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Correlation between the Degree of Glycocalyx Damage and the Incidence of Acute Kidney Injury in Sepsis Patients in the Intensive Care Unit: A Review of Syndecan-1 and sICAM-1

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Abstract

OBJECTIVE: This study aims to know the correlation between the degree of glycocalyx damage and the incidence of acute kidney injury (AKI) in sepsis patients in the intensive care unit. In this study, a review of syndecan-1 and sICAM-1 marker represented the severity of glycocalyx damage. Furthermore, the researchers wanted to see whether this marker in the serum of septic patients could predict the occurrence of AKI in the future of septic patients in the ICU.

DESIGN: This study is a prospective cohort nested case–control study, a case–control study conducted in a cohort population.

SETTING: This research has been carried out in the ICU, both in Hasanuddin University Hospital and Dr. Wahidin Sudirohusodo Makassar Hospital. Syndecan-1 and sICAM-1 examination was carried out in the Hasanuddin University Hospital laboratory.

PATIENTS AND PARTICIPANTS: The sample was taken from septic patients treated in the ICU of Hasanuddin University and Dr. Wahidin Sudirohusodo Makassar Hospital admitted in January 2021. The sample selection was carried out consecutively, namely, the selection of respondents based on the arrival of patients treated in the ICU until fulfilled.

MEASUREMENT AND RESULTS: Data analysis in this study used the Mann–Whitney and unpaired T-test. There was a significant difference in serum syndecan-1 levels between the two groups on day 0 and day 3 of ICU admission and changes from day 0 to day 3. However, there was no significant relationship between sICAM-1 level in the two groups on day 0 and day 3 of ICU admission likewise its changes. Changes in syndecan-1 levels between the two groups were significantly different through the unpaired t-test.

CONCLUSIONS: Syndecan-1 levels are an important measure of glycocalyx damage, statistically proven to predict the future occurrence of AKI in septic patients, whereas sICAM-1 levels were not statistically used to predict the occurrence of AKI in septic patients.

Introduction

Sepsis remains a significant health problem worldwide and a leading cause of death and critical illness. Approximately 30% of patients develop sepsis on admission or during ICU stay. The mortality rate in the ICU was 16.2% in the entire population and 25.8% in patients with sepsis in the ICU [1]. Sepsis is defined as life-threatening organ dysfunction resulting from the body's uncontrolled response to infection. Organ dysfunction can be identified with an acute change condition associated with infection of at least two points on the Sequential Organ Failure Assessment (SOFA) score, increasing the mortality rate by 10% [2].

Sepsis is associated with an intravascular fluid deficit due to vasodilation, venous pooling, and capillary leakage by changes in the endothelial barrier [3]. The vascular system is lined with endothelial cells, a unique cellular system that envelops the inner lining of blood vessels and forms the interface between circulating blood and parenchymal cells [4]. Endothelial cells in the luminal surface of blood vessels are coated by glycocalyx, forming an endothelial glycocalyx layer (EGL), a macromolecular membrane bond consisting of proteoglycans, glycoproteins, glycosaminoglycans, and plasma proteins [5].

The inflammatory cascade reaction in sepsis involves a variety of inflammatory mediators that induce a breakdown of EGL integrity [3], [6]. EGL is one of the earliest sites of trauma during inflammation. Loss of EGL in response to the release of inflammatory mediators such as cytokines and chemoattractant has been found to occur in the microcirculation model

of sepsis inflammation. Inflammatory mediators can directly damage endothelial cells, thereby changing the structure of the endothelial glycocalyx and can also cause glycocalyx degradation through the activation of parts of leukocytes, namely, PMN, macrophages, and degranulating enzymes from mast cells [7], [8].

Inflammation itself, as previously stated, through the release of inflammatory mediator cytokines, will cause damage to the integrity of the EGL, which is vital in the development of organ failure in septic patients [4]. In inflammation caused by sepsis or severe trauma, the glycocalyx becomes activated and is directly involved in widespread endothelial damage, contributing to microvascular dysfunction [9]. Markers of damage to the glycocalyx layer include syndecan-1, heparanase, and heparin sulfate. The characteristics for activation of the endothelial cell layer include soluble intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [10].

Acute kidney injury (AKI) is a complication of organ failure that is often found in sepsis. The current incidence of AKI is 40-50% in critically ill patients with sepsis, which increases the risk of death by 6–8 times [11]. Sepsis-associated AKI has a high incidence in critically ill patients admitted to the ICU. About 64.4% of patients with sepsis in the ICU experienced early AKI, that is, AKI, that occurred within 24 hours of the initial onset of hypotension. Of this 64.4% of patients (2917 patients out of a total of 4532 sepsis patients), there were 16.3% of patients included in the risk criteria, 29.4% in the injury criteria, and 18.7% in the failure criteria, based on the RIFLE criteria for the severity of AKI [12].

Leakage of blood vessels and capillaries due to vascular endothelial barrier function defects is one of the major clinical problems faced by critically ill patients. Damage to the integrity of the glycocalyx leads to severe disruption of the microcirculation, failing the systemic circulation [13]. In the renal organ, the mechanisms responsible for renal microcirculation failure are not fully understood; impaired EGL is considered an essential mechanism in the increase in microvascular permeability during sepsis, which has been associated with the development of decreased flow and congestion in the kidney [4].

With the above background, the researchers wanted to know how the relationship between acute renal impairment in patients with sepsis concerning the degree of inflammation that triggers glycocalyx damage; wherein this study, the degree of glycocalyx damage was represented by syndecan-1 and soluble ICAM-1 serum. Furthermore, the researchers wanted to see whether this marker of glycocalyx damage in septic patients could predict future acute kidney disorders in the care of patients in intensive care unit.

Methods

Research design

This study is a prospective cohort nested case–control study, namely, a case–control study conducted in a cohort population.

Place and time of research

This research has been carried out in the intensive care unit (ICU) of Dr. Wahidin Sudirohusodo Makassar Hospital and Hasanuddin University Hospital. Syndecan-1 and soluble ICAM-1 assays were carried out in the Lab. the 6th floor of UNHAS Hospital. The research has been carried out since January 2021 until the sample is sufficient.

Sample and research population

The sample of this study was septic patients who were treated in the ICU of Dr. Wahidin Sudirohusodo Makassar and ICU of Hasanuddin University Makassar Hospital starting in January 2021. The sample selection was carried out consecutively, namely, the selection of respondents based on the order of arrival of patients treated in the ICU until the number of research samples was met. Inclusion criteria: Patients age > 18 years, patients with a diagnosis of sepsis (qSOFA criteria), and patients/families of patients willing to be included in the study. Exclusion criteria: Patients with acute renal impairment before ICU admission; patients with chronic kidney disease (CKD) or diseases of the urinary tract system; patients with comorbid hypertension; patients with comorbid coronary heart disease; and patients with comorbid diabetes were excluded from the study. Dropout criteria: Patients were discharged from the ICU for <3 days.

Data collection

The data taken consisted of primary data, which included demographic data, patient clinical data, and laboratory data, including data on levels of syndecan-1 and soluble ICAM-1. Data on the occurrence of AKI were obtained by observing the AKI markers in the patient's serum, namely, creatinine values and urine production. Data on syndecan-1 and soluble ICAM-1 levels were taken from data recording in the hospital laboratory UNHAS 6th floor.

Data analysis

Data analysis in this study used the Mann–Whitney U-test.

Ethical approval

This research was conducted with the approval of the Ethics Committee for Biomedical Research in Humans, Faculty of Medicine, Hasanuddin University Makassar, with the number: 110/UN4.6.4.5.31/PP36/2021.

Results

Characteristics of the research sample

The research sample consisted of 88 total samples comprised of two groups, namely, the group with acute kidney injury (AKI) and those without acute kidney injury (non-AKI). Each group consisted of 44 samples. The mean age in the AKI group was 50.16±15,794 years and 45.41±15.063 years. The mean BMI in the AKI group was 23.59 (18.37-33.30), and in the non-AKI group, it was 22.98±3.34. There was no difference between age and BMI in the incidence of AKI (Table 1).

Table 1: Characteristics of the research sample

Variable	Median (minimum–maximum)		p
	AKI (n=44)	Non-AKI (n = 44)	
Age (years)	50.16 ± 15.79*	45.41 ± 15.06*	0.152
BMI (m/kg^2)	23.59 (18.37–33.30)	22.98 ± 3.34*	0.237
Gender			
Male	23	24	
Female	21	20	
Source of infection			
Intra-abdominal infection	17	14	
Urinary tract infection	3	5	
Lung infection	21	24	
Skin and soft-tissue infection	2	1	
CRBSI	1	0	
Syndecan-1 level D-0 (pg/ml)	3712.05 (1265.0–8935.0)	1962.63 ± 870.69*	
Syndecan-1 level D-3 (pg/ml)	4412.74 ± 1592.08*	2052.94 ± 924.75*	
sICAM-1 level D-0 (ng/ml)	19.19 ± 0.67*	19.16 ± 0.63*	
sICAM-1 level D-3 (ng/ml)	18.55 (0.10–20.40)	18.60 (0.10–20.50)	
Syndecan-1 level change (pg/ml)	540.54 ± 1350.89*	90.30 ± 628.22*	
sICAM-1 level change (ng/ml)	−0.67 (−19.63–1.48)	−0.7 (−18.18–1.14)	
Fluid balance D-1	133.27 ± 714.23	70 ± 446.16	
Fluid balance D-3	948 ± 1447.59	−110.47 ± 1163.44	
SOFA score D-0	7.73 ± 4.14	3.03 ± 2.44	
SOFA score D-3	9.21 ± 4.84	2.33 ± 3.32	

*Data are normally distributed with the Shapiro–Wilk test. CRSBI: Catheter-related bloodstream infection, BMI: Body mass index, SOFA: Sequential Organ Failure Assessment, sICAM: Soluble intercellular adhesion molecule, AKI: Acute kidney injury.

Comparison of variables between groups of day 0 ICU care

Table 2 shows a statistically significant difference in syndecan-1 levels between the two groups using the Mann–Whitney non-parametric test. Meanwhile, the difference in soluble ICAM-1 levels between the two groups was not significant through the unpaired t-test.

Comparison of variables between groups on day 3 of ICU care

Table 3 shows the difference in syndecan-1 levels between the two groups statistically significant through the unpaired t-test. Meanwhile, the difference in soluble ICAM-1 levels between the two groups was not significant through the unpaired t-test.

Table 2: Comparison of variables between groups of day 0 intensive care unit care

Variable	Median (minimum–maximum)		p
	AKI (n=44)	Non-AKI (n=44)	
sICAM-1 (ng/ml)	19.19 ± 0.67*	19.16 ± 0.63*	0.816**
Syndecan-1 (pg/ml)	3712.05 (1265.0–8935.0)	1969.35 (451.50–4037.10)*	<0.001*

*Significant with Mann–Whitney U-test (p<0.05), **not significant with unpaired *t*-test (p>0.05). sICAM: Soluble intercellular adhesion molecule, AKI: Acute kidney injury.

Table 3: Comparison of variables between groups on day 3 of intensive care unit care

Variable	Median (minimum–maximum)		p
	AKI (n=44)	Non-AKI (n=44)	
sICAM-1 (ng/ml)	18.55 (0.10–20.40)	18.60 (0.10–20.50)	0.910**
Syndecan-1 (pg/ml)	4412.74 ± 1592.08*	2052.94 ± 924.75*	<0.001***

**Not significant with Mann–Whitney U-test (p>0.05), ***significant with unpaired *t*-test (p<0.001). sICAM: Soluble intercellular adhesion molecule, AKI: Acute kidney injury.

Comparison of variables between groups from admission to ICU care on day 3

Table 4 shows the difference in the increase in syndecan-1 and soluble ICAM-1 in the two groups. Changes in syndecan-1 levels between the two groups were significantly different through the unpaired t-test. In contrast, the change in soluble ICAM-1 level between the two groups was not statistically significant through the Mann–Whitney U-test.

Table 4: Comparison of variables between groups from admission to intensive care unit care on day 3

Variable	Median (minimum–maximum)		p
	AKI (n=44)	Non-AKI (n=44)	
Change in syndecan-1 level (pg/ml)	540.54 ± 1350.89*	90.30 ± 628.22*	0.049**
Change in sICAM-1 level (ng/ml)	−0.67 (−19.63–1.48)	−0.7 (−18.18–1.14)	0.545***

**Significant with unpaired t-test (p<0.05), ***not significant with Mann–Whitney U-test (p>0.05). sICAM: Soluble intercellular adhesion molecule, AKI: Acute kidney injury.

ICU care ROC curve analysis day 0

Table 5 and diagram 1 shows Curve analysis on day 0 intensive care unit care the variables that can be considered predictors of the incidence of AKI during treatment. Syndecan-1 levels were the best predictor of AKI in this study (AUC 83.2%) with a cutoff value of 2665.0 pg/dl with a sensitivity of 70.5% and a specificity of 84.1%. Meanwhile, soluble ICAM-1 level was not a good predictor of AKI incidence (AUC 50.3%) with a cutoff value of 19.15 ng/ml with a sensitivity and specificity of 56.7% and 54.5%, respectively.

Table 5: Curve analysis on day 0 intensive care unit care

Variable	Cut off	Sensitivity (%)	Specificity (%)	AUC (%)
sICAM-1 (ng/ml)	19.15	56.8	54.5	50.3
Syndecan-1 (pg/ml)	2665.0	70.5	84.1	83.2

sICAM: Soluble intercellular adhesion molecule, AUC: Area under the curve.

ICU treatment ROC curve analysis day 3

Table 6 and diagram 2 shows Receiver operating characteristic curve analysis on day 3 intensive care unit carethat syndecan-1 levels on day 3 were the best predictor of AKI in this study (AUC 91.3%) with a cutoff value of 2854.0 pg/dl with a sensitivity of 84.1% and a specificity of 86.4%. Meanwhile, the soluble level of ICAM-1 on day 3 was not a good predictor of AKI incidence (AUC 50.3%) with a cutoff value of 18.7 ng/ml with sensitivity and specificity of 40.9% and 59.1%, respectively.

Table 6: Receiver operating characteristic curve analysis on day 3 intensive care unit care

Variable	Cut Off	Sensitivities (%)	Specificities (%)	AUC (%)
sICAM-1 (ng/ml)	18.7	40.9	59.1	50.7
Syndecan-1 (pg/ml)	2854.0	84.1	86.4	91.3

sICAM: Soluble intercellular adhesion molecule, AUC: Area under the curve.

ROC curve analysis of variable changes from admission to ICU treatment on day 3

Table 7 and diagram 3 shows Change in receiver operating characteristic curve analysis from admission to day 3 that changes in syndecan-1 levels have a sensitivity of 56.8% and specificity of 77.3% in predicting the incidence of AKI (AUC 91.3%), with a cutoff value of 2854.0 pg/dl. Meanwhile, changes in sICAM-1 level were an unfavorable predictor of AKI (AUC 50.3%) with a cutoff value of −0.305 ng/ml with sensitivity and specificity of 40.9% and 59.1%, respectively.

Table 7: Change in receiver operating characteristic curve analysis from admission to day 3

Variable	Cut Off	Sensitivities (%)	Specificities (%)	AUC (%)
ΔsICAM-1 (ng/ml)	−0.305	45.5	68.2	53.7
ΔSyndecan-1 (pg/ml)	468.4	56.8	77.3	63.2

sICAM: Soluble intercellular adhesion molecule, AUC: Area under the curve.

Discussion

Sepsis causes significant changes in microvascular blood flow characterized by increased heterogeneity of regional blood flow distribution and increased capillaries with reduced blood flow (i.e., intermittent or stopped flow) [14]. Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) derived from pathogens generate an immune response that further activates leukocytes and endothelial cells. Activation and injury to endothelial cells directly or through oxidative stress-induced changes in protective mechanisms in protective mechanisms due to breakdown of endothelial cells integrity.[15]

Damaged or activated endothelial cells undergo glycocalyx release. The glycocalyx is a layer of organized glycosaminoglycan branches that protrude from the surface of the endothelial cell membrane into the capillary lumen, which fulfills important biomechanical functions. Damage and loss of the glycocalyx layer are thought to cause changes in red blood cell flow, capillary leakage, and exposure to endothelial adhesion molecules, leading to increased platelet and leukocyte adhesion, leukocyte rolling, and transmigration; changes in the function of the capillary barrier, resulting in capillary leakage and the formation of edema; changing the shear stress strength settings needed to regulate blood flow and tone; and subsequently lead to major changes in the distribution of blood flow [5]. Origin is associated with a higher risk of aggravation of sepsis [16].

Characteristics of research subjects

There was no statistical difference between age and BMI in the incidence of AKI in this study. However, the subjects of the AKI group had a higher median age (50.16 ± 15.794 years) than the group without AKI (45.41 ± 15.063 years). Sang *et al*. in their study reported that there was a relationship between age and the occurrence of AKI in critically ill patients with COVID-19. (17)(18) Body mass index (BMI) in the two groups in this study did not show a statistically significant difference. However, the median BMI of the AKI group was slightly higher than that of the non-AKI group (23.59 ± (18.3-33.3) vs. 22.98 ± 3.34). Another study found that the BMI of patients with AKI and non-AKI showed that BMI was significantly higher in AKI patients compared to non-AKI patients [17], [18], [19].

In addition, the clinical parameter of fluid balance in the group of septic patients who had AKI had a higher median, especially on day 3. This study showed a significant difference in fluid balance between the AKI and non-AKI groups on day 3. Positive fluid balance or fluid overload is a significant risk factor for death in patients on dialysis, peritoneal dialysis, and patients with chronic renal failure on non-dialysis. It was further explained that fluid overload and inflammation are independent solid risk factors for worsening outcomes in renal patients [20].

In this study, another clinical parameter used the SOFA score, and it was found that there was a statistically significant difference, where the SOFA score was higher in the AKI group than in the non-AKI group. This is in line with Wang's (2020) study which stated that subgroup analysis showed that SOFA scores were associated with 28-day and 90-day mortality in patients with AKI undergoing continuous renal replacement therapy (CRRT) [21]. The SOFA score showed a higher predictive accuracy of mortality in critically ill patients with AKI undergoing CRRT than the APACHE-II scores.

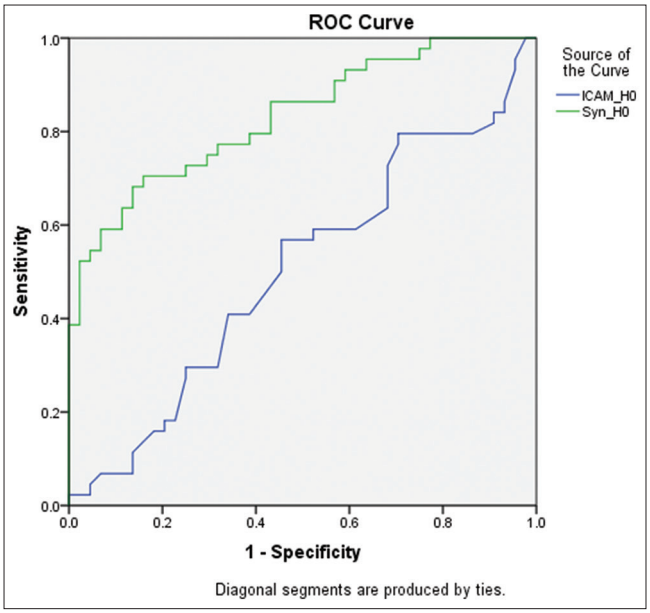

Diagram 1: ROC on day 0

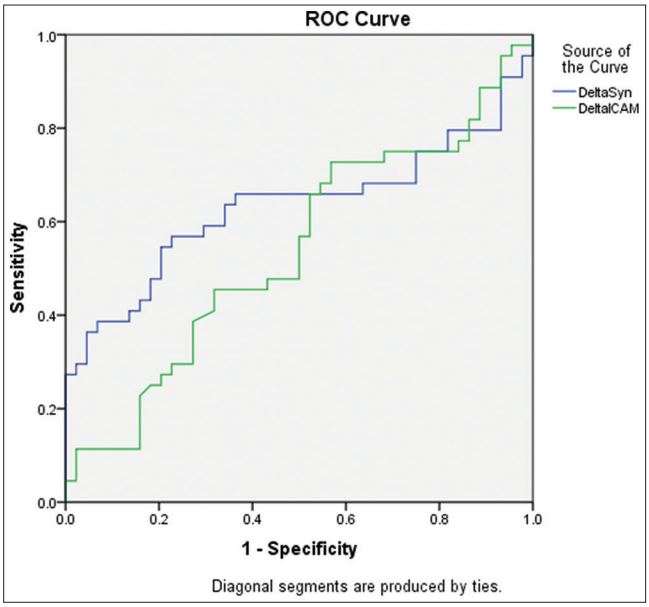

Diagram 3: Change in ROC from admission to day 3

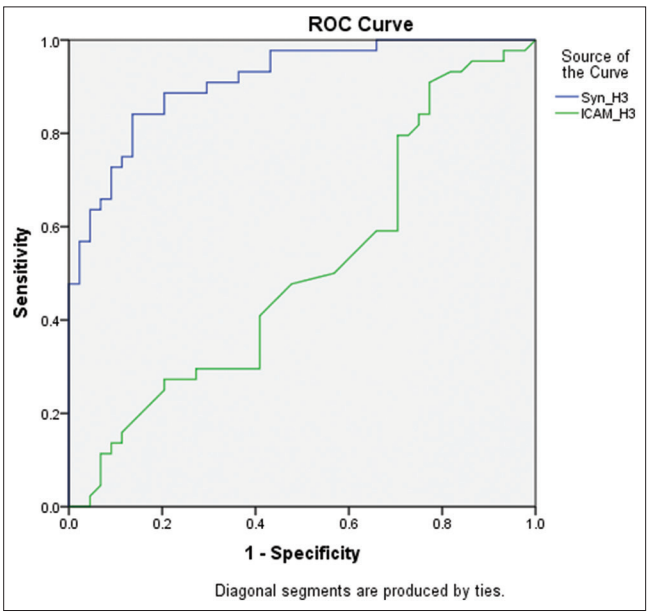

Diagram 2: ROC on day 3

Comparison between groups of variables on day 0 and day 3 ICU care

There was a significant difference in serum syndecan-1 levels between the AKI and non-AKI groups on day 0, which was signed with the Mann–Whitney U-test ($p < 0.001$), and on day 3 of ICU treatment, which was signed with the unpaired t-test ($p < 0.001$). This is consistent with Anand *et al*.'s study of 150 patients with sepsis, severe sepsis, and septic shock who compared their serum hyaluronan and syndecan levels in 50 healthy voluntary subjects. It was found that the levels of hyaluronan and syndecan were higher in the severe sepsis and septic shock groups. It was also found that in the living group, the median hyaluronan and syndecan decreased significantly ($p = 0.001$) on the next measurement (days 3, 5, and 7). ROC analysis for predicting mortality was identified at a cutoff of 898 ng/ml syndecan levels with specificity and negative predictive values of 86% and 91%, respectively [22]. Cavalcante also showed an increase in plasma syndecan-1 associated with severe acute renal impairment and poor outcomes after cardiac surgery [23].

There was no significant difference in serum-soluble ICAM-1 level between septic patients with complications of AKI and those without AKI, both at the time of admission and on the 3rd day of treatment in this study. Taken together, selectins and other adhesion molecules (sICAM-1 and VCAM-1) may serve as markers for detecting generalized endothelial activation due to sepsis. Studies investigating their use as biomarkers reveal that they can be used to monitor endothelial damage of specific organs (such as L-selectin for ARDS) [24]. Soluble ICAM-1 and soluble E-selectin can be used as additional parameters indicating [25]. De Pablo *et al*. showed that glycocalyx damage could be predicted by markers ICAM-1, which at ICU admission, sE-selectin, sVCAM-1, and sICAM-1 in patients with infectious SIRS were significantly higher than that found in patients with non-infectious SIRS [26]. However, the exact function and biological role of soluble adhesion factors are so far unclear; some of the factors that influence their plasma levels are not yet known. Soluble adhesion molecules bind to the activated endothelium and thus cannot be detected by the assay. Therefore, low levels are often associated with disease severity and endothelial activation severity [24].

Comparison of changes between groups in variables from day 0 to day 3 of ICU care

Changes in syndecan-1 levels between the two groups were significantly different through the unpaired

t-test. In contrast, the change in serum-soluble ICAM-1 level between the two groups was not statistically significant through the Mann–Whitney U-test. During sepsis, endothelial glycocalyx degradation occurs through two related release mechanisms: GAG degradation and PG release. In sepsis, both GAG oligosaccharides and PG extracellular domains (ectodomains) circulate, but the precise interactions between GAG degradation and PG release that underlie endothelial glycocalyx degradation are still not fully understood. This release mechanism is activated, including by pro-inflammatory cytokines [27].

Elevated plasma levels of syndecan-1 in severely injured adult trauma patients are associated with subsequent sepsis. At 4 hours after hospital admission, syndecan-1 levels were significantly higher in sepsis patients than in those who did not progress to sepsis (165 ng/dL vs. 70 ng/dL, $p < 0.001$) (Wei *et al*., 2018). Nelson *et al*. showed an increase in the syndecan-1 ectodomain in the blood of septic patients compared to the control group, which was 246 ng/mL (180−496 ng/mL) compared to 26 ng/mL (23−31 ng/mL) [28].

Results of ROC curve analysis of syndecan-1 and soluble ICAM1 levels

In this study, syndecan-1 levels were the best predictor of AKI, while soluble ICAM1 was not. Statistical analysis of septic patient subjects in the ICU showed that the variable syndecan-1 serum was a strong independent factor in the incidence of AKI in ICU patients, but this was not the case with soluble ICAM-1.

Limitation

Limitations of our study included that our study had a limited selection of biomarkers, and several potential markers not measured in this study, such as Ang-2 and P-selectin. Furthermore, due to the limited sample size, we did not assess potential confounding factors such as the use of drugs (such as nephrotoxic antibiotics) that may increase the risk of AKI. An ideal study would include a broader biomarker baseline survey including all subjects in a cohort study. However, our preliminary studies could serve as the basis and lay the groundwork for further investigation of more complete mechanisms and biomarkers.

Conclusions

In this study, syndecan-1 levels are an important measure of glycocalyx damage, statistically proven to predict the future occurrence of AKI in septic patients, whereas sICAM-1 levels were not statistically used to predict the occurrence of AKI among septic patients.

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