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Relationship Between Marker Levels Of Endothelial Glycocalyx Damage And Endothelial Damage Biomarkers With Disseminated Intravascular Coagulation In Sepsis Patients

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ABSTRACT

A healthy endothelium is covered by a layer of endothelial glycocalyx, which functions to maintain the endothelial lining. As a woven structure, the endothelial glycocalyx extends over the luminal surface of the endothelium. Endothelial dysfunction is hypothesized to contribute to the incidence of DIC significantly. Endothelium activation and endothelium damage are the initial manifestations of coagulopathy in sepsis. In this study, we investigated the relationship between the levels of endothelial glycocalyx damage biomarkers (syndecan-1) and endothelial damage biomarkers (PAI-1, Thrombomodulin, and ADAMTS13) and the incidence of DIC in sepsis. To analyze the relationship between glycocalyx and endothelial damage with the incidence of DIC and predictor markers of DIC incidence in sepsis patients. From October to December 2022, an analytic observational study with a cross-sectional design was conducted at Dr. Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital Makassar. The research participants were sepsis patients who met the inclusion and exclusion criteria. The statistical test utilized SPSS version 25 with the Kolmogorov-Smirnov test for data normality, the bivariate test utilized the unpaired t-test, and the multivariate analysis employed multiple logistic regression tests and examined the Odds Ratio value. The statistical test results were significant if the p-value < 0.05. This study included 55 patients diagnosed with sepsis, with a distribution of 29 men and 26 women. The results showed no relationship between syndecan-1, PAI-1, and thrombomodulin levels and the incidence of DIC in septic patients (p=0.480,0.122, 0.088). There is a relationship between ADAMTS13 levels and the incidence of DIC in septic patients (p=0.024). Using multiple logistic regression tests, the ADAMTS13 biomarker is a biomarker that can be used as a screening biomarker for

DIC events in sepsis patients (OR=0.889, CI 95% =0.802-0.986). There is a relationship between endothelial damage with the ADAMTS13 biomarker and DIC in sepsis, and the ADAMTS13 biomarker can be used as a screening tool for DIC in sepsis.

1. Introduction

The definition of sepsis is life-threatening organ dysfunction resulting from dysregulation of the host's immune response to infection. Each year, an estimated 30 million people worldwide develop sepsis and 5.3 million die as a result [2].

Disseminated Intravascular Coagulation (DIC) is a common consequence of sepsis. DIC can be caused by infection, cancer, trauma, and other conditions. DIC is a clinicopathological syndrome characterized by the activation of systemic coagulation, production of intravascular fibrin, and contribution to organ failure [3], [4].

Endothelium activation and endothelium damage are the initial manifestations of coagulopathy in sepsis and play a crucial role in maintaining the balance of hemostasis. The endothelium is extremely important during sepsis in maintaining the equilibrium between coagulation and anticoagulation states [5], [6].

A healthy endothelium is covered by an Endothelial Glycocalyx (GE) layer which maintains the endothelial layer. As a woven structure, the endothelial glycocalyx extends across the luminal surface of the endothelium. The glycocalyx consists of glycosaminoglycans (syndecan, glypican, and hyaluronan) and plasma proteins, such as albumin. This layer plays a crucial role in regulating the function of endothelial cells [7].

Endothelial dysfunction is hypothesized to contribute to the incidence of DIC significantly. In this study, we investigated the relationship between the levels of endothelial glycocalyx damage biomarkers (syndecan-1) and endothelial damage biomarkers (PAI-1, Thrombomodulin, and ADAMTS13) and the incidence of DIC in sepsis.

2. Research Objectives

This study aims to analyze the relationship between damage to the endothelial glycocalyx with syndecan-1 markers and endothelial damage with biomarkers PAI-1, Thrombomodulin, and syndecan-1 with the incidence of DIC and predictors of DIC events in sepsis patients.

3. Research Method and Sample

3.1 Research Method

This cross-sectional study was conducted at Dr. Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital between October and December 2022. Patients ≥ 18 years old met the inclusion criteria. Patients with age> 65, cancer, liver cirrhosis, and severe trauma were excluded. The number of subjects sampled is 55. The examination was done on syndecan-1, PAI 1, ADAMTS13, and thrombomodulin levels by immunoassay with ultrasensitive enzyme-related immunosorbent assay (ELISA) using the Elabscience

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USA ELISA Kit, with results expressed in ng/mL.

3.2 Statistical Analysis

Statistical tests were conducted using SPSS version 25 with the Kolmogorov-Smirnov test for data normality, bivariate tests using unpaired t-tests, and multivariate analysis using multiple logistic regression tests and examining the Odds Ratio value; statistical test results are significant if the p-value < 0.05.

4. Results

The research subjects who met the criteria were 55 patients. The research variable categories see in Table 1 and 2. The mean age and platelet level was 48.36 years and 207.25 ($x10^3$). Syndecan-1, ADAMTS13, PAI-1, and Thrombomodulin values were 10.2 ng/ml, 8.75 ng/ml, 2.17 ng/ml, and 10.63 ng/ml.

With a p-value = 0.305, there was no significant difference between DIC and non-DIC patients in shock. (Table 3). Table 4 shows in the DIC group, there was a significant difference in INR and platelets (1.81 vs. 1.44, p=0.001; 177,482.8 vs. 240,461.5, p=0.049). Levels of syndecan-1, a marker of glycocalyx damage, tended to be higher in the DIC group than in the non-DIC group, although this difference was not statistically significant (10.435 ng/ml vs. 9.954 ng/ml, p=0.48). Measurements of endothelial damage did not appear to differ significantly with the PAI-1 and Thrombomodulin biomarkers, but they did significantly with the ADAMTS13 biomarker, whose value decreased in the DIC group (6.925 ng/ml vs. 10.801 ng/ml, p=0.024). PAI-1 and thrombomodulin levels increased in the DIC group, but the difference was not statistically significant (p=0.399 and p=0.688, respectively).

We performed a multivariate analysis of the endothelial glycocalyx components and endothelial damage. Since the relationship between Syndecan-1 and Thrombomodulin levels and the incidence of DIC was not bivariately significant, we continued the multivariate analysis only on the variables PAI-1 and ADAMTS13. Table 5 demonstrates that the ADAMTS13 variable has a more significant relationship with the incidence of DIC than PAI-1, as an increase in ADAMTS13 levels increases the likelihood of DIC occurring in sepsis by 0.889%.

Inferred from the images and analysis of the ROC and AUC curves, the ADAMTS13 predictive value for the incidence of DIC in sepsis is 67.8% with a 95% confidence interval (CI) between 53.4% and 82.2%. The PAI-1 value is deemed insignificant.

5. Discussion

This study determined the incidence of DIC in septic patients using the SIC scoring method [8]. We investigated biomarkers of endothelial glycocalyx degradation and endothelial damage related to the pathophysiology of DIC, primarily caused by sepsis.

In this study, there was no significant difference in the clinical presentation of shock between sepsis with and without DIC. This demonstrates that clinical parameters are insufficient for predicting the incidence of DIC in sepsis.

We found that septic patients with DIC tended to have higher levels of syndecan-1, PAI-1, and thrombomodulin and significantly lower levels of ADAMTS 13 compared to septic patients without DIC. Similar to Mao's study, the same group experienced an increase in syndecan-1 [9]. In sepsis accompanied by DIC, researcher Hatanaka discovered an increase in syndecan-1 levels [10]. Comparing PAI-1 to other studies, we discovered virtually identical results. Masuda found that the PAI-1 value in septic patients with

DIC was significantly higher than in those without DIC [11]. Madoiwa attempted to use a different score, specifically the JAAM score but discovered no significant difference [12].

Thrombomodulin levels in septic patients with DIC rose twofold in Rodrigues' study compared to septic patients without DIC. In a different study that utilized SIC scoring, high thrombomodulin levels were measured 24 hours after the DIC diagnosis was made [14].

Vincent's research yielded results that were distinct from ours. They attempted to determine the relationship between low levels of ADAMTS13 and DIC but found no correlation between the two groups [15].

The progression of sepsis is indirectly caused by endothelial injury and microthrombi formation [16]. This process is initiated by an overabundance of pro-inflammatory cytokines such as IL 6 [16]. The absence of ADAMTS13 will inhibit the proteolysis of UlVWF [17]. Platelets are highly reactive to UlVWF. This 18 UlVWF will quickly obstruct small blood vessels [16].

A decrease in ADAMTS13 activity can occur prior to the onset of thrombocytopenia [19]. In sepsis, procoagulant activation occurs when UlVWF increases due to decreased ADAMTS13 levels, thereby facilitating the development of thrombotic microangiopathy [18], [20]. Except for the ADAMTS13 biomarker, when the AUC analysis was performed on the potential values of the four biomarkers as screening and prognosis for DIC in sepsis, the results were not significant.

Vincent's research yielded different findings than ours. Using ISTH scoring, they attempted to determine the relationship between low ADAMTS13 levels and DIC scoring. They discovered no significant correlation between the two groups [15]. Zhang demonstrated that syndecan-1 could be used to predict the occurrence of DIC [21].

A single parameter for predicting and screening DIC cases has a low predictor factor value, so combining this parameter with multiple other marker parameters can improve the case's sensitivity and specificity [22].

The variation in scoring that can be used to establish the diagnosis of DIC accounts for the disparity in these results between studies. Three scores are used to evaluate DIC: the ISTH score, the JAAM score, and the SIC score [8].

The advantage of our study is that we employ a more straightforward valid scoring method, namely the SIC scoring, which is easier to use for diagnosing DIC since the examination component of this scoring is available in the vast majority of hospitals.

6. Conclusion

There is a relationship between endothelial damage with the ADAMTS13 biomarker and DIC in sepsis, and the ADAMTS13 biomarker can be used as a screening tool for DIC in sepsis.

7. Limitation

The weakness of our study is that it was not conducted as a serial evaluation; therefore, future research must be conducted serially to determine the dynamics of changes that occur in the glycocalyx and endothelium and how they affect hospital management.

8. Authors' Contributions

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SA, HR, RM, and SK were the principal investigators, while FM, AS, EP, and AS contributed to the study's conception and design. All authors contributed to the drafting, revising, and evaluating of the content. All authors have read and approved the manuscript's contents and attest to its accuracy and integrity in every respect.

9. Ethics Approval

This research has been approved by the Ethics Committee for Biomedical Research on Humans, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia, based on recommendation letter Number: 752/UN4.6.4.5.31/PP36/2022.

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Table 1. Characteristics of research subjects

Variables, total n =55	n	%
Sex		
Male	29	52,73
Female	26	47,27
Sepsis source		
Pneumonia	18	32,73
Abdominal infection	19	34,55
Urinary tract infection	8	14,55
SSTI	8	14,55
BSI	2	3,64
SIC Score		
≥4	29	52,73
<4	26	47,27
Shock		
Yes	32	58,18
No	23	41,82

Table 2. Distribution of age variables, platelet levels, levels of markers of glycocalyx damage, and endothelial biomarkers for all study subjects

Variables	n	Median	Min	Max	Mean	SD
Age, years	55	52	18	60	48,363	11,044
SOFA score	55	8	2	15	8,491	3,120
Platelet, mmk	55	141.000	4.000	640.000	207.254,5	158.568
Syndecan-1, ng/mL	55	9,901	5,176	16,807	10,208	2,494
ADAMTS-13, ng/mL	55	8,725	0,2	30,599	8,757	6,407
PAI-1, ng/mL	55	0,760	0,062	12,538	2,172	3,196
Thrombomodulin, ng/mL	55	15,819	0,8	46,876	16,846	10,632

Table 3. Comparison of sex and shock in sepsis patients with DIC (SIC score >4) and without DIC (SIC score <4)

Variable	Total n	DIC, n(%)		P-value*
		With, n=29	Without, n=26	
Sex				
Female	26	13(44,83)	13(50)	0,701
Male	29	16(55,17)	13(50)	
Shock				
Yes	32	15(51,72)	17(65,38)	0,305
No	23	14(48,28)	9(34,62)	

* Chi-square test; The test results are significant if p<0.05

Table 4. Differences in mean from age, SOFA score, INR, platelet count, levels of syndecan-1, ADAMTS-13, PAI-1, and thrombomodulin in sepsis patients with (SIC score >4) and without DIC (SIC score <4)

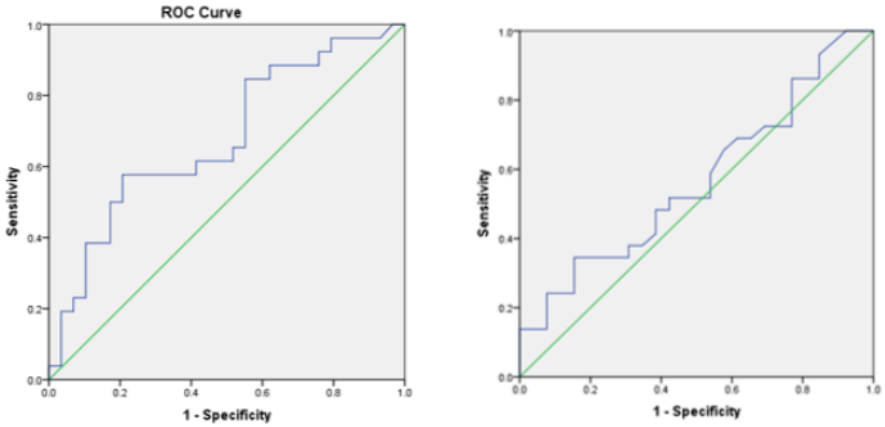
Mean Variable	DIC		P-value*
	With, n=29	Without, n=26	

Age, years	48,201	48,538	0,624
SOFA score	8,66	8,31	0,683
INR	1,81	1,14	0.,001
Platelets, x103	177,48	240,61	0,143
Syndecan-1, ng/mL	10,435	9,954	0,480
ADAMTS-13, ng/mL	6,925	10,801	0,024
PAI-1, ng/mL	2,809	1,462	0,122
Thrombomodulin, ng/mL	17,399	16,229	0,688

* Independent t-test for age, SOFA score, INR, platelets, ADAMTS-13 and PAI-1syndecan-1, and thrombomodulin; The test results are significant if p<0.05

Table 5. Multivariate analysis of the endothelial components with DIC

variable	p	OR(IK95%)
PAI-1	0.107	1.199(0.961-1.494)
ADAMTS13	0.026	0.889(0.802-0,986)



a. ADAMTS13 b. PAI-1

Figure 1. ROC curve for ADAMTS13 and PAI-1 analysis for the incidence of DIC in septic patients

Table 6. ROC and AUC Curve Analysis of ADAMTS13 and PAI-1 Variables for the incidence of DIC

Variable	AUC	p	CI	
			Lower	Upper
ADAMTS13	0.678	0.023	0,534	0.821
PAI 1	0.434	0.395	0.281	0.586

* Receiver operating characteristic (ROC) curve analysis test;
AUC=*area under* ROC *curve*, 95%CI=95% confidential interval

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