Systemic immune-inflammation index as a marker for septic patients

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Abstract

Objective: **This study aimed to ascertain how procalcitonin levels and the systemic immune-inflammation index (SII) correlate in patients with sepsis.**

Design: **This was a retrospective cross-sectional analysis. Procalcitonin level and total blood count information were taken from the patient's medical file. Neutrophils, lymphocytes, and platelets were used to calculate the SII value.**

Setting: **We conducted this study in the Medical Record Installation at Wahidin Sudirohusodo Hospital from January to December 2023.**

Patients and participants: **Two hundred nineteen septic patients' information was taken from the patient's medical files.**

Measurement and results: **The majority of individuals died (64.8%), were over 65 years old, and were male (58.9%). In nonsurvival sepsis, the median procalcitonin was significantly higher (27.15) ($p<0.05$), and the median SII was significantly lower (2065.7) ($p<0.01$). There was a significant negative correlation between SII values and procalcitonin levels; the higher the procalcitonin level, the lower the SII value ($p<0.01$, $R<0.250$). SII's cut-off from the receiver operating characteristic (ROC) curve was roughly 1131.26×10^9/l, indicating that it might be prognostic, with a sensitivity of 83% and a specificity of 25%.**

Conclusion: **The SII value decreases with increasing procalcitonin levels. With an 83% sensitivity, the initial SII value with a cut-off of 1131.26×10^9/l can be utilized as a marker for sepsis prognosis.**

Key words: Sepsis, SII, procalcitonin.

Introduction

In the development of clinical syndromes, sepsis is characterized by the dysregulation of the body's response to infection, which is linked to both innate and adaptive immune responses. This leads to life-threatening organ failure. (1) According to estimations, sepsis has caused 11 million fatalities since 2017 and 49 million cases each year, or 19.7% of all deaths worldwide. According to the sequential sepsis-related organ failure assessment (SOFA) score, organ dysfunction is defined as acute alterations caused by infection. (2-4) A common test for septic patients is procalcitonin (PCT), a precursor of the calcitonin hormone produced by thyroid C cells. When a bacterial infection occurs, PCT levels are known to rise, and they may fall as the patient recovers. Procalcitonin can be used as a diagnostic tool for infectious events and as a means of differentiating between bacterial and viral inflammation because its production is insignificant in viral infections. (5,6) However, because of limited resources and expenses, not all laboratories can perform this procalcitonin test; hence, easy-to-performed laboratory tests are necessary for earlier sepsis treatment. One of the inflammatory indicators determined by

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neutrophil, lymphocyte, and platelet counts that Hu et al. found in 2014 and that can provide information about the state of systemic inflammation and local immune response is the systemic immune-inflammation index (SII). (7) SII's roles in the prediction of life span in patients with acute renal failure, malignancies, and cardiovascular diseases have been documented. SII levels in septic patients can be an independent predictor of mortality, according to research by Mangalesh et al. (2022). (8,9) Because lymphocytes, neutrophils, and platelets play a crucial part in the immunological response, SII is used to identify individuals who are at risk of developing a serious infection. Because it is a standard blood test, it is quick, easy, and accessible at all medical facilities.

To the best of the researchers' knowledge, SII has not been commonly utilized in septic patients, particularly when combined with procalcitonin, which has been used as a sepsis parameter. However, research on SII in cardiovascular cases, cancers, and coronavirus disease 2019 (COVID-19) has been extensively conducted. Consequently, we were curious to see SII's potential as a marker of sepsis. Thus, by comparing SII with procalcitonin, examining the relationship between SII values and procalcitonin levels and sepsis outcomes, and figuring out the cut-off value of SII in predicting the worsening of septic patients, we hope to explore the potential of SII as a marker in sepsis management.

Material and methods

Settings and design

From January 2023 to December 2023, a retrospective cross-sectional study was carried out at Wahidin Sudirohusodo Hospital's Medical Record Installation using secondary data from the medical records of patients older than 18 years old who were diagnosed with sepsis by the clinicians based on SOFA score. Patients with routine blood examination and procalcitonin data at the time of the initial sepsis diagnosis met the inclusion criteria for this study. Patients with known hematologic malignancies and incomplete medical record data were omitted. The ArchitectPlus ci4100 equipment (Abbott, Germany) was used to quantify procalcitonin levels using the Chemiluminescence Immunoassay (CMIA) method; a normal value is less than 0.05 ng/l.

SII values were derived from the results of regular blood tests, with formula:

SII = (absolute neutrophil count×platelet count)/(absolut lymphocyte) (7)

The SOFA score, displayed in **Table 1**, is the basis for sepsis diagnosis.

Study group

Two groups of participants were: (1) Survivors, those who survived and were released from the hospital, and (2) Non survivors, those who did not survive or passed away following hospitalization.

Data analysis

The statistical software SPSS version 25 was used to analyze the data. The data were tested using the Kolmogorovmirnov test to determine whether they were normal, the Mann-Whitney test for differences, the Spearman correlation test to examine the relationship between SII and procalcitonin, and the receiver operating characteristic (ROC) curve to ascertain the cut-off of SII in patients with sepsis. Results from statistical tests were considered significant if the p-value was less than 0.05. With Ethical Clearance number 438/UN4.6.4.5.31/PP36/2024, the study's ethical feasibility was verified by the Faculty of Medicine, Health Research Ethics Committee-Hasanuddin University Hospital-Wahidin Sudirohusodo Hospital in Makassar.

Results

Summary of the study participants

In this study, 219 participants, 90 females (41.1%) and 129 males (58.9%), were diagnosed with sepsis by medical personnel. The majority (64.8%) passed away, and the age range was 20-93 years, with a mean of 54.4±15.7 years and a median of 55 years. **Table 2** provides an overview of the study participants.

Analysis of the relationship between septic patients' SII score and procalcitonin level

Spearman's correlation test was used for correlation analysis. The findings revealed a significant inverse relationship ($p<0.01$) between procalcitonin levels and SII values in septic patients. The SII value decreased as procalcitonin levels rose. The association between SII and procalcitonin was classified as weak, with a correlation coefficient of $R<0.250$ (**Figure 1**).

Procalcitonin level and SII score analysis on sepsis outcome

The Kolmogorov-Smirnov test was used to determine whether the data was distributed normally. With a mean of 3229.92±2885.30, the SII values ranged from 36.2 to 19531.90 (median 2573.30). Procalcitonin values in the individuals ranged from

0.05 to 200.0 (median 19.30), with a mean of 40.87±52.12.
The procalcitonin and SII data distribution were not normally distributed according to the normality test ($p<0.001$). The median SII score was substantially lower in sepsis non-survivors (2065.7) than in survivors (3412.0) ($p<0.01$), according to the Mann-Whitney test. Non-survivor septic patients had a substantially higher median procalcitonin value (27.15) than survivors (14.40) ($p<0.05$). As indicated in **Table 3**, this points to a substantial correlation between SII values, procalcitonin levels, and septic patient outcomes.
Figure 2 compares procalcitonin levels and SII values according to sepsis outcomes using the Mann-Whitney test. As seen in **Figure 3**, the area under the curve (AUC) of SII was 55%, with a cut-off of 1131.26×10^9/l (sensitivity 83% and specificity 25%), indicating that SII may have prognostic significance.

Discussion

There were 219 participants in this study, with a higher proportion of men than women, more non-survivors than survivors, with the majority being over 65 years old. With a $p<0.01$, the SII value was considerably lower in non-survivor septic patients than in survivors. This supported the findings of a study by Jiang D. et al. (2023), which showed that low SII values were associated with a higher mortality risk within 28 days. SII results will be low due to low platelet and neutrophil numbers. Endothelial dysfunction and organ failure may result from prolonged platelet activation that enhances the inflammatory response.
Theoretically, a low SII score is linked to a bad prognosis and may suggest significant inflammation or myelosuppression. (8)
Based on the body's immune reaction, sepsis is classified into two phases: the hypoinflammatory (immunosuppressive) phase and the hyperinflammatory (cytokine storm) phase. The hyperinflammatory phase, marked by a cytokine storm and an increase in inflammatory markers, is the first stage of sepsis. The body's immune response advances to the hypoinflammatory or immunosuppressive phase after most patients (60%) survive the hyperinflammatory period. During this stage, immunological activity declines as a result of homeostasis. Furthermore, invasive microorganisms are frequently not eliminated by patients, leaving them vulnerable to opportunistic infections that can worsen sepsis. Low SII values in non-survivors can result from neutropenia and thrombocytopenia brought on by this immunosuppression. (10)
The findings of a study by Liu C. et al. (2023) differed. Compared to survivors, non-survivors had significantly higher SII scores. (9) A worse prognosis is linked to an elevated SII score, subtly indicating more significant inflammation (hyperinflammatory phase). (11) Pro-inflammatory cytokines are released during the early stages of sepsis due to a severe inflammatory response. The innate immune system, which includes neutrophils and macrophages, is a quick-acting, nonspecific initial line of defense against infection. T and B cells make up the adaptive immune system, which mounts antigen-specific defenses. Restoring immunological equilibrium and reducing tissue damage and inflammation during infection depends on adaptive immune system reactions. Persistent lymphopenia (≤0.6 cells/µl$\times10^3$) on day 4 following sepsis diagnosis was linked to a higher mortality rate, according to Drewry et al. (2023). The SII value increased as the lymphocyte count decreased. (12)
During sepsis, neutrophils will carry out phagocytosis, oxidative processes, and apoptosis delay, which will compromise immunity and cause ongoing inflammation. As a result, problems arise, and sepsis gets worse. The neutrophil count is consistent with the SII value. (12)
Because of endothelial damage, coagulation system activation, inflammatory response, and direct pathogen interaction with platelet surface receptors, sepsis can result in platelet activation. Increased cytokine levels and endothelial dysfunction are linked to a decreased platelet count in sepsis. Thrombocytopenia is linked to a higher risk of death and the severity of sepsis. Consequently, the SII value decreases as the platelet count decreases. (12)
Because the body's defense mechanism against infectious agents is probably still functioning properly, including neutrophils that can perform phagocytosis functions well so that sepsis can be resolved, the SII value is higher in living subjects. This is further supported by the fact that there are still enough platelets in the body to resolve endothelial injury.
SII and procalcitonin levels in septic patients were found to be significantly correlated negatively ($p<0.01$). The SII value decreases as procalcitonin levels rise. The correlation coefficient indicated a poor association ($R<0.250$) between procalcitonin levels and SII readings.
The research's limitations included failing to consider the underlying illness, the severity of sepsis, and the therapy received.
According to the findings, procalcitonin levels and

SII values in septic patients were negatively correlated; the higher the procalcitonin level, the lower the SII value. As a prognostic indicator, the first SII value with a cut-off of $1131.26\times10^{9}/l$ (83% sensitivity) can be used to show when septic patients are getting worse. Future studies must consider the underlying condition, the severity of sepsis, and how patients receive medication to determine the efficacy of SII.

Declaration of competing interest
No potential conflict of interest relevant to this article was reported.

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Table 1. SOFA score (4)

System	Score				
	0	1	2	3	4
Respiration • PaO2/FiO2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with the help ofres-piration instrument	<100 (13.3) with the help ofrespi-ration instrument
Coagulation • Platelets, $\times 10^3/\mu l$	≥150	<150	<100	<50	<20
Liver • Bilirubin, mg/dl (µmol/l)	<1.2 (<20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	≥12.0 (≥204)
Cardiovascular	MAP≥70 mmHg	MAP<70 mmHg	Dopamine≤5 µg/kg/min or dobutamine (all doses)	Dopamine 5.1-15 µg/kg/min or epi-nephrine≤0.1 µg/kg/min or nore-pinephrine≤0.1 µg/kg/min	Dopamine>15 µg/kg/min or epineph-rine>0.1 µg/kg/min or norepinephrine>0.1 µg/kg/min
Central nervous system • Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Kidney • Creatinine, mg/dl (µmol/l) • Urine output, ml/day	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) <500	>5.0 (440) <200

Legend: SOFA=sequestial sepsis-related organ failure assessment; PaO2=arterial partial pressure of oxygen; FiO2=fraction of inspired oxygen; MAP=mean arterial pressure.

Table 2. Characteristics of the study participants

Characteristics (n=219)	n (%)	Mean±SD	Median (min-max)
Gender			
- Male	129 (58.9)		
- Female	90 (41.1)		
Age (year)		54.4±15.7	55 (20-93)
- ≤35	28 (12.8)		
- 36-45	35 (16)		
- 46-55	49 (22.4)		
- 56-65	43 (19.6)		
- >65	64 (29.2)		
Outputs			
- Non-survivor	142 (64.8)		
- Survivor	77 (35.2)		

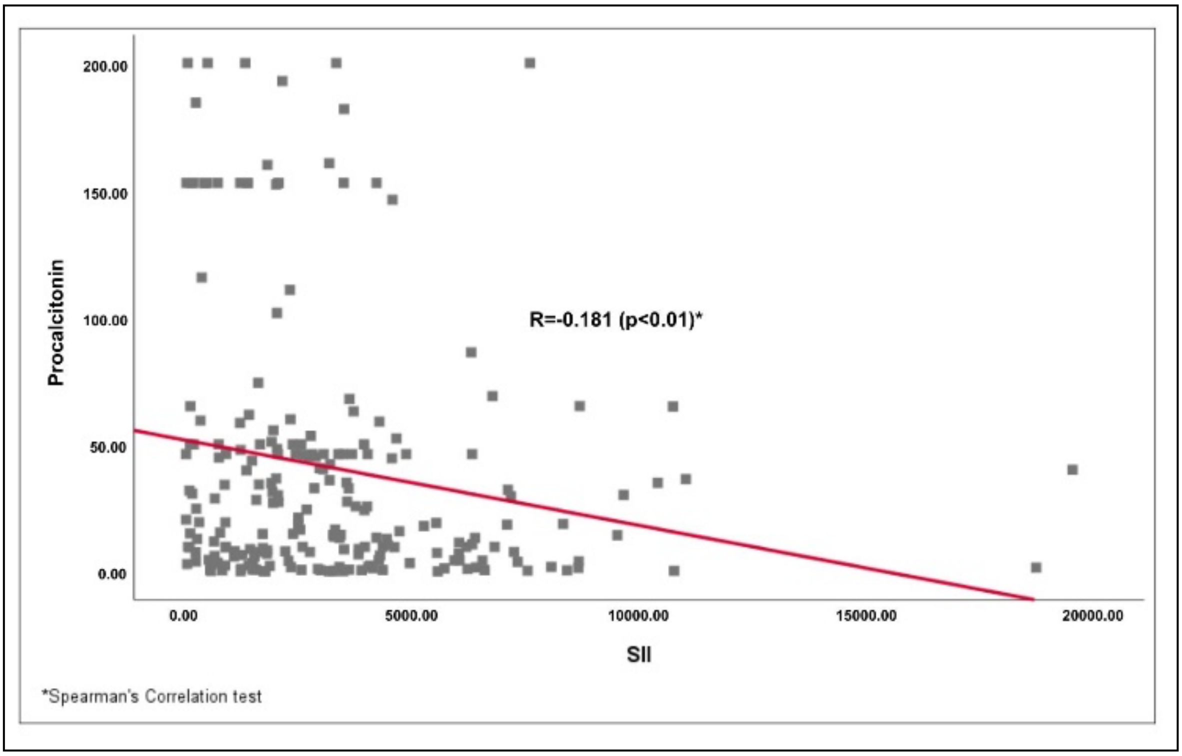
Legend: SD=standard deviation.

Table 3. Comparison of SII and procalcitonin based on sepsis outcomes

Variables		Non-survivor (n=142)	Survivor (n=77)	p
SII ($\times 10^9$/l)	Range	36.20-19531.90	252.80-10747.80	0.002
	Median	2065.70	3412.00	
PCT (ng/ml)	Range	0.05-200.00	0.06-192.95	0.048
	Median	27.15	14.40	

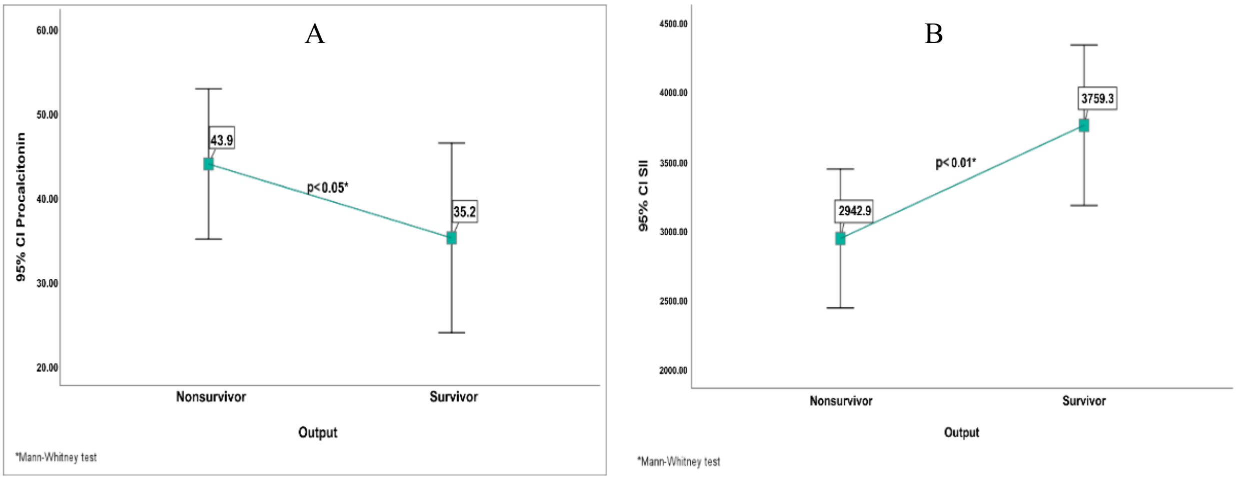
Legend: SII=systemic immune-inflammation index; PCT=procalcitonin.

Figure 1. Correlation between systemic immune-inflammation index values and procalcitonin levels



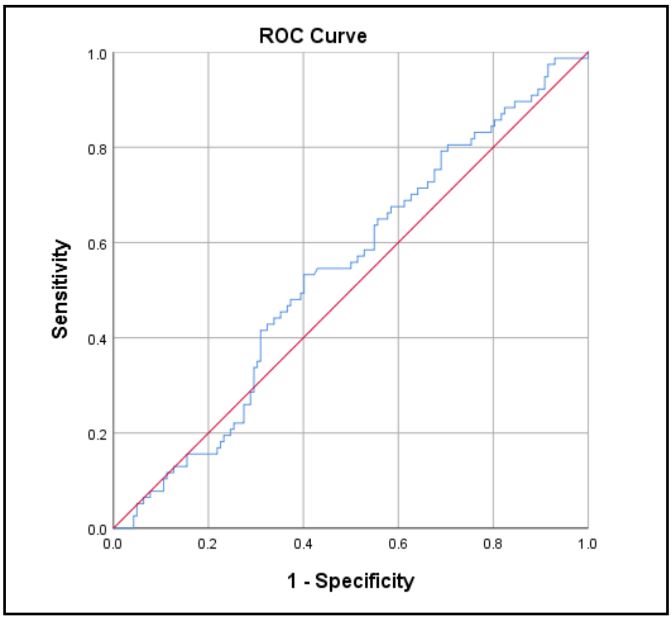
Legend: R=Correlation coefficient.

Figure 2. Comparison of procalcitonin (A) and systemic immune-inflammation index (B) levels by outcome in septic patients



Legend: CI= confidence interval; SII=systemic immune-inflammation index.

Figure 3. ROC curve of SII value



Legend: ROC=receiver operating characteristic; SII=systemic immune-inflammation index.

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