higher in those who died (mean 0.151) compared to those who survived (mean 0.028) (p<0.015) with a cut-off value of 0.020.

A further study with a higher number of subjects was recommended to confirm the results by considering the primary diagnosis, comorbid conditions, and therapy in patients with sepsis.

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