Original article

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Relationship of estimated plasma volume and syndecan-1 values to Sequential Organ Failure Assessment (SOFA) score of septic patients in Intensive Care Unit

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Abstract

***Objective*: This study aimed to investigate the relationship between estimated plasma volume values and syndecan-1 levels in relation to Sequential Organ Failure Assessment (SOFA) scores in septic patients in the Intensive Care Unit (ICU).**

***Design*: Cross-sectional study.**

***Setting*: Intensive Care Unit at Wahidin Sudirohusodo Hospital, Makassar.**

***Patients and participants*: A total of 30 patients with sepsis criteria aged 18-65 years and hospitalized in the ICU.**

***Measurement and results*: Measurement of estimated plasma volume status (ePVS), syndecan-1, and SOFA score in the first 24 hours and 72 hours after sepsis diagnosis was established. There was a significant and positive relationship between syndecan-1 and SOFA score measured in the first 24 hours and 72 hours after sepsis diagnosis, with a p-value <0.05. Estimated plasma volume was not significantly related to the SOFA score measured in the first 24 hours and 72 hours after sepsis diagnosis, with a p-value >0.05.**

***Conclusions*: Decreased syndecan-1 levels were strongly associated with decreased SOFA scores in septic patients in the ICU.**

Keywords: Plasma volume estimation, sepsis, SOFA, syndecan-1.

Introduction

Sepsis is a life-threatening organ dysfunction due to dysregulation of the body's response to infection and is associated with morbidity and mortality. (1) The pathogenesis mechanism of sepsis is very complex, and endothelial dysfunction is one of the important factors causing organ dysfunction. (2) Degradation of glycocalyx in sepsis causes the endothelial wall to become thin and sparse. (3,4) Disruption of the glycocalyx layer of the vascular endothelium has been described as one of the major pathophysiological events in the development of shock and multiple organ dysfunction syndrome (MODS) through increased capillary leakage and microthrombus formation, which ultimately leads to tissue hypoperfusion. (5) The Sepsis-3 Consensus recommends the Sequential Organ Failure Assessment (SOFA) to identify organ dysfunction or failure in critically ill patients with suspected infection. The SOFA score describes the level of organ dysfunction over time and can also be used to assess the effect of therapy on the course of organ dysfunction. (5,6)

Serum syndecan-1 is a core protein in heparan sulfate proteoglycans, found in the endothelial glycocalyx and its levels have been used to measure glycocalyx degradation. (7) Serum syndecan-1 levels have been shown to correlate significantly with SOFA scores in patients with sepsis. (8-10) Previ-

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ous clinical studies have shown that high serum syndecan-1 levels are associated with capillary leakage and increased inflammatory markers and correlate with the severity of sepsis. (5,11,12)

Patients with sepsis due to extensive systemic inflammation are at risk of fluid imbalance and the potential for increased capillary leakage. In addition, fluid resuscitation in the early stages of septic shock has the potential consequence of large fluid accumulation. It can result in hypertension, peripheral edema, pulmonary edema, respiratory failure, and increased cardiac workload. (13) Plasma volume, which describes the relationship between interstitial and intravascular spaces, can be used as a marker of volume overload in patients. Duarte et al. have used hemoglobin and hematocrit to estimate plasma volume in patients with heart failure, where high plasma volume values were associated with a poorer prognosis for heart failure patients. The estimated plasma volume status (ePVS) value, compared to Simplified Acute Physiology Score (SAPS) 3 and SOFA scores, can be a simple predictor of the prognosis of critically ill patients with sepsis. The ePVS assessment method is easier to calculate by using only hematocrit and hemoglobin values from the patient's routine blood test results. (14)

In the above context, endothelial damage characterized by increased syndecan-1 and the potential for plasma volume disorders in septic patients, which are thought to contribute to the progression of sepsis as reflected in the SOFA score, this study was conducted to see how the relationship between syndecan-1 and ePVS to the SOFA score in septic patients in the ICU.

Methods

This study used an analytical observational design with a cross-sectional approach. The study population was septic patients treated in the ICU of Wahidin Sudirohusodo Hospital. Samples were taken by consecutive sampling. Inclusion criteria included meeting the criteria for sepsis, characterized by a severe infection accompanied by a > 2-point increase in SOFA score from baseline, aged 18-65 years, and hospitalized in the Intensive Care Unit (ICU). Pregnant women, hemorrhagic shock, had a history of cardiac infarction <24 hours, not post-transfusion patients less than three days, had a history of chronic renal failure, congenital heart disease, hematological disorders, chronic lung disease, malignant disease, systemic autoimmune disease and acquired immune disease, and patients or their families refused to be included in the study, were excluded. The research was conducted at Wahidin Sudirohusodo Hospital, with ethical approval recommendations from the Research Ethics Committee of Hasanuddin University, Wahidin Sudirohusodo Hospital, Makassar, as per letter number 1007/UN4.6.4.5.31/PP36/2024. The research was conducted from January 1, 2025, to April 31, 2025. ePVS, syndecan-1, and SOFA scores were measured in the first 24 hours and 72 hours after the diagnosis of sepsis. The ePVS value was calculated using the formula from Duarte et al., namely ePVS (ml/g) = (100 - hematocrit [%]) / hemoglobin (g/dl). Syndecan-1 was taken from serum samples and measured using a human soluble syndecan-1 immunoassay with an enzyme-linked immunosorbent assay kit. Data analysis was performed using SPSS 27 through the Spearman correlation test.

Results

This study included 30 septic patients with an age range of 19-64 years, with approximately 53.3% of the patients being male. Most patients had a normal body mass index (BMI) and were admitted for various indications for ICU care, including post-laparotomy care, post-neurosurgery care, post-spinal care, and other post-surgical care, as well as non-surgical care due to respiratory tract infections (**Table 1**).

Syndecan-1 levels, ePVS, and SOFA scores experienced a significant decrease in values from the first 24 hours compared to 72 hours after diagnosis with a p-value <0.05 (**Table 2**). Syndecan-1 levels correlated significantly with SOFA scores in the first 24 hours with a strong correlation coefficient of 0.869 with a p-value <0.05, while the ePVS value with SOFA scores in the first 24 hours did not correlate with a p-value >0.05 (**Table 3**). Syndecan-1 levels correlated significantly with SOFA scores in the first 72 hours with a strong correlation coefficient of 0.647 with a p-value <0.05, while the ePVS value with SOFA scores in the first 72 hours did not correlate with a p-value >0.05 (**Table 4**).

The relationship in the high and low procalcitonin groups of the median procalcitonin value in the first 24 hours with the result that in the low group, only syndecan-1 correlated with the SOFA score where the strong correlation coefficient was 0.800 with a p-value <0.05. In the high procalcitonin group, there was a positive correlation between ePVS and the SOFA score with a strong correlation coefficient of 0.748 with a p-value <0.05. Likewise, syndecan-1 also correlated with the SOFA score with a strong correlation coefficient of 0.864 with a p-value <0.05 (**Table 5**).

Discussion

Relationship of syndecan-1 with SOFA score

In this study, a positive correlation was observed

between syndecan-1 and the SOFA score at both 24 hours and 72 hours after diagnosis with sepsis. This finding aligned with research by Zhou et al. in 2022, which revealed a positive correlation between syndecan-1 levels and SOFA scores, with a correlation coefficient of 0.687 at 24 hours of treatment. (15) Similar results were found in a 2016 study by Anand et al., which showed a significant association between syndecan-1 levels and SOFA and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. (9) In contrast to the results of this study, Ostrowski et al. (16) reported no correlation between syndecan-1 and the SOFA score. However, Kajita et al. (2021) denied this, arguing that the difference was related to the time of sampling, which was only captured at one point in time, thus yielding different results. In relation to confounding factors, especially resuscitation fluids, the study by Kajita et al. noted that high syndecan-1 levels in the blood circulation 72 hours after admission to the ICU were closely associated with a positive cumulative fluid balance. The still-high syndecan-1 levels were not only due to ongoing glycocalyx decay but also to the failure of glycocalyx reconstruction. (17)

Syndecan-1 values obtained in the first 24 hours of this study were almost all above 40 ng/dl, and remained elevated even after examination over the next 72 hours. This finding aligned with the results of Hatanaka et al. in 2021. (18) Additionally, a 2011 study by Sallisalmi et al. revealed a strong correlation between syndecan-1 levels and SOFA scores on the first day of patient admission to the ICU, with a correlation coefficient of 0.654. (7)

According to the results of a review of the glycocalyx by Uchimido et al., the dynamics of septic patients who survived were not solely due to fluid management. (4) In a pilot study in cardiac surgery patients by Chappel et al. in 2014, which compared the values of atrial natriuretic peptide (ANP), syndecan-1, heparan sulfate, and hyaluronan, it was found that the loading volume of fluid given significantly increased the mean syndecan-1 from 24.8±8.1 μg/g to 45.4±14.9 μg/g albumin. (4) Likewise, a study by Saoraya et al. (3) found that syndecan-1 levels correlated with the volume of continued fluid administration at 24 and 72 hours. The hypothesis is that the level of glycocalyx damage reflects fluid requirements during early resuscitation, as syndecan-1 is associated with the severity of sepsis and the degree of endothelial damage. (6)

Relationship between ePVS value and SOFA score

The ePVS value in the first 24 hours and the next 72 hours after diagnosis with sepsis did not correlate with the SOFA score in this study. However, the median ePVS value in this study was 7.1 dl/g in the first 24 hours after diagnosis with sepsis, and this value decreased to 5.75 dl/g in the following 72 hours. The high ePVS value in sepsis and septic shock patients in the ICU of Wahidin Sudirohusodo Hospital aligned with the ePVS value obtained in the study by Kim et al. The cut-off from the study by Kim et al. was 7.09 dl/g, and it was stated that death occurred 1.39 times higher in ePVS above 7.09 dl/g. (14) The high ePVS value provides an overview of the potential for increased intravascular volume, which can be correlated with fluid resuscitation as part of the initial management of sepsis, aiming to improve tissue perfusion. This is in accordance with the opinion of Kim et al. in a retrospective study in 2022, which concluded that there was a correlation between the ePVS value and the amount of patient resuscitation fluid before entering the ICU. (14)

The results showed no statistical correlation between ePVS and SOFA scores, possibly because increased ePVS reflected a relative plasma volume excess, although the number of red blood cells remained unchanged. In the context of fluid resuscitation, increased ePVS could indicate overload. But it could only reflect temporary dilution, not true volume excess. Additionally, high syndecan-1 levels on the third day may also indicate that endothelial damage was still ongoing, resulting in a decrease in ePVS. The absence of correlation may be due to the relatively small sample size. The correlation at the initial diagnosis of sepsis, before resuscitation, was a negative correlation between ePVS and SOFA score. However, a prospective study is needed to directly assess how fluid administration affects changes in ePVS values between before and after periods.

In the results of this study, although the decrease in ePVS values did not correlate with SOFA scores either in the first 24 hours or in 72 hours in septic patients in the ICU, there was an interesting finding that in the low procalcitonin group, only syndecan-1 correlated with SOFA scores while in the high procalcitonin group, there was a positive correlation between ePVS and SOFA scores, while syndecan-1 also correlated with SOFA scores. This provided statistical evidence that an increase in syndecan-1 and ePVS was positively associated with an increase in SOFA scores within the first 24 hours. These results, comparing syndecan-1 and SOFA scores, were in line with the study by Zhou et al. Additionally, in the high procalcitonin group, a significant relationship was observed between ePVS values and

syndecan-1, with a correlation coefficient of 0.619. (15) These results provided an illustration that there was a potential correlation between syndecan-1 levels and ePVS values.

These results suggest that although the ePVS value in the predictor test does not provide statistical evidence of an effect on increasing the SOFA score, the statistical relationship in the high procalcitonin group illustrates a positive correlation with the SOFA score. Ultimately, this study provides information supporting the importance of combining several modalities in the management and evaluation of fluid in septic patients.

A limitation of this study was that its design was observational and cross-sectional, which meant it could not establish a causal relationship between variables. Additionally, we did not control several factors, including fluid resuscitation and the type of fluid administered, as well as control over the administration of vasopressors in managing hypotension at the time of initial sepsis diagnosis.

Conclusion

The decrease in ePVS and syndecan-1 levels at 72 hours of septic patient care in the ICU is in line with the decline in SOFA scores at 72 hours of septic patient care in the ICU. Changes in syndecan-1 levels are strongly associated with changes in SOFA scores in septic patients in the ICU. These results suggest that the use of syndecan-1 levels and ePVS values, as modified by Duarte et al., can serve as an additional modality and predictor in early fluid management for septic patients in the ICU, and its use should be combined with other modalities. Further prospective studies are needed with larger samples, serial measurements, and multicenter designs to establish the causal relationship between ePVS, syndecan-1, and SOFA scores in septic patients treated in the ICU.

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Table 1. Characteristics of research subjects

Variable	Frequency (n)	Percentage (%)
Gender		
- Male	16	53.3
- Female	14	46.7
Age (years)		
- 18-25	6	20
- 26-33	5	16.7
- 34-41	3	10
- 42-49	5	16.7
- 50-57	4	13.3
- 58-65	7	23.3
BMI		
- Normal	26	86.7
- Overweight	4	13.3
Indications for ICU care		
- Surgery:		
1. Post-laparotomy surgery	9	30
2. Post-head surgery	12	40
3. Post-spinal surgery	4	13.3
4. Post-other surgery	2	6.7
- Non-surgery:		
Respiratory tract infection	3	10

Legend: BMI=body mass index; ICU=intesive care unit.

Table 2. Comparative data of syndecan-1 levels, ePVS values, and SOFA scores based on measurement time

Variable	24 hours	72 hours	p-value*
	Median (min-max)	Median (min-max)	
ePVS (dl/g)	7.1 (4.9-9.0)	5.75 (2.9-7.6)	0.001
Syndecan-1 (ng/ml)	63.7 (39.8-93.8)	42.25 (39.6-63.8)	0.017
SOFA score	6.0 (3.0-12.0)	4.0 (2.0-9.0)	0.003

Legend: ePVS=estimated plasma volume status; SOFA=Sequential Organ Failure Assessment.
Data were tested using the Wilcoxon signed-rank test. *A p-value <0.05 was considered statistically significant.

Table 3. Correlation of syndecan-1 levels and ePVS with SOFA scores 24 hours after sepsis diagnosis

Variable	SOFA scores	
	r	p-value*
Syndecan-1	0.869	0.001**
ePVS	0.292	0.117

Legend: ePVS=estimated plasma volume status; SOFA=Sequential Organ Failure Assessment.
*significant at $p<0.05$,**significant at $p<0.01$, Spearman correlation test.

Table 4. Correlation of syndecan-1 levels and ePVS with SOFA scores 72 hours after sepsis diagnosis

Variable	SOFA scores	
	r	p-value*
Syndecan-1	0.647	0.001**
ePVS	-0.097	0.610

Legend: ePVS=estimated plasma volume status; SOFA=Sequential Organ Failure Assessment.
*significant at $p<0.05$, **significant at $p<0.01$, Spearman correlation test.

Table 5. Correlation of syndecan-1 levels and ePVS with SOFA scores 24 hours after sepsis diagnosis in high and low procalcitonin groups

Variable	Low procalcitonin group (n=15)		High procalcitonin group (n=15)	
	r	p-value	r	p-value
Syndecan-1 vs SOFA	0.800	0.001*	0.864	0.001*
ePVS vs SOFA	-0.102	0.718	0.748	0.001*
Syndecan-1 vs ePVS	0.093	0.741	0.619	0.014**

Legend: ePVS=estimated plasma volume status; SOFA=Sequential Organ Failure Assessment.
*significant at $p<0.01$, **significant at $p<0.05$, Spearman correlation test.

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