Evaluation of the Association Between the Neutrophil to Lymphocyte Ratio and Mortality in the Patients Followed up with the Diagnosis of Sepsis

Sepsis Tanısıyla Takip Edilen Hastalarda Nötrofil Lenfosit Oranı ile Mortalite Arasındaki İlişkinin Değerlendirilmesi

The Association Between Neutrophil to Lymphocyte Ratio and Mortality in Sepsis

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Özet

Amaç: Nötrofil lenfosit oranı (NLR) tam kan sayımından kolayca ölçülebilen bir biyomarkerdır. NLR'nin daha önce birçok kanser türünde yaşam oranını tahmin etmedeki gücü araştırılmıştır. Ancak sepsis tanısıyla izlenen hastalardaki mortaliteyi tahmin etmedeki gücü ile ilgili yapılmış az sayıda çalışma mevcuttur. Bu çalışma ile amacımız NLR ile yoğun bakım ünitesinde (YBÜ) sepsis tanısıyla izlediğimiz hastaların mortalitesi arasındaki ilişkinin değerlendirilmesidir. Gereç ve Yöntem: 1 Eylül 2014- 31 Aralık 2015 tarihleri arasında hastanemiz dahiliye yoğun bakım ünitesinde sepsis tanısı ile izlenen hastalar retrospektif olarak değerlendirildi. Her hastaya ait demografik, klinik ve laboratuvar verilerine medikal kayıtlardan ulaşıldı. Bulgular: Toplam 104 hasta çalışmaya dahil edildi. Yoğun bakım ünitesinde mortalite oranı %57.7 idi. YBÜ'sinde yaşayan ve ölüm gerçekleşen hastalar nötrofil sayısı, lenfosit sayısı ve NLR yönünden değerlendirildiğinde istatiksel olarak anlamlı bir fark saptanmadı (p>0.05). Yaşayan ve ölüm gerçekleşen hastalar değerlendirildiğinde eritrosit dağılım hacmi (RDW), C reaktif protein (CRP), total bilirubin, INR değerleri her iki grup arasında istatiksel olarak anlamlı bulundu (p<0.05). NLR quartillere ayrıldığında NLR quartilleri arttıkça YBÜ'sinde mortalite oranı artmakla birlikte quartiller arasında mortalite yönünden anlamlı bir fark saptanmamıştır (tüm p>0.05). Hastalar 6 ay sonu mortalite yönünden değerlendirildiğinde NLR ile arasında anlamlı bir ilişki saptanmadı (p>0.05). Tartışma: Çalışmamızda sepsis hastalarında NLR ile YBÜ'sindeki mortalite oranı ve uzun dönem mortalite oranı arasında anlamlı bir ilişki bulunmamıştır.

Anahtar Kelimeler

Nötrofil Lenfosit Oranı; Sepsis; Mortalite

Abstract

Aim: Neutrophil-to-lymphocyte ratio (NLR) is an easily measurable biomarker from complete blood count. NLR has been investigated previously as a potential predictor of survival rates in various types of cancers. However, there is a limited number of studies performed regarding the usefulness of NLR for predicting mortality in patients with sepsis. Our aim in this study was to evaluate the association between NLR and mortality of the patients with sepsis in an intensive care unit (ICU). Material and Method: We retrospectively assessed the patients who were followed up with the diagnosis of sepsis in the internal medicine ICU of our hospital between September 1, 2014 and December 31, 2015. Demographic, clinical, and laboratory data were obtained from the patients' medical records. Results: A total of 104 patients were included in the study. ICU mortality was 57.7% in patients with sepsis. When survivors and non-survivors in theICU were assessed regarding neutrophil counts, lymphocyte counts, and NLR, no statistically significant difference was determined (p>0.05). While the mortality rate in ICU increased with increasing quartile of NLR, no significant difference was determined in ICU mortality (all p>0.05). Also there was no relationship between NLR and hospital mortality and 6-months mortality in patients with sepsis (p>0.05). Discussion: No significant correlation was found between NLR and mortality rate in the ICU and long-term mortality in patients with sepsis.

Keywords

Neutrophil-To-Lymphocyte Ratio; Sepsis; Mortality

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Introduction

Sepsis, a major public health concern, is described as a syndrome of physiological, pathological, and biochemical abnormalities induced by infection. Although the true incidence is unknown, sepsis is among the leading causes of mortality and critical illness worldwide [1]. Despite modern ICU treatments and antibiotic treatments, the mortality associated with sepsis remains high. The pathophysiology of sepsis is not clearly understood [2]. Many biomarkers, including acute phase proteins and cytokines, are used both in clinical practice and in research to determine the underlying inflammatory conditions in the ICUs [3].

In sepsis, polymorphonuclear neutrophils mediate major antimicrobial activities on the one hand and contribute to the development of multiple organ failure on the other hand [4]. The physiological immune response of circulating white blood cells to a wide range of stressful events such as tissue injury, severe trauma, major surgery, burns, and sepsis syndrome is characterized by elevation of neutrophils and decline in lymphocyte counts [5]. Zahorec [5] showed that changes occur in neutrophil and lymphocyte counts as a response of the immune system to surgical stress, systemic inflammation, or sepsis, and, there was a correlation between the degree of neutrophilia and lymphocytopenia and the severity of the disease.

Neutrophil-to-lymphocyte ratio (NLR) is an easily measurable biomarker from complete blood count; Zahorec has stated that it can be used in clinical practice in the ICU [5]. NLR has been investigated previously as a potential predictor of survival rates in various types of cancers [5-9]. However, there are not many studies regarding the usefulness of NLR in predicting mortality in patients with sepsis [3,10]. Our aim in this study was to evaluate the association between NLR and mortality of the patients with sepsis in the ICU.

Material and Method

We retrospectively assessed the patients followed up with the diagnosis of sepsis in the internal medicine ICU of our hospital between September 1, 2014 and December 31, 2015. The study was approved by the local ethics committee. Patients aged ≥ 18 years admitted to the ICU with a diagnosis of sepsis were included in the study. Assessment of sepsis, severe sepsis, and septic shock were performed according to American College of Chest Physicians/Society of Critical Care Medicine Conference definitions [11].

Patients aged ≤ 18 years, pregnant women, patients with known hematological disease, patients with diseases causing trauma, intoxication, and immunosuppressive disease, receiving immunosuppressive therapy, previous chemotherapy (within the last 6 months) were excluded from the study. Demographic, clinical, and laboratory data were obtained from the patients' medical records. Age, gender, comorbid diseases (Charlson comorbidity index score) [12], Simplified Acute Physiology Score II [13], and Glasgow coma score values measured during admission to the ICU were obtained from the patients' medical records. Circulating neutrophil and lymphocyte counts and NLR were obtained from the values measured at the time of admission. The value range considered to be normal for leukocyte were 5.2-12.4 x10^3µL for neutrophil and 0.9-5.2 x10^3µL for lymphocyte.

Our primary aim was to evaluate the association between NLR and ICU mortality and secondary aim was to evaluate the association between NLR and the hospital mortality and 6-month mortality in patients with sepsis. Mortality data were obtained from the patients' medical records.

The SPSS 20 program was used for statistical analysis. Mean and standard deviation and additionally median and minimum-maximum values of quantitative data of variables were given. Frequency and percentage values were given for qualitative observations. Interclass differences of qualitative observations were interpreted using Chi-square analysis. The intergroup differences of quantitative data were interpreted using Mann Whitney U test during dual comparisons and Kruskal Wallis test during multiple comparisons. The quartile values were obtained for NLR values and the difference was investigated in the classes created according to the quartile values. A multiple logistic regression model was obtained to investigate the mortality based on NLR classification and the odds ratio was interpreted. Statistical significance was evaluated at a confidence level of 95%.

Results

A total of 104 patients were included in the study. Fifty-two of 104 patients (50%) were males and their mean age was 75.12±12.25 years (min 18-max 92). Baseline demographic data of the patients are shown in Table 1. While vasopressor support was performed in 88 patients (84.6%) during follow-up

Table 1. Patients' characteristics

All patients (n=104)			
Age (median)	78 (18-92)	Malignancy	18 (17.3%)
Gender		Alzheimer's disease	44 (42.3%)
Men	52(%50)	SAPS II Score (median)	70.65 (15-94.7)
Women	52(%50)	Charlson Comorbidity Index (median)	3 (2-7)
Diagnosis		Glasgow Coma Score (median)	8 (1-12)
Sepsis	37(%35.6)	Intensive care unit follow-up day	12.86±13.26
Septic shock	42(%40.4)	Creatinine (mg/dL)	3.12±2.59
Severe sepsis	15 (%24)	CRP (mg/L)	165.65±116
Source of the infection		Hct	35.79±7.12
Respiratory system	51 (49%)	RDW	17.19±3.31
Urinary system	46 (44.2%)	Albumin (mg/dL)	2.78±0.57
Soft tissue	5 (4.8%)	INR	1.65±1.51
Abdomen	2 (1.9%)	Total bilirubin	1.11±0.84
Comorbidities		Number of cell measured at the time of admission to ICU	
Diabetes mellitus	46 (44.2%)	(White Cell) (10^3/µ)	13.6
Congestive heart failure	9 (8.7%)	(Neutrophil) (10^3/µ)	12.3
Chronic renal failure	28 (26.9%)	(Lymphocyte) (10^3/µ)	0.9
Chronic obstructive pulmonary disease	9 (8.7%)	NLR	16.35
Cerebrovascular accident	27 (26%)		

in ICU, mechanical ventilation support was provided in 44 patients (42.3%) during follow-up in ICU. Again, hemodialysis was performed in 25 patients (24%). Total parenteral nutrition was used in 98 patients (94.2%). Bacteria could be identified bacteriologically in 44 patients (42.3%). Gram-positive cocci, gram-negative bacilli, and yeasts were identified in 31.8%, 68.2%, and 2.3% of the patients, respectively.

ICU mortality was 57.7% in patients with sepsis. When survivors and non-survivors in the ICU were assessed regarding neutrophil counts, lymphocyte counts, and NLR, no statistically significant difference was determined (p>0.05). When survivors and non-survivors were evaluated, red cell distribution width (RDW), C reactive protein (CRP), total bilirubin, and INR values were found to be statistically significant between the two groups (p<0.05) (Table 2). No significant difference was determined between the two groups regarding platelet counts, hemoglobin, mean corpuscular volume, mean platelet volume, and albumin/globulin ratio (p>0.05).

When NLR was divided into quartiles, no significant difference was determined between quartiles regarding age, gender, SAPS score, and comorbid diseases (Table 3). While mortality rate in the ICU increased with increasing quartile of NLR, no significant difference was determined in ICU mortality (first quartile=reference value; second quartile=0.368 (95% CI, 0.116 to 1.173); third quartile=0.502 (95% CI, 0.157 to 1.61); fourth quartile=0.368 (95% CI, 0.116 to 1.173); all p>0.05).

The hospital mortality rate was 66.3%. No significant difference was determined between NLR and hospital mortality (p>0.05). When NLR was divided into quartiles, no significant difference was determined in hospital mortality rate (first quartile=reference value; second quartile=0.773 (95% CI, 0.274 to 2.622); third quartile=0.773 (95% CI, 0.274 to 2.622); fourth quartile =0.361 (95% CI, 0.522 to 5.969); all p>0.05).

The six-month mortality rate was 70.2%. No significant difference was determined between NLR and mortality (p>0.05). When NLR was divided into the quartiles, no significant difference was determined in 6-months mortality (first quartile=reference value; second quartile 0.515 (95% CI, 0.77 to 3.437); third quartile=0.288 (95% CI, 0.52 to 1.598); fourth quartile =0.227 (95% CI, 0.40 to 1.282); all p>0.05).

Discussion

White blood cell count is a commonly used parameter for the diagnosis and follow-up of the diseases encountered in daily practice. Jilma et al. [14] determined that circulating neutrophil counts increased and circulating lymphocyte counts decreased as a general immune response to endotoxemia. Four to six hours after endotoxemia, circulating neutrophil counts increased by 300% and circulating lymphocyte counts decreased by 85% [14]. Decrease in lymphocyte counts results from increased catecholamine, prolactin, and cortisol levels, migration of lymphocytes toward the reticuloendothelial system, and apoptosis [15,16].

The hypothesis of an association between NLR and neutrophilia and lymphocytopenia developing in systemic inflammatory and stress conditions and the severity of the clinical course was demonstrated for the first time by Zahorec [5]. In this study, Zahorec defined a correlation between the severity of clinical course and the severity of neutrophilia and lymphocytopenia in 90 oncological patients who were followed up with a diagnosis of stress, systemic inflammation, and sepsis. Consequently, he stated that the ratio of neutrophil and lymphocyte counts was an easily measurable parameter for determining prognosis during ICU follow-up of the patient and it could be used routinely

Table 2. Patients' characteristics according to survivors and non-survivors

	Survivors (54)	Non-survivors (60)	p		Survivors (54)	Non-survivors (60)	p
Age (median)	78	77	0.626	SAPS II Score (median)	59.7(15-84.9)	77(23.1-94.7)	<0.002
Men	19 (43.2%)	33 (55%)	0.234	Charlson Comorbidity Index (median)	2 (2-6)	3 (2-7)	<0.001
Women	25 (56.8%)	27 (45%)		Glasgow Coma Score (median)	10 (6-12)	8 (1-10)	0.01
Diagnosis							
Sepsis	16 (36.4%)	21 (35.0%)		Intensive care unit follow-up day	12.92±10.24	12.81±15.33	0.367
Septic shock	18 (40.9%)	24 (40.0%)	0.964	Creatinine (mg/dL)	2.90±2.61	3.29±2.59	0.534
Severe sepsis	10 (22.7%)	15 (25.0%)					
Source of infection							
Respiratory system	15 (34.1%)	36 (60.0%)		Albumin (mg/dL)	2.84±0.45	2.73±0.64	0.228
Urinary system	26 (59.1%)	20 (33.3%)	0.062	INR	1.25±0.28	1.97±1.95	0.001
Soft tissue	2 (4.5%)	3 (5.0%)		Total bilirubin	0.85±0.45	1.31±1.01	0.036
Abdomen	1 (2.3%)	1 (1.7%)					
Comorbidities							
Diabetes mellitus	16 (36.4%)	30 (50%)	0,167	CRP (mg/L)	134.35±98.94	190.30±123.3	0.028
Congestive heart failure	3 (6.8%)	6 (10%)	0.569	Hct	36.48±7.21	35.25±7.07	0.528
Chronic renal failure	11 (25%)	17 (28.3%)	0.705	RDW	16.38±1.95	17.83±3.98	0.006
Chronic obstructive pulmonary disease	2 (4.5%)	7 (11.7%)	0.202	(White Cell) (10^3/μ)	13.7	13.5	0.885
Cerebrovascular accident	12 (27.3%)	15 (25%)	0.794	(Neutrophil) (10^3/μ)	12,35	11.90	0.966
Malignancy	5 (11.4%)	13 (21.7%)	0.170	(Lymphocyte) (10^3/μ)	1	0.8	0.188
Alzheimer's disease	16 (36.4%)	28 (46.7%)	0.293	NLR	12.42	17.16	0.199

Table 3. Patients' characteristics according to the quartile of NLR

	<8.21	8.21-16.7	16.7-27.75	>27.75	p
Age (median)	80	75	79	75	0.155
Men	12 (46.2%)	11 (42.3%)	11 (42.3%)	16 (61.5%)	0.541
Sepsis	12 (46.2%)	10 (38.5%)	6 (23.1%)	9 (34.6%)	
Septic shock	8 (30.8%)	11 (42.3%)	11 (42.3%)	12 (45.2%)	0.595
Severe sepsis	6 (23.1%)	5 (19.2%)	9 (19.2%)	5 (34.6%)	
Respiratory system	16 (61.5%)	6 (23.1%)	15 (57.7%)	14 (53.8%)	
Urinary system	10 (38.5%)	17 (65.4%)	8 (30.8%)	11 (42.3%)	0.062
Soft tissue	-	3 (11.5%)	2 (7.7%)	-	
Abdomen	-	-	1 (3.8%)	1 (3.8%)	
Diabetes mellitus	13 (50%)	12 (46.2%)	12 (46.2%)	9 (34.6%)	0.705
Congestive heart failure	2 (7.7%)	2 (7.7%)	2 (7.7%)	3 (11.5%)	0.947
Chronic renal failure	8 (30.8%)	11 (42.3%)	4 (15.4%)	5 (19.2%)	0.118
Chronic obstructive pulmonary disease	2 (7.7%)	-	4 (15.4%)	3 (11.5%)	0.235
Cerebrovascular accident	5 (19.2%)	8 (30.8%)	6 (23.1%)	8 (30.8%)	0.717
Malignancy	3 (11.5%)	7 (26.9%)	2 (7.7%)	6 (23.1%)	0.206
Alzheimer's disease	13 (50%)	8 (30.8%)	11 (42.3%)	12 (46.2%)	0.531
SAPS II Score (median)	69.5	70.9	62.4	74.1	0.480
Intensive care unit follow-up day	15.29±9.08	11.05±7.81	11.62±12.54	13.48±20.42	0.150
Creatinine (mg/dL)	3.38±3.28	3.12±2.11	2.56±1.32	3.4±3.22	0.940
CRP (mg/L)	108.75±70.28	178.24±111.2	198.93±148.46	176.75±107.79	0.102
Albumin (mg/dL)	2.89±0.58	2.60±0.65	2.73±0.42	2.90±0.58	0.199
(White Cell) (10^3/μ) (median)	10.9	14.1	12.7	18.5	0.010
(Neutrophil) (10^3/μ)	8.3	12.40	11.90	15.25	0.000
(Lymphocyte) (10^3/μ)	2	1.3	0.6	0.4	0.000

in daily clinical practice.

The authors of another study stated that NLR measured at the time of admission to the hospital due to acute decompensated heart failure was associated with 30-day mortality and it could be used for risk classification [17]. Again, Suliman et al. [18] found that increasing quartile of NLR was associated with increased mortality and Azab et al. [19] found that NLR was associated with admission to ICU and prolonged hospitalization in the patients with acute pancreatitis.

Following from these research studies, in our study we investigated the association between NLR measured at the time of admission to ICU of the patients followed up with a diagnosis of sepsis in the ICU and the mortality rate of patients with sepsis; no correlation was found. Similarly, in the study performed by Salciccioli et al. [3], no correlation was determined between NLR and 28-day mortality in patients with sepsis. Our patients followed up in the ICU were divided into quartiles with respect to NLR (<8.21, 8.21-16.7, 16.7-27.75, >27.75) and while an increase was observed with increasing quartile of NLR, no statistical significance was determined. Similarly, the patients in the study performed by Salciccioli et al. [3] were also divided into quartiles regarding NLR, but no correlation was found between the quartiles with respect to mortality in patients with sepsis.

Contrary to this, in the study performed by Riche et al., NLR measured at the time of admission to ICU of the patients followed up with a diagnosis of septic shock was found to be significantly lower in the patients who died before the fifth day of admission [10]. However, one of the limitations of this study is that long-term mortality (14 day or 28 day) was not investigated. Again, reduced level of circulating neutrophils determined in the study performed by Bermejo-Martin et al. [4]. is associated with mortality. The aforementioned study proceeded from the hypothesis that low neutrophil count might cause difficulty in developing sufficient initial immunity. In sepsis, neutrophil adhesion to vascular endothelium and leukocyte aggregates occur and, as a result, circulating neutrophil count may decrease. In patients with multiple organ failure due to sepsis, localization of neutrophils ranging from an intense infiltration of the lung to sequestration and aggregation in renal blood vessels were seen [20]. Neutrophils in the circulation can exist in varying functional states and consequently a cross-sectional assessment relating to the neutrophil or lymphocyte counts may be inadequate to understand the effect of these parameters on diseases such as sepsis [3].

In our study, when NLR and 6-month mortality rate was evaluated, no significant correlation was determined. Again when NLR was divided into the quartiles, no significant correlation was found between NLR and 6-month mortality. In the study performed by Salciccioli et al. [3], a correlation was found between NLR and 1-year mortality in the critically ill patients followed up in the ICU, but a separate classification for sepsis patients was performed only for 28-day mortality. Although NLR, hospital mortality, and 6-month mortality were defined to be an independent factor in the study performed by Akilli et al. [21]. a separate subgroup analysis was not performed for patients with sepsis, who comprised 9.4% of the cases in this study. In both of the studies, the correlation between long-term mortality and NLR was defined for critically ill patients and not for patients with sepsis. In our study, the correlation between long-term mortality and NLR in patients with sepsis was defined for

the first time.

In conclusion, no significant correlation was found between NLR and mortality rate in the ICU and long-term mortality in patients with sepsis. When the pathophysiology of sepsis is considered to be due to varying functional states of neutrophils or lymphocytes, we think that the neutrophil or lymphocyte count alone may not be adequate to understand the effects of these blood cells in sepsis. Since there are not many studies performed on this subject, further studies are required to investigate the correlation between NLR and sepsis.

Competing interests

The authors declare that they have no competing interests.

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