Original Article

Caspian Journal of Internal Medicine 2025 (Summer); 16(3): 444-450
DOI: 10.22088/cjim.16.3.444

Relationship between eosinopenia and neutrophil-lymphocyte ratio with sepsis-related mortality in the intensive care unit

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Received: 25 March 2023
Revised: 14 June 2024
Accepted: 8 July 2024
Published: 23 June 2025

Abstract

Background: Early diagnosis of sepsis can lead to rapid initiation of treatment and reduced mortality. The aim of this study was to investigate the relationship between eosinopenia and neutrophil-lymphocyte ratio (NLR) with sepsis-related mortality in the intensive care unit.

Results: Out of 100 patients studied, 59 patients survived and 41 patients died and the mean age of the patients was 63.27±16.13 years. Out of 40 patients with eosinopenia, 19(46.3%) died and out of 60 patients with normal eosinophil, 22(53.7%) died (P=0.28). The NLR on the first day in died patients was significantly higher than in the surviving patients (P=0.009). The increase in SOFA Score (p<0.001 and OR=1.49) and the increase in NLR (P=0.02 and OR=3.38) has a direct relationship with the mortality rate.

Conclusion: The results of the present study in sepsis patients showed that patients who had a higher neutrophil-to-lymphocyte ratio had higher mortality and there was no relationship between eosinopenia and mortality rate.

Keywords: Mortality, Sepsis, Eosinophils, Lymphocytes, Neutrophils.

Citation:
Amri P, Nejadnaderi A, Gholinia H, Heidarnia F, Bayani M. Relationship between eosinopenia and neutrophil-lymphocyte ratio with sepsis-related mortality in the intensive care unit. Caspian J Intern Med 2025; 16(3): 444-450.

Sepsis is a life-threatening body response to a severe infection that can trigger a severe immune response, tissue damage, and organ failure (1). The prevalence of sepsis in ICU patients is different, and the mortality rate is 20-60% based on the severity of the disease (2, 3). Sepsis can be caused by many gram-positive, gram-negative, and fungal microorganisms. Early diagnosis of sepsis is essential to reduce patient mortality (4) . A definitive sepsis diagnosis is time-consuming by culturing one of the body fluids, such as blood, spinal fluid, and urine. Thus, clinicians often tend to make such diagnoses based on a variety of biomarkers, such as white blood cell (WBC) count, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-8, platelet (PLT), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels (5, 6). Among the diagnostic tests for sepsis, procalcitonin seem to be the most reliable biomarker in predicting mortality of ICU-admitted patients. However, this test is expensive and time-consuming (more than 24 hours to obtain results) (7, 8). Since eosinopenia is associated with the body's response to acute infection, peripheral blood eosinophil count is another inexpensive and available diagnostic marker that has recently been proven valuable in such clinical settings (9, 10). A significant reduction in the number of circulating eosinophils in acute infection was first proposed by Zappert et al. (11) and was used as an effective diagnostic marker at the beginning of the 20th century. Abidi et al. proved for the first time that eosinopenia is a good marker with high sensitivity and specificity for diagnosing infection in patients admitted to the ICU (12, 13). However, eosinopenia is not a sign of a specific infection but rather a response to acute inflammation (14).

Neutrophil to lymphocyte ratio (NLR) is another inflammatory biomarker used as a marker of systemic inflammation and is defined as dividing the absolute number of neutrophils by the absolute number of lymphocytes.

The NLR can be used as an adjunct test in determining the prognosis of various diseases, such as cancer, pneumonia, and sepsis (15, 16). Several studies have reported that high NLR in peripheral blood smears is associated with poor prognosis and exacerbation of inflammatory diseases (17, 18). The CRP test, on the other hand, is inexpensive, rapid, and available, that can indicate an abnormal state in the body, including infection, 6-8 hours after the exposure, reaching a maximum serum level after 48-72 hours, and decrease rapidly after inflammation resolved (19, 20).

To the best of our knowledge, few studies have been performed about the relationship between the reduction of eosinophil count and survival in critically ill patients in the ICU (21, 22). Thus, the present study evaluated the prognostic value of eosinophil count and Neutrophil to lymphocyte ratio (NLR) in ICU-admitted patients and whether eosinopenia could predict mortality rate in critically ill patients.

Methods

All ICU-admitted patients diagnosed with sepsis at Ayatollah Rouhani Hospital, Babol, Iran, (From April 1, 2018 to April 1, 2019) were included in this cross-sectional study. Patients discharged or died within the first 24 hours of hospitalization and those with a drug history that could affect leukocyte counts were excluded from the study. This study was approved by the Ethics Committee of Babol University of Medical Sciences. After admission into the ICU, age, gender, Glasgow Coma Scale (GCS) and patients' initial health status based on acute physiology and chronic health evaluation II (APACHE II) score (23) and sequential organ failure assessment (SOFA) score (24) were recorded for each patient.

On the first day of hospitalization in the ICU, the number of white blood cells, neutrophils, eosinophils, the neutrophils to lymphocytes ratio and CRP levels were recorded. Finally, the patients were divided into two groups (survived and died). Duration of stay in the ICU and the outcome of patients (mortality within 28 days) were recorded. The eosinopenia (< 0.04× 109/L), neutrophil, lymphocyte count, NLR (≥ 5 vs < 5), and CPR level (≥ 50 mg/L vs < 50 mg/L) were compared among the patients who survived or died.

Statistical analysis: Data were analyzed using SPSS software V. 22. The variables of GCS, APACHE score, SOFA score, eosinopenia, NLR and CRP level in two groups were compared based on the Mann- Whitney U test and the neutrophil count was compared using the t-test method.

The relationship between the survival rate and the number of eosinophils were analyzed based on Kaplan-Meier. Cox regression analysis was used to evaluate the risk of these parameters with mortality. A p-value < 0.05 was considered statistically significant.

Results

During the one-year, 100 patients with sepsis were included in the study and 51 (51.0%) patients were males, and the mean age of the patients was 63.27±16.13 years. Moreover, 41 (41.0%) patients died. The mean Glasgow Coma Scale (GCS) in the survived was significantly higher than in dead patients (p<0.001). Furthermore, the APACHE-II and SOFA scores significantly differed between survived and dead patients. The length of stay in the ICU also differed significantly between the two groups. The NLR on the first day in dead patients was significantly higher than in survived patients (P=0.009) (table 1). Out of the 40 patients with eosinopenia, 19 (46.3%) patients died and out of 60 patients with normal eosinophil, 22 (53.7%) died (P=0.28).There was no significant difference in the relationship between gender and eosinopenia in survived and dead patients (table 2).

The mean survival of patients with eosinophils less than 40 cells/mm3 was 18.06 days with a median of 16 days, and the mean survival of patients with eosinophils greater than 40 cells/mm3 was 19.76 days with a median of 23 days (P=0.44) (figure 1). Based on receiver operator characteristic (ROC) curve (figure 2), the area under the curve for predicting mortality related to eosinopenia was 0.49 (CI= 0.37-0.61) (figure 2).

Based on the table 1, the NLR on the first day in dead patients (10.21±9.51) was significantly higher than in the surviving (6.01±2.62) patients (P=0.009). Based on the table 3 the increase in SOFA score (p<0.001 and HR=1.49) and the increase in NLR (P=0.02 and HR=3.38) were introduced as risk factors of mortality in the sepsis patients. The increase in GCS (P=0.001 and HR=0.74) is a protective factor against death in these patients.

Table 1. Comparison of quantitative variables on the first day of admission in survived and dead patients

Variables	Outcome of patients		P-value*
	Survived, mean±SD N=59	Died, mean±SD N=41	
GCS	12.66±2.12	2.74±2.74	<0.001
APACHE II Score	15.29±5.34	17.80±6.05	0.01
SOFA Score	3.03±2.25	6.20±2.93	<0.001
ICU hospitalization duration, days	16.17±9.12	10.98±5.82	0.01
WBC count, cells/µL	12040.68±6154.08	9753.66±5147.77	0.18
Neutrophil count, cells/µL	9969.44±5525.55	7986.85±4007.29	0.18
Eosinophil count, cells/µL	124.42±129.09	273.00±504.89	0.92
CRP level, cells/µL	47.02±29.19	54.95±30.14	0.16
NLR	6.01±2.62	10.21±9.51	0.009

Abbreviations: GCS, Glasgow coma scale; APACHE II, The acute physiology and chronic health evaluation II; SOFA, Sequential organ failure assessment; ICU, Intensive care unit; WBC, White blood cell; CRP, C-reactive protein; NLR, Neutrophil to lymphocyte ratio. *All p-values were calculated using the Mann-Whitney U test, except for the NLR that was obtained using the student's t-test.

Table 2. Comparison of studied variables in survived and dead patients

Variables	Eosinophil count, × 10^9/L		p-value*	NLR		p-value*	CRP levels, mg/L		P-value*
	≥ 0.04, n (%)	< 0.04, n (%)		≥ 5, n (%)	< 5, n (%)		≥ 50, n (%)	< 50, n (%)	
Male	17 (42.5)	34 (56.7)	0.16	33 (48.5)	18 (56.3)	0.47	5 (43.1)	26 (61.9)	0.06
Female	23 (57.5)	26 (43.3)		35 (51.5)	14 (43.8)		33 (56.9)	16 (38.1)	
Survived	26 (65.0)	43 (71.7)	0.48	35 (51.5)	24 (75.0)	0.02	32 (55.2)	27 (64.3)	0.36
Died	14 (35.0)	17 (28.3)		33 (48.5)	8 (25.0)		28 (44.8)	15 (35.7)	

Abbreviations: NLR, Neutrophil lymphocyte ratio; CRP, C-reactive protein. *All p-values were calculated using the chi-square test.

Table 3. Cox regression analysis of the factors affecting the risk of death

Variables	Mean	HR	95% CI	P-value
Eosinopenia	0.60	0.70	0.34-1.46	0.34
GCS	11.71	0.74	1.28-1.77	0.001
APACHE-II	16.32	0.93	0.88-1.05	0.15
SOFA	4.33	1.49	1.28-1.77	< 0.001
NLR	0.68	3.38	1.18-9.69	0.02
CRP	0.58	0.73	0.32-1.67	0.46

Abbreviations: OR, Hazard ratio; GCS, Glasgow coma scale; APACHE II, The Acute physiology and chronic health evaluation II; SOFA, Sequential organ failure assessment; CRP, C-reactive protein; NLR, Neutrophil to lymphocyte ratio.

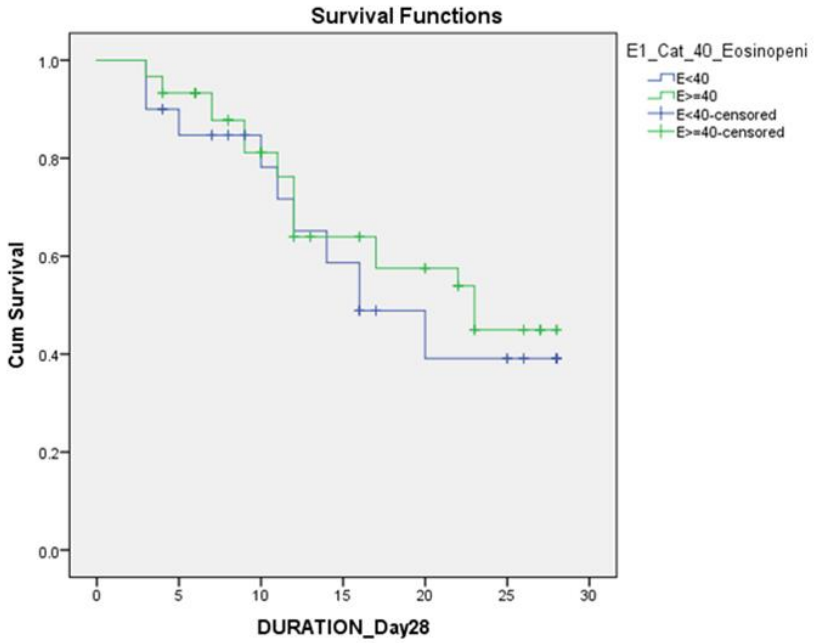

Figure 1. Survival chart of patients based on (E) eosinophil count and Kaplan-Meier survival analysis

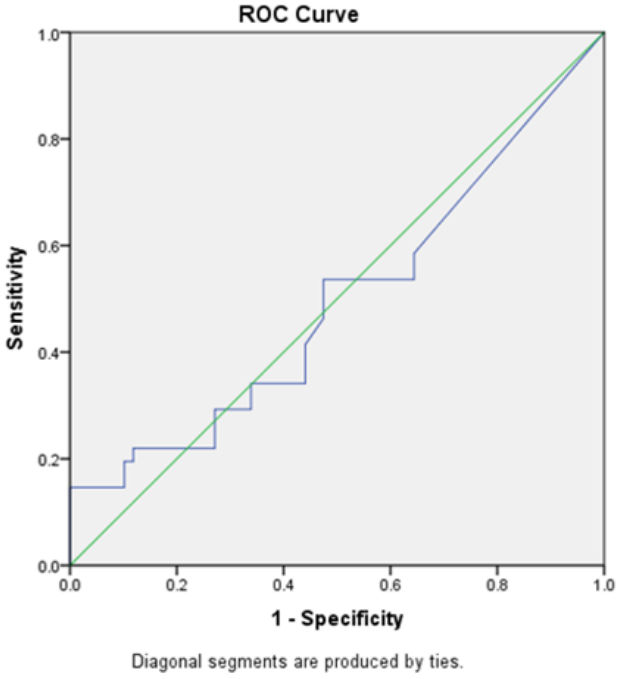

Figure 2. ROC curve shows the relationship between the sensitivity and specificity of eosinopenia

Discussion

Sepsis is one of the most common causes of treatable death. Early diagnosis and appropriate treatment of patients with sepsis can reduce mortality (23). The aim of this study was to investigate the relationship between eosinopenia and the neutrophil to lymphocyte ratio (NLR) in the mortality rate of patients with sepsis. According to the results of the present study, the mean GCS score was significantly lower in dead patients with sepsis. Furthermore, the mean scores of APACHE-II and SOFA were higher in dead patients. In this study, based on the definition of eosinopenia, eosinophil counts were subdivided into less than or greater than 40 cells/mm3 better to assess the relationship between the variables and this index. The prevalence of eosinopenia in the studied patients was 40%. The mean survival of patients with eosinophils less than 40 cells/µL and greater than 40 cells/µL on the first day was not significantly different (18.06 vs 19.76 days).

Infection-induced eosinopenia appears to be secondary to adrenal corticosteroid stimulation due to infection-related stress. Nonetheless, such decrease may also be due to the sequestration of peripheral eosinophils by localization in inflammatory areas caused by chemotactic substances released during the acute phase, drainage of lymph nodes or spleen, with extensive intravascular migration or peripheral destruction of eosinophils, inhibition of mature eosinophil excretion from bone marrow, and inhibition of eosinophil production (12-14). In a similar study, Ali et al. found that eosinophil counts of less than 50 cells/mm3 at the time of ICU admission were a predictive factor of sepsis in critically ill patients. However, eosinophil count at the time of ICU admission was not a specific determinant of mortality(24). Similar to our study, in a study on 160 patients with sepsis in 2014, Garnacho-Montero reported no evidence of diagnostic or prognostic value for eosinopenia on the first day of ICU admission (27). Setterberg et al. found no association between eosinophils and the diagnosis of bacteremia and concluded that the absence of eosinophils in peripheral blood could not be used as a reliable clinical marker for bloodstream infection (28). It seems that the main reason for the similarity of the results of these studies with our study is the inclusion and exclusion criteria and the method of study.

Contrary to our study, Kulaylat et al. introduced eosinopenia as a potential marker for determining the severity and risk of mortality in patients with infection admitted to the ICU and suggested further investigations (25). Joy et al. (2020) showed that eosinophil counts of less than 50 cells/mm3 are a highly specific marker but have low sensitivity for differentiation between SIRS and sepsis; and normal eosinophil does not reject sepsis. However, they questioned the role of eosinopenia in determining the possibility of mortality (26). In a study with results contrary to the present results, Rahimirad et al. stated that the prevalence of eosinopenia in discharged and dead patients was 30.7% and 69.3%, respectively. Based on the results of this study, blood eosinophil count can be considered a simple and inexpensive marker to determine the severity of the disease and mortality in patients admitted to the ICU (22). According to the study of Hota et al., eosinophil count is a simple and effective diagnostic marker in patients with sepsis (27). Abidi et al. in Morocco showed that eosinopenia is an excellent diagnostic marker for the differentiation of infectious and non-infectious diseases but is an average marker for differentiating between SIRS and infection in critically ill patients recently admitted to ICU. They showed that an eosinophil count of fewer than 40 cells/mm3 was independently associated with a higher mortality risk. Counting the number of eosinophils at admission and during the first seven days of ICU admission can be used as a marker to predict mortality in critically ill patients recently admitted to ICU and can be a helpful tool in the ICU (21). It seems that the difference in opinions about the relationship between eosinopenia and mortality is probably due to the difference in the race of humans, or the type of microbes that cause sepsis, or the difference in the underlying diseases of the patients.

In our study based on the ROC curve analysis to investigate the relationship between the survival rate and the number of eosinophil of patients with sepsis on the first day of hospitalization in the intensive care unit, considering the level under the graph is less than 0.7, the cut-off point cannot be determined. As a result, eosinopenia cannot be used as a marker of morbidity and mortality. One of the strengths of our study is evaluating the neutrophil-to-lymphocyte ratio (NLR) index in the sepsis patients. According to the results, the NLR on the first day of admission was significantly associated with higher mortality in patients. The NLR was greater than 5 in 80% of daed patients. An increase in NLR seems to indicate a more severe inflammatory response of the immune system in response to infections and thus predicts higher mortality. In the study of Liu et al., the NLR in died patients was higher than in survived patients (28), which is consistent with the results of the present study. A study by Ljungström et al. found that the NLR counts higher than 5 indicates more mortality. They concluded that combination of biomarkers could improve the diagnosis of confirmed bacterial sepsis in critically ill patients (29).

However, a study by Westerdijk et al. concluded that the NLR was less appropriate than conventional inflammatory markers for diagnosing sepsis in ICU patients (30). It seems that the reason for the difference in the conclusion is the difference in the race of the patients, and perhaps the simultaneous measurement of APACHE and SOFA score in our study has increased the accuracy of the present study. In multivariate Cox regression analysis, changes in CRP did not affect mortality in patients with sepsis. In a similar study like our study, Liu et al. found no statistical difference in CRP between survived and dead patients (30). In another study, Garnacho-Montero et al. reported that CRP poorly predicts sepsis patients' outcomes (31). However, our study showed that eosinopenia and CRP cannot be used as single indicators to determine the prognosis; they can be helpful in combination with the patient's general condition and other clinical indicators. The results of multivariate Cox regression analysis showed that a decrease in GCS can increase mortality in patients with sepsis, while an increase

in SOFA score and an increase in NLR are risk factors for mortality in these patients. An increase in SOFA and Apache scores indicates more organ involvement and, as a result, higher mortality.

However, in our study, SOFA score had a greater relationship in sepsis patients. The strengths of the present study include the simultaneous evaluation of the Glasgow Coma Scale (GCS), acute physiology and chronic health evaluation (APACHE II), and the Sequential Organ Failure Assessment (SOFA) Score in examining mortality in patients with sepsis. This study is one of the few studies that evaluated patient survival based on eosinopenia, CRP levels and NLR; therefore, the possibility of comparing the results is primarily limited.

The limitation of the present study was that the study was conducted in one center, and if it was conducted in a multicenter, its validity would be higher. The results of the present study showed that there is no relationship between eosinopenia and mortality in sepsis patients admitted to ICU. Patients who have a higher neutrophil-to-lymphocyte ratio will have higher mortality. The neutrophil NLR could be an effective marker in the prognosis of patients with sepsis.

Acknowledgments

The researchers would like to express their gratitude to the Research Center of Babol University of Medical Sciences, the esteemed officials of Ayatollah Rouhani Hospital in Babol, and all the dear ones who helped the researchers conduct this study.

Funding: This study was supported by the Vice-Chancellery for Research and Technology of Babol University of Medical Sciences (grant code: 9809126).

Ethics approval: This study was approved by the Research Ethics Committee of Babol University of Medical Sciences (code: IR.MUBABOL.REC.1398.362).

Conflict of interests: There is no conflict of interest to be declared.

Authors' contribution: All authors contributed to this project and article equally. All authors read and approved the final manuscript

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