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Original Article

The Prognostic Importance of Neutrophil–to–Lymphocyte Ratio and Platelet–to–Lymphocyte Ratio in Adult Patients with Sepsis Who Underwent Hemoperfusion in General Intensive Care Unit

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ABSTRACT

Objective: Sepsis is a major cause of mortality and morbidity in the intensive care units. The goal of this study is to investigate whether changes in the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are a prognostic marker for patients with sepsis (according to sepsis stages, and patient's and disease's characteristics) who have been followed up in the intensive care unit and who have received HA330 resin-directed hemadsorption column for sepsis.

Methods: The study included a group of 100 (male [healed: 19, exitus: 42], female [cured: 29, exitus: 10]) sepsis patients who were followed up in the intensive care unit between December 2019 and December 2021 and who received HA-330 sepsis adsorption column.

Results: Although a strong positive correlation was found between the neutrophil-to-lymphocyte ratio and the baseline platelet-to-lymphocyte ratio values ($r = 0.725$ and $P = .001$), a weak positive correlation was found between the baseline neutrophil-to-lymphocyte ratio and the comorbidity values ($r = 0.253$ and $P = .001$). In addition, the period found for hemoperfusion in those who healed was statistically significantly higher in exitus patients ($P = .001$). It was noted that the improvement in repeated neutrophil-to-lymphocyte ratio measurements in the healing and death observations was identical ($P > .05$). The repeated neutrophil-to-lymphocyte ratio measurement values were found to be statistically significantly different for those with healing ($P = .014$). In addition, repeated neutrophil-to-lymphocyte ratio measurement values were found to be statistically significantly different from those with exitus ($P = .001$). It was observed that the change of repeated platelet-to-lymphocyte ratio measurements in the observations with healing and death was statistically significant ($P < .05$).

Conclusion: It is thought that it may be a cheap and useful biomarker in the prognosis of patients who are followed up in the intensive care unit and are treated with HA-330 sepsis adsorption column since the rate of neutrophils and lymphocytes in patients with hematological healing and death differs greatly.

Keywords: Sepsis, hemoperfusion, neutrophils, lymphocytes, blood platelets, ratio, intensive care units

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INTRODUCTION

Sepsis is characterized by a life-threatening organ dysfunction and manifested by an irregular host response to the severe infection. It is a syndrome that includes physiological, pathological, and biochemical abnormalities, the pathobiology of which has not been fully elucidated, hence becoming an important public health problem.[1,2] The septic shock, on the other hand, is a subset of sepsis in which vasopressors are needed to maintain mean arterial pressure (MAP) above 65 mmHg and above 2 mmol/L despite adequate fluid resuscitation and to harbor the cellular metabolism disorders and acute circulatory abnormalities.[3] Both clinical conditions have high mortality rates although several criteria have been tried to be developed to diagnose sepsis. The Systemic Inflammatory Response Syndrome (SIRS) criteria had been an accepted scoring system used in the diagnosis of sepsis. Today, sepsis is currently diagnosed by 2 or more point-infected organ dysfunction scored by the Sequential Organ Failure Assessment.[2,4-9]

Failure to make an early diagnosis and treatment of sepsis may result in multiple organ failure and death. The main treatment method to reduce the mortality rates is to recognize the infection center causing the sepsis, to initiate an effective focal antibiotic therapy, and to provide a hemodynamic support in this process.[4,10-13]

Since the clinical signs and symptoms of sepsis are nonspecific and often variable, the search for a rapid test is ongoing for the diagnosis and assessment of sepsis severity.[14-19] In this respect, several parameters are considered useful since they have the ability to show the absence or presence or the severity of the sepsis, to follow the patient clinically, to be used for classification purposes, and to predict the outcome of sepsis.[20] Two of these parameters namely the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are readily available and have intensively been studied and evaluated in the demonstration of inflammation and sepsis due to being time- and cost-effective.[21-22]

The purpose of the study is to investigate whether variations in the NLR and PLR are prognostic markers in the patients diagnosed with sepsis (according to the sepsis stages, and patient's and disease's characteristics) who are followed up in the intensive care unit (ICU) and undergoing treatment using "HA-330 Sepsis Adsorption Column" and whether there is a relationship between NLR and PLR and the hematological parameters in these septic patients.

Main Points

- In intensive care units, sepsis is a major cause of mortality and morbidity.
- They have led to the development of different modalities of care to control them. Extracorporeal treatment approaches such as hemoperfusion have also become increasingly interesting in this context.
- Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are shown as low-cost, effective, and easily applicable markers in inflammatory and infectious processes in patients with sepsis.

METHODS

This research is designed for the Biruni University Medical Faculty Department General Intensive Care as a single-center study assessing demographic and hematological parameters. The research sample included 100 (male [healed: 19, exitus: 42], female [healed: 29, exitus: 10) sepsis patients who were followed up in the ICU between December 2019 and December 2021 and applied the HA-330 Sepsis Adsorption Column (Hemoadsorption device HA-330, Jafron Biomedical Co., Ltd., China), in accordance with the study patient's inclusion criteria.

Patient inclusion criteria in the study were as follows:

- A retrospective consent form was obtained from the patients who were hospitalized in our hospital due to the diagnosis of sepsis and benefited from the treatment, or from the relatives of deceased patients hospitalized in our hospital due to the diagnosis of sepsis.
- Those who were general intensive care patients, of 18 years old and over, who met the sepsis criteria, and underwent hemoperfusion (which is an extracorporeal blood purification method consisting of passing an anticoagulated whole blood through a device, usually a column containing the adsorbent particles, to remove the cytokines in the blood of septic patients).

While diagnosing patients with sepsis, the following criteria in the guidelines of the American Intensive Care Association were discussed[23]:

- Sepsis: certain/possible infection + ≥2 SIRS criteria, and
- SIRS: systolic blood pressure (SBP) <90 mmHg or Mean Arterial Pressure (MAP) <65 mmHg or lactate >2 mmol/L (after initial fluid loading), international normalized ratio (INR) >1.5 or activated partial thromboplastin time (APTT) >60 hour, bilirubin >34 µmol/L, urine output during 2 hours <0.5 mL/kg/h, creatinine >2 mg/dL, platelets <100 × 109 L, and patients who do not have SpO_2 <90% in room air and who received HA-330 hemoadsorption.

Patient exclusion criteria from the study:

- Patients under 18 years of age and over 80 years of age and patients with bleeding diathesis;
- Those with neurodegenerative diseases.

Study Protocol

Hemoadsorption device HA-330 (Jafron Biomedical Co., Ltd., China) in combination with HP/Continuous renal replacement therapies (CRRT) were initiated. The patient had acute renal failure, and the patient had a history of diabetes and high blood pressure. Before the onset of HP CRRT, the patient has oliguria (urine 400 cm^3 in 24 hours). After HA-330, the patient's urine output reached 1100 cm^3 in 24

hours. Continuous renal replacement therapies mode used was as follows: continuous venovenous hemofiltration predilution and post-dilution every 2 hour, blood flow: 200-250 mL/min, substitution flow: 25 cm^3/kg, ultrafiltration (UF):20 ml/h, heparinization: 10 U/kg/h, patient's weight: 70 kg. The HP cartridge was added to the CRRT circuit simultaneously with the start of CRRT, and HP and CRRT were started simultaneously. After 6 hours, the HP cartridge was removed from the CRRT circuit, and CRRT was continued. After 20 hours, the second HP cartridge was added to the CRRT circuit, and it was used for 6 hours and then removed. The fluid balance was maintained neutral.

Data Collection Method

Data on sepsis patients as a sample of the study were first collected from patients who were followed up by the responsible investigators working in the ICU in compliance with the sepsis criteria and the laboratory tests and examinations were obtained before and after the HA-330 Hemoadsorption Sepsis Column application. Patients' hematological parameters, NLR/PLR ratios, were determined using hemogram values. Furthermore, patient's demographic information (age, gender, disease information, risk factors, etc.) was collected from patient records and regularly reported in the Microsoft Office Excel file.

Statistical Analysis

Statistical Package for the Social Sciences version 24.0 (IBM SPSS Corp.; Armonk, NY, USA) used in the statistical analysis of the data obtained during the research. The Kolmogorov–Smirnov test tested the suitability of the data to normal distribution, the Student's *t*-test was used to compare normally distributed features in 2 independent groups, and the Mann–Whitney *U* test was used to compare non-normally distributed features in 2 independent groups. With the Friedman test and post hoc test, the features that did not display a normal distribution at repeated times were corrected and then were examined with the Wilcoxon test. In repeated measurements, the variations between repetitive measurements in the prognosis and exit groups were explored by the 2-way analysis of variance (ANOVA) test. Using the chi-square test, the relationship of categorical features with groups was tested. Mean ± standard deviation, median for numerical variables, and number and percent values were given for categorical variables as descriptive statistics. The $P < .05$ value was accepted as significant in the statistical analysis.

Ethical Statement

All authors declare that the study was conducted in accordance with the World Medical Association Helsinki "Ethical Principles for Medical Research Containing Human Subjects." All patients were given full information about the study procedures before providing written consent. Besides, an informed consent form was obtained from patients who participated in this clinical investigation. In addition, the approval of the study by the Ethics Committee was obtained from the Biruni University Clinical Research Ethics Committee (Date: January 27, 2019, Decision no: 2019/27-14).

Table 1. Distribution of Demographic and Clinical Characteristics of the Patients

Parameters	Median	Mean ± SD	Min–max
Age	69.5	67.39 ± 15.62	20–103
Hemoperfusion duration (days)	7	5.41 ± 2.01	1–7
Intensive care unit duration (days)	14	28.73 ± 38.35	2–270
Comorbidity number	2	2.01 ± 1.05	0–4
Male, n (%)	61 (61)		
Comorbidity 1	76 (76)		
Comorbidity 2	67 (67)		
Comorbidity 3	43 (43)		
Comorbidity 4	15 (15)		
Exitus/healed	71/29 (71/29)		

n=100.
SD, standard deviation.

RESULTS

The distribution of demographic and clinical characteristics of the patients included in the study is given in Table 1.

The results of comparing the hemogram parameters of the patients included in the study according to the hemoperfusion duration and the duration of stay in the ICU are given in Table 2.

According to Table 2, a strong positive correlation was found between the initial values of NLR and PLR ($r = 0.725$ and $P = .001$). A weak significant positive correlation was found between the NLR baseline value and the number of comorbidities ($r = .253$ and $P = .001$).

The relationship between prognosis and parameters is given in Table 3.

The hemoperfusion time observed in those who healed was statistically significantly higher than the hemoperfusion time observed in those who were dead ($P = .001$) according to Table 3. It was found that in those who were healing and those who died ($P > .05$), comorbidity distributions were similar.

Based on the results of the 2-way repeated ANOVA analysis, the change in the repeated NLR measurements in the healing and death observations was similar ($P > .05$). The change of NLR repeat measurements, in other words, is independent of the status of healing and death. Again, there was no statistically significant difference between the cure and death groups in repeat measurements of NLR and PLR ($P > .05$). The repeated NLR measurement values were found to be statistically significantly different for those with healing ($P = .014$). The NLR value calculated at T5 and T7 was found to have decreased significantly compared to the initial value ($P < .05$). Repeated NLR measurement values

Table 2. Results of Comparison of Hemogram Parameters of Patients According to Hemoperfusion Duration and Intensive Care Unit Duration

Parameters		NLR (Start)	PLR (Start)	Hemoperfusion Duration/ Day	Intensive Care Unit Duration	Comorbidity Number
NLR (start)	R	1	0.716**	−0.051	−0.129	0.247*
	P		.000	.617	.200	.013
	n	100	100	100	100	100
PLR (start)	R			0.069	0.047	0.032
	P			.496	.646	.749
	n			100	100	100
NLR (avg.)	R		0.741	−0.090	−0.196	0.135
	P		.001	.374	.051	.180
	n		100	100	100	100
PLR (avg.)	R			0.004	−0.072	0.069
	P			.971	.474	.463
	n			100	100	100
NLR (7 repetition)	R		0.7	0.032	−0.363	0.256
	P		.001	.881	.008	.067
	n		52	52	52	52
PLR (7 repetition)	R			0.003	−0.152	0.161
	P			.988	.282	.255
	n			52	52	52
Hemoperfusion duration (day)	R				0.440**	0.073
	P				.001	.470
	n				100	100
Intensive care unit duration (day)	R					−0.144
	P					.153
	n					100

*$P < .05$; **$P < .001$.
R, correlation coefficient; *P*, significance value; n, number of cases; NLR, neutrophil–to–lymphocyte ratio; PLR, platelet–to–lymphocyte ratio.

were reported to be statistically significantly different from those with exitus ($P = .001$). Compared to the initial value, NLR values calculated at T5, T6, and T7 were found to be significantly lower ($P < .05$).

Based on the results of the 2-way repeated ANOVA analysis, the variance of repeated PLR measurements in the healing and death observations was shown to be statistically significantly different ($P < .05$).

DISCUSSION

The ICU is a multidisciplinary facility that provides a wide range of profiles of patients.[7,8] Over time, the population of patients treated in the ICU has also changed. Intensive care patients are now more advanced elderly and patients with complicated comorbidities due to the rise in the elderly population. Advances in malignancy therapies, developments in surgery and other diagnostic techniques, increasing expectations of the society and many other factors accompany this. Intensive care unit patients are patients who are at high risk of mortality.[9,11,13,14] Infection, respiratory distress, and other organ failure are the most important risk factors that increase mortality. An ideal prognosis method should be used to evaluate all these patient groups.[15,19] In addition, the reason for hospitalization and the presence of chronic systemic disease may also affect the prognosis of the patient.[12] Based on this, in the study, it was investigated whether

Table 3. The Relationship Between Prognosis and Parameters

	Healed	Exitus	
Parameters	**Mean ± SD (M)**	**Mean ± SD (M)**	***P***
Age	67.59 ± 1 5.40 (68)	68.13 ± 15.75 (72)	[1].200
Intensive care unit duration	42.07 ± 56.48 (20)	23.28 ± 26.47 (13)	[2].096
Hemoperfusion duration (day)	6.55 ± 1.06 (7)	4.94 ± 2.12 (5)	[2].001
Com number	1.90 ± 1.05 (2)	2.06 ± 1.05 (2)	[2].511
Gender (n: %)			
Male	19 (65.5)	42(59.2)	[3].554
Female	29 (40.8)	10 (34.5)	
Comorbidity (n%)			
Comorbidity 1	19 (65.5)	57 (80.3)	[3].117
Comorbidity 2	18 (62.1)	49 (69.0)	[3].503
Comorbidity 3	12 (41.4)	31 (43.7)	[3].834
Comorbidity 4	6 (20.7)	9 (112.7)	[3].309
NLR			
T1	22.28 ± 33.05 (8.8)	20.15 ± 28.25 (11.4)	[2].630
T2	18.81 ± 27.46 (9.1)	19.59 ± 19.02 (14.7)	[2].300
T3	15.99 ± 25.84 (5.8)	17.41 ± 19.26 (10.7)	[2].162
T4	11.29 ± 13.17 (7.1)	16.4 ± 19.96 (8.1)	[2].351
T5	*10.94 ± 13.01 (7.6)	*14.08 ± 13.23 (8.4)	[2].189
T6	9.17 ± 6.98 (7.6)	*15.48 ± 18.97 (6.7)	[2].711
T7	*9.69 ± 8.31 (6.6)	*15.4 ± 20.6 (6.4)	[2].876
	[4]0.014	[4]0.001	
PLR			
T1	45.44 ± 81.86 (22.5)	39.99 ± 46.25 (24.9)	[2].945
T2	25.08 ± 17.25 (18.2)	31.64 ± 30.99 (21.3)	[2].904
T3	25.5 ± 23.81 (19.4)	26.6 ± 37.76 (14.9)	[2].459
T4	*17.17 ± 12.94 (13.9)	*23.73 ± 29.77 (12.4)	[2].794
T5	*16.58 ± 14.42 (12.1)	*18.5 ± 20.34 (12.2)	[2].972
T6	*17.96 ± 13.52 (16.1)	*21.77 ± 29.53 (9.6)	[2].118
T7	*20.66 ± 18.09 (15.4)	*21.4 ± 31.95 (9.1)	[2].099
	[4]0.001	[4]0.001	

[1]Student's *t*–test; [2]Mann–Whitney *U* test; [3]Chi–square (Yates) correction; [4]Friedman test. *According to the initial value, it shows statistical significance according to the Friedman post hoc test ($P < .05$).
M, median; SD, standard deviation; NLR, neutrophil–to–lymphocyte ratio; PLR, platelet–to–lymphocyte ratio.

NLR and PLR changes were a prognostic marker in patients with sepsis (according to sepsis stages and characteristics of patient and disease) who were followed up in the ICU and underwent HA-330 Sepsis Adsorption Column.

In order to determine the severity of the disease during their clinical and practical treatments, promising new treatments, researchers and physicians have led patients to need to find new parameters.[24] Thus, different prognostic models have been developed to

determine the prognosis in patients and to use current treatment methods rationally. These are used in multiple ICUs and to conduct quality control at different times in the same ICU.[25] Furthermore, these parameters are used extensively for some scientific studies. In developed countries, intensive care costs account for 20-30% of hospital costs.[26] Due to the high cost of ICUs and the emotional conditions of patients and their families, the evaluation of the prognosis of these patients and the proper utilization of ICU in the last 2 decades have become an important issue.[27,28]

For clinicians today, early detection of infections is still an important issue. In general, for any suspected infection, the use of antibiotics is not recommended, as serious problems may occur with increasing bacterial resistance to antibiotics. Thus, in diagnosis, biomarkers unique to bacterial infections may be useful.[29]

Hemoperfusion with neutral microporous resin column is a blood purification technology within the scope of research, which has excellent efficacy in hemoperfusion rhythm diseases applied to septic patients, and which is of great importance in the early prevention and clearance of inflammatory mediators in the treatment of critical diseases.[30] Hemoperfusion can cleanse inflammatory mediators specifically and effectively and regulate the immunity of the body. Thus, by allowing the damaged organs to recover rapidly and the patient's symptoms to disappear, it offers excellent efficacy in the treatment of essential diseases.[31-32] Studies have shown that HA330 adsorption therapy can support the recovery of organ functions in patients with sepsis.[33-35]

In most sepsis studies, age was found to be above 60 years.[36] The reduction in physiological ability and response to factors that cause stress is an expected outcome in elderly patients with the lifetime accumulation of molecular and cellular damage as a result of aging, and this increases the risk of elderly patients to become critically ill.[37] In a study of patients undergoing and admitted to intensive care, the number of elderly patients and the number of patients with sepsis increased from year to year. There are also opinions arguing that severe sepsis is a disease specific to old age. Most elderly patients who were discharged were found to have cognitive or functional sequelae and it was reported that these elderly patients had a higher risk of being critically ill.[38] The average age of sepsis patients was found to be 69.5 years in this study.

Neutrophils and lymphocytes are one of the main cellular components of the defense system against infection.[39] Depending on the stage of sepsis, the patient's immunological status and the etiology of the infection, and the number of white blood cells may change during sepsis.[40] The clinician should be reminded of an infection by the increased neutrophil count and the reduced lymphocyte count. One of the basic inflammation biomarkers that can be measured in routine hematological tests is NLR. A useful index in the diagnosis of sepsis and many diseases in adult patients has been found to be NLR.[41]

The fact that repeated NLR measurement values in those with healing and those with exitus are statistically significantly different in the study indicates that NLR is an important parameter for patients with sepsis. In the research by Lorente et al.[42] the NLR value was found to be higher than the survivor in the diagnosis of sepsis, and this outcome was correlated with mortality. In the study, the time observed for hemoperfusion in those who recovered was statistically significantly greater than the time observed for hemoperfusion in exitus-patients.

In the study, it was observed that the change of repeated PLR measurements in the observations with healing and death was statistically significant ($P < .05$). Duman et al[43] found no statistically significant difference in PLR between patients with sepsis, septic shock, and severe sepsis ($P = .737$). However, similar to our study, Zencir et al[44] found PLR was significantly higher in the group with in-hospital mortality in infective endocarditis ($P = .008$).

Therefore, although PLR is shown as a low-cost, easily applicable marker in inflammatory and infectious processes, we believe that further studies are needed to determine how much PLR will benefit the clinician in terms of showing mortality.[45-47]

Limitation

The limitations of our study are that it was retrospective, conducted on a limited number of intensive care patients, and absolute lymphocyte or absolute neutrophil values were not included in the evaluation.

CONCLUSION

In this study, because of the large difference in the rate of neutrophils and lymphocytes in patients with sepsis who are followed up in the ICU and undergoing HA-330 Sepsis Adsorption Column, and in patients who are healing from hematological parameters and those who are dead, it is suggested that it could be a cheap and useful biomarker in patient prognosis. When the results of the study were analyzed, NLR and PLR parameters were found to be the parameters that can be used for early diagnosis, follow-up, treatment, and prognosis of patients hospitalized in ICUs, which are similar to previous studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Biruni University Clinical Research Ethics Committee (Date: January 27, 2019, Decision no: 2019/27-14).

Informed Consent: Informed consent form was obtained from the patients and/or their relatives.

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