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ARAŞTIRMA / RESEARCH

Which hemogram-derived indices might be useful in predicting the clinical outcomes of sepsis patients in the intensive care unit?

Yoğun bakım ünitesindeki sepsis hastalarının klinik sonuçlarını tahmin etmede hangi hemogramdan türetilmiş indeksler yararlı olabilir?

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Abstract

Purpose: The aim of our study is to investigate the prognostic value of Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) in determining mortality in patients hospitalized for intensive care unit (ICU) sepsis.

Materials and Methods: This study retrospectively evaluates all patients hospitalized with sepsis in our ICU between February 2017 and April 2018. In addition to the demographic and clinical characteristics of the patients, complete blood count parameters were also recorded. Demographic and clinical characteristics, mainly NLR, MLR and PLR results, and other laboratory results of patients with sepsis were compared between the ones with and without mortality.

Results: Four hundred and eleven patients were included in the study. 55.7% (229/411) of patients with sepsis died and 44.3% (182/411) were discharged alive. NLR, MLR and PLR were higher in the group with mortality compared to the survivor group. The cut-off value for predicting mortality in patients with sepsis was 9.2 for NLR, ≥0.8 for MLR, and ≥187.3 for PLR. The area under the curve (AUC) value for NLR was 0.825, the AUC value for MLR 0.835 and the AUC value for PLR was 0.720.

Conclusion: High NLR, MLR and PLR values are associated with mortality in sepsis patients hospitalized in ICU, and the most significant parameter for mortality indicator among the three rates was found to be MLR with the highest AUC value.

Keywords:. neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to lymphocyte ratio, sepsis, intensive care unit, mortality.

Öz

Amaç: Çalışmamızın amacı, yoğun bakım ünitesinde (YBÜ) sepsis nedeniyle yatan hastalarda nötrofil lenfosit oranı (NLO), monosit lenfosit oranı (MLO) ve trombosit lenfosit oranı (TLO mortaliteyi belirlemedeki prognostik değerini araştırmaktır.

Gereç ve Yöntem: Çalışmamızda, Şubat 2017 – Nisan 2018 tarihleri arasında YBÜ'de yatan tüm sepsisli hastalar retrospektif olarak değerlendirilmiştir. Hastaların demografik ve klinik özelliklerine ek olarak tam kan sayımı parametreleri kayıt edildi. Mortalite olan ve olmayan sepsisli hastaların başlıca NLO, MLO ve TLO sonuçları olmak üzere demografik ve klinik özellikleri ile diğer laboratuvar sonuçları karşılaştırıldı.

Bulgular: Çalışmaya 411 hasta dahil edildi. Sepsisli hastaların %55,7'si (229/411) öldü ve %44,3 hasta (182/411) sağ taburcu edildi. Mortalite olan grupta yaşayan gruba göre NLO, MLO ve TLO daha yüksek bulundu. Sepsisli hastalarda mortalite tahmini için eşik NLO için ≥9,2, MLO için ≥0,8, TLO için ≥187,3 olarak bulundu. Nötrofil lenfosit oranı için eğri altında kalan alana (AUC) değeri 0,825, MLO için AUC değeri 0,835 ve TLO için AUC değeri 0,720 olarak bulundu.

Sonuç: Yoğun bakım ünitesinde yatan sepsis hastalarında yüksek NLO, MLO ve TLO değerleri mortalite ile ilişkili olup, üç oran arasından mortalite göstergesi için en anlamlı parametre AUC değeri en yüksek olan MLO olarak bulundu.

Anahtar kelimeler: Nötrofil lenfosit oranı, monosit lenfosit oranı, trombosit lenfosit oranı, sepsis, yoğun bakım ünitesi, mortalite.

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INTRODUCTION

Sepsis, which is a life-threatening inflammatory disorder, is a systemic response of the host to infectious stimuli and consists of clinical, hemodynamic and biochemical components[1]. The incidence of sepsis increases with age, and the mortality rate due to sepsis is between 20-56%, accounting for approximately 20% of all in-hospital deaths[2-4]. Intensive care unit (ICU) is the main parameter affecting mortality, and it is also used in various scoring systems to determine the clinical results and mortality of ICU patients[1,2,5]. In addition, studies on the effectiveness of biochemical and hematological parameters in predicting clinical outcomes of patients hospitalized in ICU are ongoing[6,7].

Recently, studies have been conducted on the parameters obtained from complete blood counts (CBC) to diagnose the infection, to evaluate the treatment response and clinical outcomes. For this purpose, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) were evaluated in terms of their relationship with hospital mortality in different disease groups. Generally, these parameters were separately evaluated in the studies[8-11]. The studies using all 3 parameters together as a mortality prediction model in sepsis patients hospitalized in ICU, are lacking. Therefore, we designed this study to investigate the relationship between NLR, MLR and PLR and mortality in septic patients admitted to ICU and to find the most effective parameter in mortality prediction.

MATERIALS AND METHODS

This study covers retrospective evaluation of adult patients who were followed up for at least 24 hours in Ankara Numune Training and Research Hospital 8 General Intensive Care Units (3rd level, 96 beds) during the study period February 2017 - April 2018 with their electronic files and written records.

Before the study, consent was obtained from the local ethics committee (date: 21/12/2018, no: E-18-2334). Our study was carried out in accordance with the Helsinki Declaration principles. Written informed consent forms were obtained from all subjects.

The patients were diagnosed with sepsis with clinical and laboratory findings according to the "Third International Consensus Definitions" criteria[12]. All patients with sepsis were treated in accordance with the "International Guidelines for Management of Sepsis and Septic Shock" according to the protocol of our unit[13]. Only patients diagnosed with sepsis at the time of admission were included in the study. Patients with sepsis during ICU admission were excluded from the study. Patients hospitalized for ICU other than sepsis (trauma, intoxication, neurological and metabolic disorders, cardiovascular and respiratory causes, etc.) were excluded from the study.

Patients' age, gender, number of comorbid conditions (diabetes mellitus, hypertension, malignancy / immunodeficiency, respiratory system disease, heart disease, renal disease, central nervous system disease, etc.), acute physiology and chronic health evaluation (APACHE) II score, Sepsis-related organ failure assessment (SOFA) score, duration of mechanical ventilation, ICU stay, bacteremia and mortality data were recorded[14,15].

Laboratory analysis

Venous blood samples were taken in tubes containing ethylenediamine tetra-acetic acid during hospitalization of patients with sepsis to the ICU. Hemoglobin, white blood cell (WBC), neutrophil count, lymphocyte count, monocyte count, and platelet count were measured by a twice-daily calibrated Cell-Dyn 3700 automated hemocytometer (Abbott, Abbott Park, IL, USA).

NLR was calculated as the neutrophil count divided by the lymphocyte count; MLR was calculated as the monocyte count divided by the lymphocyte count, and PLR was calculated as the platelet count divided by the lymphocyte count. Serum concentrations of CRP were measured by a Tinaquant CRP (Latex) highly sensitive immuno-turbidimetric assay on the Roche Modular P analyzer according to the manufacturer's instructions (CRP latex HS, Roche kit, Roche Diagnostics, GmbH, Mannheim, Germany).

Positive blood cultures (bacteremia) were identified by using the BACTEC FX automatic blood culture detection system (Becton Dickinson, Sparks, MD, USA) in the medical microbiology laboratory. Hemogram parameters were evaluated at the time of patients' admission to the ICU. Demographic and clinical characteristics and laboratory parameters

were compared in patients with sepsis with and without mortality.

Statistical analysis

SPSS software 17.0 (SPSS, Chicago, IL) was used for statistical analysis. T-test and / or Mann-Whitney's U-test were used to compare non-parametric continuous variables in independent samples between groups, and chi-square test or Fisher's exact test for categorical variables. Results are given as mean and standard deviation for those with continuous variables normally distributed and as median [interquartile range (IQR)] for those with abnormal distribution. Categorical variables were expressed as frequency and percentage distribution. Diagnostic screening tests to determine the cut-off for NLR, MLR, PLR and receiver operating characteristic (ROC) curve analysis were performed (sensitivity, specificity, positive predictive value, and negative predictive value). The area under the curve (AUC) value was calculated from the ROC. A p value of <0.05 was considered as statistically significant.

RESULTS

During the study period, 1345 patients were followed in our ICU. According to the exclusion criteria, 934 patients were excluded from the study, and 411 patients were enrolled into the study because they were admitted to ICU with the diagnosis of sepsis. The mean age of the patients included in the study was found to be 76.1±13.7 years. Of all the study patients, 229 (55.7%) died while 182 of them (44.3%) were discharged. Bacteremia rate in blood culture of all patients with sepsis included in the study was found to be 29.9% (123/411). The results of the patients with and without mortality in terms of age, gender, WBC and neutrophil count were found to be statistically similar (p> 0.05). The number of comorbid diseases, duration of MV, ICU stay, bacteremia ratio, APACHE II and SOFA scores were found to be significantly higher in patients with mortality compared to patients without mortality (p <0.05). Hemoglobin, platelet, lymphocyte and monocyte count were lower, CRP, NLR, MLR and PLR were higher in the group with mortality compared to the survivor group (p <0.05) (Table 1 and 2).

Receiver operating curve analysis was implemented for NLR, MLR and PLR for the prediction of mortality in patients with sepsis. The cut-off value in mortality prediction in patients with sepsis was 9.2 for NLR, ≥0.8 for MLR, and ≥187.3 for PLR (p = 0.0001). In the mortality prediction of patients with sepsis, the AUC value for NLR was 0.825, the AUC value for MLR was 0.835 and the AUC value for PLR was 0.720. ROC graph, AUC value, p value, sensitivity, specificity, positive predictive value, and negative predictive value are presented in Figure 1.

Table 1. Comparison of demographic and clinical features between survivors and non-survivors

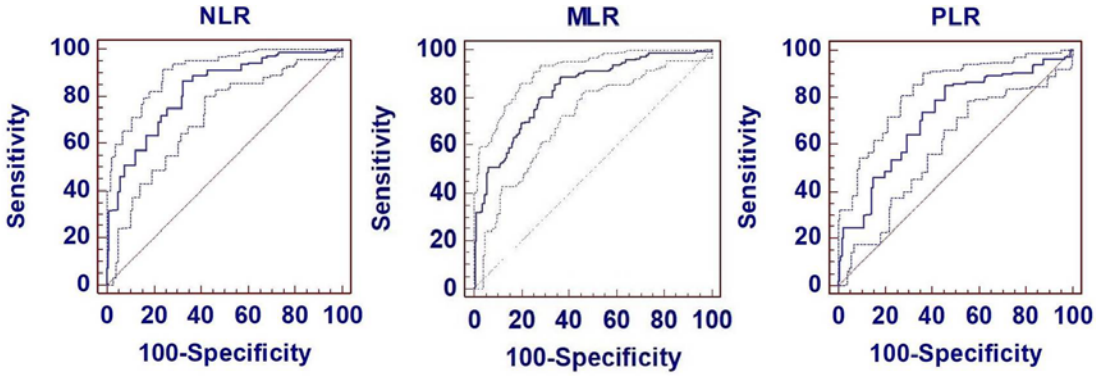
Variables	Survivors (n=182)	Non-survivors (n=229)	P value
WBC count (x10^9/L), [a]	12.7±7.2	13.4±8.4	0.413
Hemoglobin (g/dL), [a]	10.8±2.1	9.1±1.2	<0.001*
Platelet (x10^9/L), [a]	269.4±143.8	192.5±91.3	<0.001*
CRP (mg/L), [a]	83.3±57.1	161.9±81.2	<0.001*
Neutrophil (10^9/L)	10.0 (0.93)	9.98 (0.48)	0.063
Lymphocyte (10^9/L)	1.15 (1.4)	0.46 (0.7)	<0.001*
Monocyte (10^9/L)	0.66 (0.06)	0.55 (0.07)	0.012*
NLR	6.74 (6.13)	10.43 (8.68)	<0.001*
MLR	0.60 (0.41)	1.52 (3.01)	0.024*
PLR	178.74 (202.99)	251.84 (331.59)	<0.001*

[a] mean ± standard deviation, [b] median (interquartile range), APACHE II: acute physiology and chronic health evaluation score, SOFA: sepsis-related organ failure assessment score, ICU: intensive care unit, MV: mechanical ventilation *Statistically significant p values are highlighted.

Table 2. Comparison of laboratory variables between survivors and non-survivors

Variables	Survivors (n=182)	Non-survivors (n=229)	P value
Age, (years), [a]	75.1±11.0	82.1±7.9	0.161
Male gender, n (%)	75 (41.2)	103 (44.9)	0.216
Comorbid conditions, [b]	2 (1)	3 (3)	<0.001*
APACHE II score, [b]	20 (8)	24 (11)	0.004
SOFA score, [b]	7 (5)	10 (6)	<0.001*
Duration of MV, (days), [b]	5 (4)	8 (14)	0.001
ICU stay, (days), [b]	27 (34)	29 (54)	<0.001*
Bacteremia, n (%)	27 (14.8)	96 (41.9)	<0.001*

[a] mean ± standard deviation, [b] median (interquartile range) CRP: C-reactive protein, MLR: monocyte-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, WBC: white blood cell *Statistically significant p values are highlighted.



Variables	AUC	95% Confidence interval	p values	Cutoff level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NLR	0.825	0.785-0.861	0.0001	≥9.2	86	68	77	78
MLR	0.835	0.796-0.870	0.0001	≥0.8	86	78	83	81
PLR	0.720	0.673-0.763	0.0001	≥187.3	85	54	70	74

AUC: area under the curve, PPV: positive predictive values, NPV: negative predictive values, ROC: receiver operating characteristic, MLR: monocyte-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio,

Figure 1. ROC curve for NLR, MLR AND PLR, predicting mortality of patients with sepsis in intensive care unit.

DISCUSSION

Mortality prediction is an important problem in various clinics and especially in ICUs. Biomarkers or laboratory parameters are used to diagnosis and predict clinical outcomes in patients with sepsis. New word-wide parameter researches continues[10]. Our study is planned for evaluating the predictive value of NLR, MLR and PLR for mortality, in patients with sepsis. Reduced hemoglobin, platelet, lymphocyte, monocyte count and increased CRP, NLR, MLR and PLR were found to be associated with mortality. In general, AUC values of NLR, MLR and PLR values are between 0.7-0.9 and can be considered as a moderately strong mortality prediction parameter[16]. When looked more thoroughly, MLR has the highest AUC value in mortality prediction (AUC: 0.835) and was found to be the most effective parameter, followed by NLR (AUC: 0.825) and finally PLR (AUC: 0.720) in descending order.

Infections are the main causes of morbidity and mortality. Accurate diagnosis and antimicrobial therapy started at the right time are imperative to improve survival in sepsis. Molecular methods give faster and more accurate results in the diagnosis phase, but they are expensive and cannot be used in all centers. At this stage, biomarkers have an important role in detecting bacterial infection and predicting clinical outcomes. Although various biomarkers have been evaluated for the diagnosis and prognosis of sepsis, the gold standard biomarker has not been found yet[17]. In order to evaluate the clinical results, studies have been conducted in recent years that separately evaluate NLR, MLR and PLR, which are easily calculated and give fast results[8,17,18].

Key cell types of the innate immune system and the first line of cellular defense against infection are neutrophils. Lymphocytes are involved in the adaptive immune response. The immune system response to various insults results in an increase in neutrophil count and a decrease in lymphocyte count. When the infection continues, a large amount of neutrophils are produced and neutrophil apoptosis is reduced. Apoptosis of neutrophils in sepsis is more beneficial in contrast to apoptosis of lymphocytes[18]. Furthermore, the increase in neutrophil count is due to rapid mobilization of neutrophils from a marginal pool in the bone marrow, in addition to decreased apoptosis of neutrophils. Lymphocyte count decreases with the migration of active lymphocytes to inflammatory tissues and increasing lymphocyte apoptosis[8]. As a result, NLR increases in infectious diseases and turns into an inflammatory marker[17]. With antibiotic therapy, NLR is significantly reduced. This makes NLR an important parameter for evaluating the clinical response and results to treatment[8]. In addition, it has been proven that NLR can be used to classify disease risk, optimize treatment, and manage patients with sepsis[10].

For example, it has been reported that NLR being > 10.45 on day 2 and > 7.91 on day 5 is an independent predictor for in-hospital mortality[19]. Approximately 5 to 15 different cut-off values were obtained for NLR in the diagnosis of patients with sepsis, presence of bacteremia and mortality[9,10,17,20-23]. In our results, the cut-off value for NLR in predicting the mortality of sepsis was 9.2. The reason for the difference in these values is, due to the use of NLR for different purposes such as diagnostic or clinical results and diagnostic differences in study groups.

Monocytes are an important component of the innate immune response that functions in conjunction with the adaptive immune system through antigen presentation to lymphocytes. The studies on predicting the diagnostic or clinical results of MLR in infections, are limited. Zhou et al. evaluated and showed MLR as a significantly independent factor for second-line chemotherapy in metastatic gastric cancer. No significant relationship between NLR and disease progression was found in these patients[24]. In another study, it was concluded that both NLR and MLR could be useful with AUC values of 0.708 and 0.688, respectively, in the diagnosis of bacterial infections[25]. In our results, MLR was found to be above 0.8 as a parameter superior to NLR and PLR with the highest AUC (0.835) value in predicting mortality of patients with sepsis.

The role of platelet and leukocyte interactions as a critical stage in sepsis has emerged in recent years. The innate and adaptive immune responses are modulated by the interaction of neutrophils, monocytes, lymphocytes, and platelets. In the early stages of sepsis, thrombocyte / neutrophil complexes increase, in severe and complicated sepsis, platelets due to peripheral sequestration or sepsis decrease[26]. Therefore, PLR becomes available as one of the markers of inflammatory events and a marker of mortality[23,27]. Kim et al. concluded that NLR and PLR values were higher in the group with Bell's palsy compared to the control group and this was rumoured to be associated with inflammation[28]. Similarly, the mortality relationship between increased NLR and PLR values in acute pulmonary embolism and some types of cancer has been shown[29-31]. Zheng et al. reported that both very high and very low PLRs were associated with mortality in critically ill patients with acute kidney injury[32]. As a result of our study, it has been shown that a PLR of 187.3 in sepsis patients in ICU can be used as a prognostic factor for mortality. In a study conducted on patients with sepsis, including a large case series, it was reported that PLR> 200 indicates increased mortality[33]. The cut-off value in this study is slightly higher than our study, and this may be due to the fact that the approximate age of the patients included in the study was 65 years and lower than the average age of our patients. For PLR, differences are observed between the cut-off values (approximately between 140 and 210) found in the studies mentioned above[30,31,34,35]. Differences between cut-off values may be due to age and diagnostic heterogeneity of the patients included in the study.

As far as we know, there is no study evaluating all NLR, MLR and PLR together in predicting mortality in sepsis patients previously hospitalized in ICU. Studies evaluating all 3 parameters have been conducted in the emergency room or with the aim of confirming the diagnosis of sepsis and bacteremia[11,18,36,37]. The study consisting a large number of case series performed by Zhao et al., stated that NLR > 9.8, lymphocyte-to monocyte ratio (LMR) ≤ 2.18, and PLR > 249.89 are important determinants of 28-day mortality in patients with sepsis admitted to the emergency department[11]. Djordjevic et al. reported that NLR, MLR and PLR are independent predictors for mortality in patients with peritonitis, pancreatitis, and sepsis secondary to trauma[18]. The cut-off NLR, MLR and PLR values given to determine both diagnostic and clinical results in diseases caused by non-infectious causes such as male breast cancer patients, nasopharyngeal carcinoma, and rheumatic heart disease differ[36-38].

The reason for the different cut-off and AUC results in the studies for NLR, MLR and PLR may be due to the use of different cohorts, the presence of patients with different age and diagnosis groups, differences in disease severity, differences in the number of patients in the groups, and the presence or absence of a control group in the groups. In addition, it is not clearly known which value will be used as diagnostic and clinical outcome and which parameter is more effective. Our study is the first study comparing the effectiveness of NLR, MLR and PLR in mortality prediction in patients with sepsis hospitalized only in ICU. According to the results of our study, NLR, MLR and PLR AUC values were between 0.7-0.9 in predicting the mortality of patients with sepsis, in addition to being moderately strong predictors of mortality, MLR was found to be the highest, then NLR and last PLR significantly predicted mortality according to the AUC order. Besides the efficiency of these 3 parameters, another advantage is that they can be found cheap, simple, fast and easily in almost all healthcare facilities. Consequently, using these parameters together with other (CRP, erythrocyte sedimentation rate) markers may provide important advantages to the clinician in predicting the outcome of sepsis[37].

Since this is a single-center study with retrospective cohort analysis, our results cannot be generalized and there are limitations in this regard. In addition, our patients could not be evaluated in subcategories such as sepsis, severe sepsis, septic shock, systemic inflammatory response syndrome, and multi-organ failure. We could not evaluate NLR, MLR, PLR and other parameters intermittently during hospitalization. In addition, we had no results for gram positive and negative bacteremia.

In conclusion, our study is the first study evaluating the combined effectiveness of NLR, MLR and PLR for mortality prediction in septic patients in ICU. We found that NLR, MLR, and PLR were significantly higher in septic patients with mortality compared to the ones without mortality, and being above certain values was found to be significant in terms of showing mortality. Considering the limitations of our current study, prospective studies to be conducted in the future may further help to demonstrate the effectiveness of NLR, MLR and PLR in predicting clinical outcomes in patients with sepsis.

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