Original article

Crit Care Shock (2025) 28:247–254

Dynamics of inflammatory biomarkers on mortality risk in septic patients admitted to the Intensive Care Unit

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Abstract

***Background*: Sepsis remains a major cause of mortality worldwide. Inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and procalcitonin (PCT) have been proposed as predictors of sepsis severity and outcomes.**

***Objectives*: This study aimed to analyze the dynamics of NLR, CRP, and PCT clearance in relation to mortality risk in intensive care unit (ICU) patients diagnosed with sepsis.**

***Methods*: This retrospective cohort study included 64 septic patients admitted to the ICU of Dr. Wahidin Sudirohusodo Hospital from August to October 2024. Clinical and laboratory data were collected on days 1 and 5. Patients were classified into survivor and non-survivor groups.**

***Results*: NLR and PCT values were significantly higher in non-survivors ($p<0.05$). CRP levels did not differ significantly. Logistic regression showed that NLR and PCT clearance on day 5 were independently associated with increased mortality risk ($p<0.05$).**

***Conclusion*: NLR and PCT may serve as useful biomarkers for mortality prediction in ICU patients with sepsis. Monitoring their dynamics can help guide clinical decision-making.**

Introduction

Sepsis is characterized by suspected or confirmed infection accompanied by clinical and laboratory evidence of organ dysfunction (based on the Sequential Organ Failure Assessment [SOFA] score), as a result of an immune response to infection. Sepsis triggers a systemic cytokine-chemokine response, leading to extensive immune activation and dysfunction, which can manifest as neutrophilia and lymphopenia. (1) In 2017, there were 48.9 million sepsis cases and 11 million sepsis-related deaths worldwide. (2) It is estimated that 2.9 million deaths occur globally each year due to sepsis, 44% of which occur in children under five years old, with one-fourth caused by neonatal sepsis. (3) According to Batara et al. (2018), the incidence of sepsis in Indonesia remains high, at approximately 30.29%, with a mortality rate ranging from 11.56% to 49%. (4)

Acute inflammation, such as infection (sepsis), causes the liver to produce C-reactive protein (CRP), a protein that belongs to the pentraxin family. CRP plays a key role in complement system activation via the C1 complex and is considered a major defense mechanism in humans. CRP is an acute-phase reactant and a sensitive biomarker of sepsis. Its blood concentration rises within 2 hours of symptom onset and peaks within 48 hours. (5,6) According to the Surviving Sepsis Campaign (SSC)

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Guidelines 2016, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Clinically, this is described as a SOFA score increase of ≥2 points, associated with an in-hospital mortality risk of >10%; a SOFA score <9 is associated with a 35% risk of death. (5)

The neutrophil-to-lymphocyte ratio (NLR) reflects the patient's response to inflammatory injury, based on the physiological relationship between neutrophils and lymphocytes under systemic stress, such as in sepsis. Neutrophils are key innate immune cells that rapidly respond to microbial infections and produce high levels of cytokines. Conversely, lymphopenia is a hallmark of sepsis-induced immunosuppression (Drewry et al., 2014). Therefore, NLR is considered a subtle and sensitive marker of inflammation, as it is affected by only minor changes in its numerator and denominator. (7)

Changes in procalcitonin (PCT) levels have been suggested by several studies as a marker of bacterial infection. Numerous studies confirm that PCT-guided antibiotic de-escalation can reduce antibiotic duration and dosage without increasing complications. (8) PCT's usefulness lies in its specificity and sensitivity in identifying bacterial-related inflammation. (9) High and sustained PCT levels in ICU patients have been linked to increased mortality. This study aimed to analyze the relationship between inflammatory biomarkers (NLR, CRP, and PCT clearance) and mortality in ICU patients with sepsis.

Methods

This research was an analytical observational study with a cross-sectional design. The study was conducted by measuring CRP, NLR, and PCT levels in septic patients treated in the ICU of Dr. Wahidin Sudirohusodo General Hospital, Makassar, from August to October 2024.

The study population included septic patients who met the inclusion criteria and were admitted to the ICU of Dr. Wahidin Sudirohusodo Hospital. The inclusion criteria were patients newly admitted to the ICU with a diagnosis of sepsis, aged >18 years, who had CRP, NLR, and PCT tests conducted, and who consented to participate. Exclusion criteria included: absence of CRP and PCT tests within 24 hours after clinical diagnosis of sepsis, patients undergoing or with a history of chemotherapy, and those with hematologic malignancies.

The procedure involved consecutively selecting eligible samples. Each subject was informed about the study's objectives and benefits and signed an informed consent form. Demographic data, age, gender, and diagnosis were collected, followed by clinical examinations and vital sign measurements. Sepsis diagnosis was determined, and venous blood samples were collected at ICU admission, 24 hours later, on day 3, and on day 5. These were tested for complete blood count (to obtain NLR), CRP, and PCT levels. Patient mortality in the ICU was recorded, and data were analyzed.

Results

A total of 32 septic patients were included, with an average age of 51.9 years. Most patients were under 65 years (81.2%), female (56.2%), had dysfunction of one organ (65.6%), and the most common comorbidity was hypertension (18.8%). Outcomes showed that 65% survived and 35% died (**Table 1**).

Neutrophil-lymphocyte ratio

The average NLR upon ICU admission was 16.26±14.70, increased on day 3 to 31.93±83.01, and decreased on day 5 to 21.09±41.23 (**Table 2**). These changes were not statistically significant (p=0.088).

C-reactive protein

CRP decreased from 177.29±118.08 on day 1 to 124.32±119.32 on day 5, which was statistically significant (p=0.013) (**Table 3**).

Procalcitonin

PCT decreased significantly from 26.47±31.07 on day 1 to 21.05±63.21 on day 5 (p=0.001) (**Table 4**).

Positive regression coefficients (B) indicated that increased NLR and PCT were associated with higher mortality, while decreased CRP was also linked to increased mortality. However, based on Wald statistics and p-values, these associations were not statistically significant (p>0.05) (**Table 5**). The proportion of changes in the dynamics of inflammatory biomarkers in ICU patients based on measurements up to day 5 is shown in **Figure 1**.

Discussion

Sepsis is generally triggered by a dysregulated host response to infection and manifests as acute organ dysfunction resulting from an abnormal immune response. (10) Previous studies have shown that the development, progression, and prognosis of sepsis are closely related to the inflammatory response and the immune status of the patient. (11,12) As is well known, neutrophils play a critical role in innate immunity as the first line of defense, providing rapid sensing and elimination of pathogens. Lymphocytes, on the other hand, are essential components of adaptive immunity, offering a broader and more

specific repertoire for antigen recognition. Hence, the NLR reflects the balance between innate and adaptive immunity. Moreover, NLR is an easily accessible biomarker obtained from a complete blood count and has been reported to be associated with various conditions such as inflammation, cerebral infarction, cancer, and trauma. (13–15)

The association between NLR and sepsis shows that leukocytosis and lymphopenia are characteristic features of severe sepsis. NLR has been widely used as an early detection marker and diagnostic indicator for sepsis and is considered more effective than conventional inflammatory markers. (16–18) Two key inflammatory cytokines involved in apoptosis and capable of causing cell lysis —PCT and CRP— increase significantly during bacterial infections. (19) PCT, a 116-amino acid glycoprotein precursor of calcitonin, significantly increases during bacterial infection but rarely during viral infections, making it a sensitive marker for distinguishing bacterial and viral infections. (20)

CRP is an acute-phase protein mainly synthesized and secreted by the liver, which can increase hundreds to thousands of times its normal level within 8–12 hours after microbial invasion or inflammatory stimulation. It gradually returns to baseline following adequate treatment, reflecting the infection's severity to some extent. (21)

Our study was consistent with previous retrospective studies, showing that NLR and PCT levels were significantly higher in non-survivors than in survivors ($p<0.01$), whereas CRP levels did not differ significantly between the two groups. (22) This suggests that NLR and PCT may serve as potential prognostic markers in sepsis, offering an effective stratification tool to assess disease severity and predict outcomes. However, CRP, despite being a major acute-phase protein, did not show a significant correlation with disease severity. (23–26)

A study by Mierzchala-Pasierb et al. found no significant differences in CRP levels across subgroups classified by disease severity. This may be attributed to the fact that CRP peaks 24–48 hours after the onset of infection or tissue injury, limiting its timeliness. (27–29)

This study had several limitations. First, the sample size was relatively small, increasing the risk of selection bias. Second, the pathophysiological mechanisms leading to death in septic patients, such as the hemodynamic effects, were not explored in this study.

Conclusion

Inflammatory biomarkers such as NLR, CRP, and PCT can provide insight into the mortality risk of septic patients. An increase in NLR and PCT levels over five days may enhance the ability to predict mortality in septic patients, while a decline in CRP on day 5 was observed in those who died. These inflammatory markers can serve as practical tools to assess disease severity and prognosis in critically ill septic patients.

Table 1. Sample characteristics

Variable	n	%
Gender		
- Female	18	56.2
- Male	14	43.8
Number of organ dysfunction		
- 1 organ	21	65.6
- 2 organs	8	25
- 3 organs	3	9.4
Comorbidities		
- Diabetes mellitus	3	9.4
- Hypertension	6	18.8
- Diabetes mellitus + hypertension	2	6.3
- Diabetes mellitus + malignancy	2	6.3
- Malignancy	4	12.5
- Tuberculosis + malignancy	1	3.2
- None	14	43.5
Patient outcome		
- Survived	21	65
- Died	11	35

Table 2. NLR differences over time

Variable	n	Min	Max	Mean	SD	p-value
NLR day 1	32	1.51	74.69	16.26	14.70	0.148
NLR day 3	32	4.39	481.00	31.93	83.01	
NLR day 5	32	3.36	243.00	21.09	41.23	

Legend: NLR=neutrophil-to-lymphocyte ratio; SD=standard deviation.

Table 3. CRP differences over time

Variable	n	Min	Max	Mean	SD	p-value
CRP day 1	32	0.21	474.00	177.29	118.08	0.013
CRP day 5	32	4.40	500.00	124.32	119.32	

Legend: CRP=C-reactive protein; SD=standard deviation.

Table 4. PCT differences over time

Variable	n	Min	Max	Mean	SD	p-value
PCT day 1	32	0.18	141.37	26.47	31.07	0.001
PCT day 5	32	0.03	351.37	21.05	63.21	

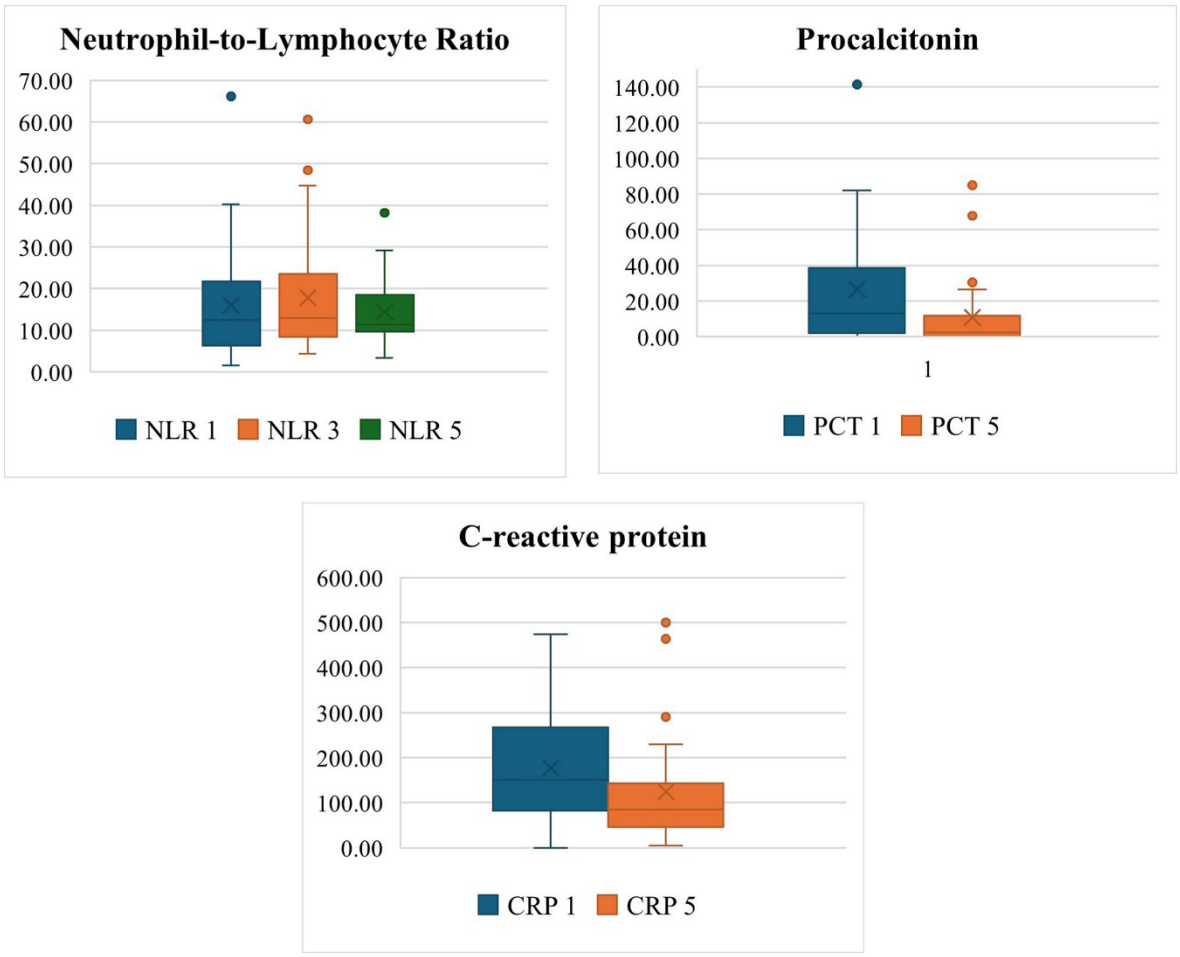
Legend: PCT=procalcitonin; SD=standard deviation.

Table 5. Regression analysis of NLR, CRP, and PCT on mortality

Variable	B	Standard error	Beta	t	Significance
NLR change	.004	.003	.295	1.602	.120
PCT change	-.001	.002	-.082	-.450	.656
CRP change	.000	.001	.109	.578	.568

Legend: NLR=neutrophil-to-lymphocyte ratio; CRP=C-reactive protein; PCT=procalcitonin.

Figure 1. Differences in serum inflammatory marker levels on day 1, 3, and 5



Legend: NLR=neutrophil-to-lymphocyte ratio; PCT=procalcitonin; CRP=C-reactive protein.

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