

The relationship between neutrophil lymphocyte ratio and 28-day mortality in intensive care patients

Hamit Yildiz

Department of Critical Care and Internal Medicine, Gaziantep University, Turkey - E-mail: drhyildiz@hotmail.com

Summary. The aim of this study is to investigate the relationship between neutrophil to lymphocyte ratio (NLR) at admission to ICU and 28-day mortality in patients with sepsis and septic shock, which is an important cause of mortality in the intensive care unit (ICU). Data of consecutive 398 patients with sepsis and septic shock who interned to ICU were retrospectively reviewed and included in the study. NLR, 28-day mortality and other laboratory datas were collected retrospectively from the ICU archive. 111(27.89%) patients died within 28 days after admission to ICU. NLR was higher in patients with sepsis group ($p<0.01$). However, 28-day mortality was higher in septic shock group ($p<0.001$). There was no significant relationship between NLR at admission to ICU and 28-day mortality ($p>0.05$). Patients with sepsis admitted to ICU were found to have higher NLR at admission. This study supports that NLR at admission has no effect on 28-day mortality.

Key words: neutrophil to lymphocyte ratio, sepsis, intensive care, 28-day mortality

Introduction

Nowadays, sepsis is the most serious disease that can present both as an indication for hospitalization and as a complication during hospitalization. Despite the use of broad-spectrum antibiotics and all supportive treatments, mortality varies between 30-70% (1,2). Sepsis is defined as uncontrolled systemic inflammatory response of the host to infection (3,4). As sepsis progresses, morbidity and mortality rate increase (5,6). Therefore, early diagnosis is very important in terms of preventing tissue damage and preventing the development of multiple organ failure. Early diagnosis of the disease allows to detect the source of infection in a short time, to start the necessary antibiotherapy and to prevent the development of multiple organ failure.

In recent years, neutrophil lymphocyte ratio has been found to be an indicator of systemic inflammation and is associated with prognosis in many cardiovascular diseases, malignancies and chronic inflammatory diseases. Studies have been reported to correlate

with erythrocyte sedimentation rate (ESR), C-reactive rate (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) values (7-9).

The aim of this study is to investigate the usefulness of neutrophil lymphocyte ratio, which is a practical, inexpensive and easily accessible test for the prognosis determination and follow-up of sepsis known to have inflammation as the its pathogenesis, as a predictor of 28-day mortality.

Materials and Methods

A total of 398 patients with sepsis and septic shock diagnosed by internal medicine intensive care unit between March 2017 and June 2019 were included in this study. Patients who fulfilled the criteria of sepsis, which were declared by the European Society of Intensive Care for at least 24 hours, were included in the study. Younger than 18 year-old, neutropenic, granulocyte colony stimulating factor treatment

for any reason, patients with a history of malignancy and known rheumatic disease were excluded from the study. Demographic data, 28-day mortality, neutrophil lymphocyte ratio, leukocyte count, hemoglobin level platelet count, acute phase reactants and other biochemical parameters were obtained by examining the files of the patients.

In this study, the data were analyzed by using the histogram, Kolmogorov-Smirnov and Shapiro-Wilk tests. The data did not have a normal distribution were given as median (minimum/maximum). Destructive statistics of categorical measurements were given as frequency and percentage [n(%)]. Mann-Whitney U test to compare continuous variables that did not fit the normal distribution between the groups. Non-parametric Spearman's correlation test was used to determine the relationship between continuous variables. SPSS 24.00 (for Windows) was used for statistical analysis. The data was evaluated at 95% confidence interval and $p < 0.05$ was considered significant.

Results

The patients were divided into two groups as sepsis (group 1) and septic shock (group 2). Of all patients included in the study, 155 (38.9%) were female and 243 (61.1%) were male. The median age of all patients was 66 (51.75/76) years. 68 (55.76%) of the patients in group 1 were female and 121 (55.76%) were male. The median age of group 1 patients was 67 (52/76) years. 87 (32.60%) of the group 2 patients were female and 122 (67.40%) were male. The median age of group 2 patients was 62.50 (49/76) years. The 28-day mortality of group 1 patients was 36.87% and the 20-day mortality of the group 2 patients was 61.88%. The exitus rate in group 1 was 73.06% ($n = 217$), whereas the exitus rate in group 2 was 73.06% ($n = 181$) ($p: 0.012$). There was a statistically significant difference between the groups in terms of 28-day mortality ($p: 0.01$). The comparison of group 1 and 2 patients in terms of NLR, leukocyte count, hemoglobin level and platelet count is given in table 1. NLR was found statistically higher in group 1 than group 2 patients ($p < 0.001$). The comparison of the group 1 and 2 patients in terms of biochemical laboratory changes is given in table 2. Table 3 shows

the relationship between neutrophil lymphocyte ratio and 28-day mortality at admission.

Discussion

Sepsis is a life-threatening clinical syndrome caused by uncontrolled response to infection and multiple organ failure due to organ dysfunction. During sepsis syndrome, the pathophysiology of which is not fully understood, various disorders develop and these disorders are evaluated with some criteria. In sepsis syndrome, changes such as leukocyte counts $< 4.000 \mu\text{L}$ or $> 12.000 \mu\text{L}$ or more than 10% immature band cells may occur. The number of white blood cells during sepsis may vary depending on the stage of sepsis or septic shock, the immunological status of the patient and the etiology of the infection.

Early diagnosis of sepsis is very important for reducing morbidity and mortality. Although microbiological culture is accepted as the gold standard method for the diagnosis of sepsis, it can be both time consuming and misleading. There is a risk of false negativity due to antibiotic use prior to culture or false positivity due to contamination during culture. In recent years, new tests and markers have been discovered to detect bacteremia and sepsis which are very fast and cost effective. In the daily evaluation of patients with sepsis, new markers are emphasized beyond the commonly used acute phase reactants such as C-reactive protein and procalcitonin (10). Neutrophil lymphocyte ratio is an indicator of inflammation that can be easily obtained from whole blood count. Although there are various data suggesting that NLR is associated with negative survival in malignancy and cardiovascular disease, there is no consensus yet in patients with sepsis (11-13).

In this study, NLR was found to be higher in patients with sepsis than patients with septic shock. This may be interpreted that there is not correlation between disease activity and NLR in patients with septic patients. However, increased cytokine synthesis during periods of severe sepsis and septic shock may disrupt the functions of the immune system cells and may cause this proportional change not to increase further (14). Therefore, it may be more beneficial to establish NLR at admission that follow-up. Although the relationship between mortality and NLR in pa-

Table 1: Comparison of the groups in terms of neutrophil lymphocyte ratio, leukocyte count, hemoglobin level and platelet count

| | Group 1 (n=217) | Group 2 (n=181) | P |
|-------------------------|-------------------------|-----------------------|--------|
| NLR | 22.71(0.01/615.38) | 14.42(2.04/412.80) | <0.001 |
| Leukocyte count (μL) | 13.830(4260/71970) | 16.035(4770/84750) | 0.039 |
| Hemoglobin level (g/dL) | 10.30(2.90/20.20) | 10.6(6.80/17.10) | 0.068 |
| Platelet count (μL) | 171.000(14.000/647.000) | 147.500(9.000/695000) | 0.113 |

Table 2: Comparison of groups in terms of biochemical laboratory changes

| | Group 1 (n=217) | Group 2 (n=181) | P |
|-----------------------|---------------------|--------------------|-------|
| Glucose (mg/dL) | 153(47/11183) | 153(47/11183) | 0.762 |
| Urea (mg/dL) | 113(5.41/527) | 81.9(15/232.90) | 0.663 |
| Creatinine (mg/dL) | 2.15(0.31/10.28) | 0.90(0.27/8.33) | 0.804 |
| Albumin (g/dL) | 2.8(1.3/4.2) | 3.1(1.8/4.0) | 0.712 |
| GGT (U/L) | 65(10/2381) | 77(18/1181) | 0.716 |
| LDH (U/L) | 506.50(127/22801) | 487(119/2801) | 0.380 |
| Phosphorus (mg/dL) | 406(1.04/17.70) | 388(10.1/14.10) | 0.025 |
| ESR (mm/saat) | 48(2/144) | 44(2/132) | 0.804 |
| CRP (mg/L) | 176.87(4.87/578.78) | 67.58(1.68/379.46) | 0.654 |
| Procalcitonin (ng/mL) | 24.72(10.05/125.43) | 14.48(9.12/99.47) | 0.181 |
| Magnesium (mg/dL) | 2.20(0.6/4.80) | 2.20(0.6/4.80) | 0.738 |
| Calcium (mg/dL) | 8.3(2.8/10.7) | 8.25(2.40/12.8) | 0.521 |
| AST (U/L) | 65.5(6/6227) | 40.5(10/2357) | 0.273 |
| ALT (U/L) | 28(1/4229) | 21(3/429) | 0.421 |
| ALP (U/L) | 126(12/2493) | 11550(1271) | 0.573 |
| Globulin (g/L) | 3.4(1,2/4.3) | 3.09(1.70/4.40) | 0.549 |
| Uric acid (mg/dL) | 8.05(2/17.8) | 5.60(0.90/21) | 0.594 |

Table 3: Relationship between neutrophil lymphocyte ratio and 28-day mortality at admission to ICU

| | r | p |
|--------------------------------|-------|-------|
| Group 1 NLO – 28-day mortality | 0.085 | 0.186 |
| Group 2 NLO – 28-day mortality | 0.005 | 0.954 |

tients with sepsis has been investigated, the predictive value of the NLR measured at admission and how it changes in the early period are not well understood (15,16). In a prospective study conducted by Smart et al. involving patients with requiring intensive care hospitalization, it has been found that high NLR measured in emergency department has an independent relationship with hospital mortality and 6-month mortality (17). In addition, high NLR was associated with multiple organ failure and sepsis as a risk factor.

In a recent study conducted by Riche et al, it has been reported that there is relationship between NLR and risk of death in patients with sepsis (16). However, there are studies in the literature in which there is no relationship between NLR and mortality in patients with sepsis (15). As a matter of fact, in this study, no statistically significant relationship was found between NLR and 28-day mortality in both sepsis and septic shock patients.

There are some limitations in this study. The limitations of our study are retrospective planning and lack of data on microorganisms that may cause myelosuppression. Prospective studies involving a higher number of patients in this area are needed to identify and compare possible microorganisms that may affect hematopoietic cell production in bone marrow.

Conclusion

Neutrophil lymphocyte ratio, which is an easy and inexpensive method to be obtained in intensive care units can use as an inflammatory marker. Using NLR at admission to ICU is not recommended for monitoring disease activity in patients with sepsis. No correlation was found between NLR and 28-day mortality in this study.

References

1. Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N. Eng J Med* 1999;340:207-14
2. Heyland DK, Hopman V, Coe H, et al. Long-term health related quality of life in survivors of sepsis. *Crit Care Med* 2009;37:3599-605
3. Bone RC, Balk RA, Cerra FB, et al. American Collage of Chest Physicians Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use innovative therapies in sepsis. *Crit Care Med*. 1992;20:864-874.
4. Hotchkiss RS., Karl JE. The pathophysiology and treatment of sepsis. *N Eng J Medicine* 2003;348:138-150.
5. Salvo I, Cian W., Musicco M., et al. The sepsis study group. The Italian sepsis study: preliminary results on the incidence and evolution of SIRS, sepsis, severe sepsis and septic shock. *Intensive Care Med*. 1995;21:244-249
6. Muckart DJJ, Bhagwanjee S. American Collage of Physicians/Society of Critical Care Medicine Consensus Conference: definition of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. *Crit Care Med* 1997;25:1789-1795
7. Buyukkaya E, Karakas MF, Karakas E, et al. Correlation of neutrophil to lymphocyte ratio with the presence and severity of metabolic syndrome. *Clin Appl Thromb Hemost* 2014;20:159-63
8. Turkmen K, Erdur Fm, Ozcicek F, et al. Platelet-lymphocyte ratio better predicts inflammation than neutrophil-lymphocyte ratio in end-stage renal disease patients. *Hemodial Int* 2013;17:391-6
9. Imtiaz F, Shafique K, Mirza SS, et al. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med* 2012;5:2.
10. Kawczynski P, Piotrowski A. Procalcitonin and C-reactive protein as a markers of neonatal sepsis. *Ginekol Pol* 2004;75:439-44
11. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratislavske Lekarske Listy*, vol.102, no.1, pp. 5-14,2001.
12. Kang MH, Go SI, Song HN. The prognostic impact of the neutrophil to lymphocyte ratio in patients with small cell lung cancer. *British Journal of Cancer*, vol. 111, no.3, pp. 452-460,2014.
13. Ayça B, Akın F, Celik O, et al. Neutrophil to lymphocyte ratio is related to stent thrombosis and high mortality in patients with acute myocardial infarction. *Angiology*, vol. 66, no. 6, pp. 545-552,2015.
14. Makino I, Tajima H, Kitagawa H, et al. A case of severe sepsis presenting marked decrease of neutrophils and interesting findings on dynamic CT. *Am J Care Rep*. 2015; 16: 322-327.
15. Saliccioli JD, Marshall DC, Pimentel MA, et al. The association between the neutrophil to lymphocyte ratio and mortality in critical illness: an observational cohort study. *Crit Care* 2015;19:13
16. Riche F, Gayat E, Barthelemy R, et al. Reversal of neutrophil-to-lymphocyte count ratio in early versus late death from septic shock. *Crit Care* 2015;19:439
17. Akilli NB, Yortanlı M, Mutlu H, et al. Prognostic importance of neutrophil-lymphocyte ratio in critically ill patients: short- and long-term outcomes. *Am J Emerg Med* 2014;32:1476-80

Correspondence:

Hamit Yildiz, Assist Prof Dr
Department of Critical Care and Internal Medicine, Gaziantep University, Turkey
Kilisyolu Uzeri, Sahinbey, 27310, Gaziantep
Tel. +90 342 3606060
E-mail: drhyildiz@hotmail.com