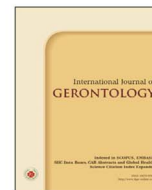




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Original Article

Evaluation of the Relationship between Neutrophil-Lymphocyte Ratio and Clinical Outcomes in Geriatric Patients in the Post Anesthetic Care Unit

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SUMMARY

Background: Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are simple markers that evaluate physiological stress and inflammatory response in the perioperative period. It is affected not only by surgical trauma but also by anesthesia techniques. In this study, we aimed to examine the correlation between anesthesia technique, malignancy and age triad, and NLR and PLR ratio in patients over 65 who underwent surgery and were admitted to the post-anesthesia care unit (PACU).

Methods-Results: A total of 452 patients over 65 were evaluated. When compared in terms of anesthesia techniques, it was determined that the number of patients with malignancy and the length of hospital stay were higher in the general anesthesia group. Leukocytes, neutrophils, and NLR rates were higher in the spinal/epidural group in the preoperative period. NLR and the rate of change of neutrophils, leukocytes, and lymphocytes were higher in the group with malignancy. While a weak correlation was determined between the rate of change and hospitalization, no difference was found in the length of stay in PACU.

Conclusion: The use of NLR and PLR as potential biomarkers for preoperative risk assessment and classification can be appropriate for several reasons. First, it is a simple and inexpensive biomarker that does not require additional research. The other is that the preoperative NLR evaluation is useful in the evaluation of support and rehabilitation of the patients in the postoperative period.

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1. Introduction

Measurement of leukocyte changes, including neutrophil-lymphocyte ratio (NLR), can be a useful method to evaluate the inflammatory response in the perioperative period.^{1,2} It has been reported that a high level of NLR in the preoperative period is associated with negative postoperative outcomes.³ NLR is a simple, inexpensive, and reproducible marker that evaluates physiological stress and inflammatory response in the perioperative period. It has the advantage of being fast and easy to use.⁴ NLR is a systemic inflammatory marker and a potential determinant of risk and outcome in many diseases.⁵ Although it was found that the normal value of NLR varies between 1.65 ± 0.79 and 2.8 ± 1.6 in different studies and populations,^{6,7} normal limits are not clear yet.⁸ Although the exact mechanism is not fully elucidated, neutrophils indicate systemic inflammation, whereas lymphocytes act in the opposite direction.^{9,10} In the perioperative period, changes occur at all stages of the immune system, depending on the extent of the surgery, the age of the patient, general health conditions, the drugs used, and changes in the general physiological response to blood transfusions. The choice of anesthesia technique is one of the most important parameters.^{11,12} At the same time, it is thought that the NLR ratio is useful for predicting the results in patients with malignancy.¹³ Some studies in elderly patients showed that chronic inflammation associated with aging is an

important risk factor for mortality and morbidity.¹⁴ In this study, we aimed to examine the correlation between anesthesia technique, malignancy and age triad, and NLR and platelet-lymphocyte ratio (PLR) in patients over 65 who underwent surgery and were admitted to the post-anesthesia care unit (PACU).

2. Material and method

We approve of the study by Ankara City Hospital institutional review board (E2-22-1453) and informed consent from human subjects. A total of 452 patients over the age of 65 who were admitted to the 5-bed PACU of the general operating room between 2019–2022 were included in this retrospective study. Patients who had been operated on due to trauma and hematological patients (such as leukemia, myelodysplastic syndrome, and myelofibrosis) were excluded from the study. Demographic, clinical, laboratory, and comorbid information were obtained from the patient's medical records. Anesthesia management documents of the patients were found in the archive of the anesthesia clinic, and anesthesia technique, operation time, complications, and other information were noted.

2.1. Statistical analysis

Descriptive statistics for continuous variables were tabulated as mean \pm standard deviation or median, minimum, and maximum,

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depending on the distribution. The normality of numerical variables was controlled with Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests. In the comparison of two independent groups, independent Samples T-test and Mann-Whitney U test were used when numerical variables showed normal distribution and did not show normal distribution, respectively. In the comparison of differences between categorical variables according to groups, Pearson Chi-Square was used for 2×2 tables with expected items of 5 or more, and Fisher's Exact Test was used for tables with expected items less than 5. Spearman's Rho correlation coefficient was used to examine the relationships between numerical variables when the variables do not show a normal distribution. Statistical analyses were performed with Jamovi (Version 2.2.5.0) and JASP (Version 0.16.1) programs, and the significance level was accepted as 0.05 (p-value) in statistical analysis.

3. Results

The mean age, gender, comorbidities, length of stay in hospital and PACU, and complication rates of the patients were evaluated in 2 different categories according to the anesthesia technique and presence of malignancy (Table 1 and Table 2).

A statistically significant difference was found between the two groups in terms of mean age, in which the mean age was higher in spinal/epidural anesthesia (S/EA) applied patient group. When the groups were compared in terms of gender, male gender was more common. The presence of malignancy in the GA group was statistically significantly higher than in the S/EA group. When groups were compared according to comorbidities, no difference was found in anesthesia technique except for Parkinson's disease (more in the GA group). There was no difference between the groups regarding

Table 1
Demographic and clinical characteristics of patient groups according to the type of anesthesia.

	Groups by type of anesthesia		p
	Group GA (n = 230)	Group S/EA (n = 222)	
Age (years) [†]	76.2 ± 8.0	82.3 ± 7.7	< 0.001**
§	75.0 [65.0–100.0]	83.0 [65.0–97.0]	
Gender [‡]			
Male	125 (54.3)	84 (37.8)	0.001*
Female	105 (45.7)	138 (62.2)	
Comorbidities, yes [‡]	197 (85.7)	204 (91.9)	0.051*
Diabetes mellitus, yes [‡]	61 (31.0)	61 (29.9)	0.902*
Hypertension, yes [‡]	124 (62.9)	139 (68.1)	0.323*
Chronic obstructive pulmonary disease, yes [‡]	27 (13.7)	28 (13.7)	0.999*
Alzheimer, yes [‡]	9 (4.6)	19 (9.3)	0.095*
Dementia, yes [‡]	5 (2.5)	14 (6.9)	0.071*
Neuropathy, yes [‡]	1 (0.5)	1 (0.5)	0.999*
Parkinson's disease, yes [‡]	8 (4.1)	1 (0.5)	0.018*
Epilepsy, yes [‡]	3 (1.5)	3 (1.5)	0.999*
Malignancy, yes [‡]	95 (41.3)	22 (9.9)	< 0.001*
Hospitalization time (day) [§]	9.0 [1.0–96.0]	7.0 [1.0–89.0]	0.029**
Length of stay in PACU (hour) [§]	9.0 [1.0–48.0]	13.5 [1.0–30.0]	0.190**
Complication (post-op), yes [‡]	85 (37.0)	100 (45.0)	0.098*

‡: n (%), †: mean ± standard deviation, §: median [min–max].

PACU: Post-anesthesia care unit.

* Pearson Chi-Square or Fisher's Exact test. ** Mann-Whitney U test.

Table 2
Comparison of patients with and without malignancy in terms of demographic and clinical characteristics.

	Patients according to presence of malignancy		p
	No (n = 336)	Yes (n = 118)	
Age (years) [†]	80.8 ± 8.3	74.7 ± 7.1	< 0.001**
§	82.0 [65.0–100.0]	74.0 [65.0–91.0]	
Gender [‡]			
Male	132 (39.3)	79 (66.9)	< 0.001*
Female	204 (60.7)	39 (33.1)	
Comorbidities, yes [‡]	300 (89.3)	103 (87.3)	0.673*
Diabetes mellitus, yes [‡]	87 (29.0)	35 (34.0)	0.409*
Hypertension, yes [‡]	194 (64.7)	70 (68.0)	0.626*
Chronic obstructive pulmonary disease, yes [‡]	47 (15.7)	9 (8.7)	0.112*
Alzheimer, yes [‡]	28 (9.3)	0 (0.0)	0.003*
Dementia, yes [‡]	18 (6.0)	1 (1.0)	0.055*
Neuropathy, yes [‡]	1 (0.3)	1 (1.0)	0.446*
Parkinson's disease, yes [‡]	9 (3.0)	0 (0.0)	0.119*
Epilepsy, yes [‡]	5 (1.7)	1 (1.0)	0.999*
Malignancy, yes [‡]	7.0 [1.0–96.0]	13.0 [1.0–64.0]	< 0.001**
Hospitalization time (day) [§]	11.0 [1.0–48.0]	10.0 [1.0–27.0]	0.984**
Length of stay in PACU (hour) [§]	140 (41.7)	45 (38.1)	0.574*

‡: n (%), †: mean ± standard deviation, §: median [min–max].

PACU: Post-anesthesia care unit.

* Pearson Chi-Square or Fisher's Exact test. ** Mann-Whitney U test.

the length of the PACU stay and the complications' development. However, the height of hospital stay was significantly longer in the GA group (Table 1).

When the patients were compared according to the presence and absence of malignancy, age was statistically significantly lower in the group with malignancy. The number of males and females was significantly lower in the non-malignant group. The length of stay in the hospital was statistically significantly longer in the group with malignancy than in the group without malignancy. There was no difference between the groups regarding length of stay in PACU and frequency of complication development (Table 2).

Significant differences were detected in some measurements of preoperative and postoperative laboratory values of the patients in the groups separated according to the anesthesia technique ($p < 0.05$). While no significant difference was detected in preoperative hemoglobin values, the patients in the GA group in the postoperative period were significantly lower than in the S/EA group ($p < 0.001$).

Leukocyte and neutrophil counts and NLR were found to be higher in Group S/EA patients in the preoperative period ($p < 0.001$, $p < 0.001$, and $p < 0.001$). Preoperative and postoperative PLR values were similar between groups ($p = 0.882$ and $p = 0.400$).

When the preoperative and postoperative percentage changes of hemoglobin, leukocyte, neutrophil, NLR, and glucose values were evaluated between the groups according to the anesthesia technique, significant differences were detected ($p < 0.05$). The increase and percentage change of leukocyte, neutrophil, NLR, and glucose values in the postoperative period compared to the preoperative period was found to be significantly higher in Group GA ($p < 0.05$).

Significant differences were found in terms of preoperative and postoperative values of patients with and without malignancy ($p < 0.05$). While NLR was significantly higher in patients with malignancy than in patients without malignancy during the preoperative period ($p < 0.001$), it was lower during the postoperative period ($p = 0.019$). While the preoperative PLR rate of patients with and without malignancy was similar ($p = 0.216$), it was found to be significantly higher in patients with malignancy in the postoperative period ($p = 0.002$).

The percentage of postoperative change in NLR and PLR ratios compared to preoperative values was significantly higher in patients with malignancy ($p < 0.001$ and $p < 0.001$).

A weak correlation was found between $\Delta\%$ NLR ($r = 0.156$, $p < 0.001$) and $\Delta\%$ PLR ($r = 0.144$, $p = 0.002$) and high hospitalization. No correlation with length of stay in PACU was detected.

4. Discussion

Neutrophil and lymphocyte values, total leukocyte count, acute phase reactants, and some cytokines are biomarkers that can be used to determine the inflammatory response in the body. The complete blood count test, which is widely used in practice, is a simple, inexpensive, and fast test.^{15,16} The NLR value is a simple and easily calculated parameter. Recently, it has been shown in many studies that it can be used to describe the degree of stress and inflammation for many diseases.^{17,18}

Different anesthesia techniques during the intraoperative period may affect the NLR ratio. In a study comparing general anesthesia and spinal anesthesia, it was determined that the increase in NLR level was higher in the general anesthesia group.¹⁹ In our study, the percentage of NLR change during the perioperative period was higher in the general anesthesia group. When the length of hospital stay was evaluated, there was no difference between anesthesia techniques and the length of stay at PACU. On the other hand, the

length of hospital stay was longer in the general anesthesia group. PLR were similar in the preoperative and postoperative periods.

In a study that evaluates the effects of anesthesia technique used in patients operated for pancreatic cancer on the postoperative systemic inflammatory response, postoperative complications, and length of hospital stay, fewer postoperative complications were observed in patients who underwent TIVA during the 90-day postoperative follow-up period. However, no difference was found between the two groups regarding preoperative/postoperative NLR and PLR values.²⁰

In a study by Lee et al., which included 2616 patients undergoing colorectal cancer surgery, propofol-based total intravenous anesthesia was compared with sevoflurane-based inhalation anesthesia by crossing it with NLR. They found no difference between the two groups in terms of NLR levels in the preoperative period. Besides, NLR was found to be significantly lower in the propofol anesthesia group on the 2nd and 5th postoperative days. However, they stated that there was no difference in clinical results despite finding lower NLR values in the propofol anesthesia group.²¹ In a retrospective study by Argun et al., in which they compared the type of anesthesia (general and regional), NLR, and PLR values in 66 patients undergoing bladder cancer surgery, they found that anesthesia type was not effective on NLR and PLR, unlike our study. However, they stated that the number of patients was low and that a larger patient series was needed for further evaluation.²² Erbaş et al. investigated the effects of general and spinal anesthesia on neutrophil/lymphocyte ratio in cesarean section patients and found that the postoperative neutrophil/lymphocyte ratio was significantly lower in patients who underwent cesarean section under spinal anesthesia compared to general anesthesia.²³ In a study examining the relationship between the ASA risk score, which summarizes the physical condition of the patient in the pre-anesthesia evaluation, and the NLR, a significant relation was determined between these two parameters. The importance of the relationship between medication overuse and NLR was mentioned.²⁴ Also, in our study, the group with spinal anesthesia and malignancy, in which NLR was higher in the preoperative period, was compared with the general anesthesia and non-malignant groups, respectively.

Studies have reported that NLR can be a simple predictor of outcomes in patients with malignancy.^{25,26} Similarly, in this study, NLR and PLR values were similar when compared in the non-malignant group, while the preoperative NLR level was higher than PLR in patients with malignancy. At the same time, the percentage change of NLR, PLR, leukocyte, neutrophil, and lymphocyte count was found to be higher in the group with malignancy. No significant difference was found in terms of preoperative, postoperative, and % change values of neutrophil/lymphocyte and platelet/lymphocyte ratios, comorbidity, and gender.

Complications due to physiological changes in organ functions and increases in comorbidities with advancing age increase the percentage of admission to PACU in this group of patients.²⁷ In our study, the mean age of the patients in the spinal anesthesia group was higher than the general anesthesia group in terms of anesthesia management of the patients admitted to the PACU. At the same time, the preoperative NLR value was also higher. However, the percentage change in general anesthesia was higher. The hospital stay rate was higher in the general anesthesia group, which had a lower preoperative NLR but a higher percentage change. The difference in this percentage change ratio may be due to the fact that patients in the general anesthesia group have more malignancies.

There are various opinions about the effect of NLR on postoperative prognosis in the elderly. First, aging is associated with

high levels of pro-inflammatory cytokines.²⁸ For this reason, inflammatory markers can be an independent predictor of negative outcomes in elderly patients with decreased physiological reserve. Secondly, changes such as increased cortisol caused by surgical trauma and stress can cause neutrophilia and lymphopenia.^{28,29} Lymphocytes are the main components of the humoral and cellular immune system. While lymphopenia reflects the weakness of cellular immunity, neutrophilia may cause an imbalance in the systemic inflammatory response.^{30,31} Miniksar et al. determined that preoperative high NLR value in elderly patients with hip fractures under spinal anesthesia is a risk factor in terms of admission to the intensive care unit after surgery and postoperative mortality.³² Forget et al. reported that an NLR value higher than 5 in patients with advanced age, male gender, and comorbid disease after hip fracture surgery during the postoperative period could be important for predicting mortality.³³ He et al. reported that advanced age, diabetes, and an NLR greater than 3.5 are independent risk factors for postoperative delirium in their study, in which they examined the relationship between postoperative delirium and NLR in elderly patients who had undergone total hip arthroplasty.³⁴ In a similar study, Kinoshita et al. compared the rate of delirium and NLR after free flap surgery in the neck region of elderly patients. In that study, researchers have shown that preoperative NLR is a good predictor of delirium. At the same time, they also found that the patient group who developed delirium stayed longer in the intensive care unit.³⁵ Vaughan-Shaw et al. identified NLR as an independent predictor for 30-day results in a retrospective review of patients over 80 who underwent emergency abdominal surgery. They reported that NLR could be a potentially helpful parameter for early postoperative complications.³⁶

In this study, we found that the percentages of NLR change in patients with malignancy who underwent general anesthesia were significantly higher than those without malignancy and those who received regional anesthesia, respectively. Besides, we found a weak correlation between the percentages of preoperative-postoperative NLR change and length of hospital stay in this study. We did not find a significant relationship between the patient's length of stay in the PACU and the level of NLR.

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