Turkish Journal of Geriatrics
DOI: 10.31086/tjgeri.2019.106
2019; 22(3): 305-314

■ Mahmut Alp KARAHAN[1]

RESEARCH

THE EFFECT OF SPINAL ANESTHETIC TECHNIQUE ON NEUTROPHIL TO LYMPHOCYTE RATIO AND POSTOPERATIVE MORTALITY IN ELDERLY PATIENTS WITH CORONARY ARTERY DISEASE UNDERGOING HIP REPLACEMENT SURGERY

Abstract

Introduction: This study aimed to determine the effect of anesthetic techniques on the neutrophil-to-lymphocyte ratio in elderly patients with coronary artery disease who underwent hip replacement surgery.

Materials and Method: In this retrospective cohort study, we reviewed the medical records of 41 elderly patients with coronary artery disease who underwent hip replacement surgery between January 2015 and September 2017. The following data were collected: demographic characteristics; neutrophil-to-lymphocyte ratio measured preoperatively (T0; baseline), on postoperative day 1 (T1), and on postoperative day 2 (T2); anesthetic technique; surgery duration; postoperative complications; and postoperative 1-year mortality.

Results: In total, 41 patients were included, of which 14 (34.1%) were men and 27 (65.9%) were women; the mean age was 77.8±7.89 (range, 65–95) years. The baseline neutrophil-to-lymphocyte ratio (T0) was 6.22±3.8 increased to 10.66±11.47 on T1 and 8.75±7.81 on T2. neutrophil-to-lymphocyte ratio on T2 was significantly higher in patients receiving general anesthesia than in those receiving spinal anesthesia (p=0.032). Within 1 year after surgery, seven (30.6%) deaths were reported: one patient who received spinal-epidural anesthesia and 6 patients who received general anesthesia (p=0.044). The area under the curve for neutrophil-to-lymphocyte ratio on T2 was 0.79 (95% CI, 0.625–0.955; p=0.017) with an optimal cutoff value of 5.18.

Conclusion: Neutrophil-to-lymphocyte ratio on T2 is a risk factor for 1-year mortality in elderly patients with coronary artery disease who underwent hip replacement surgery. Spinal anesthesia was observed to be associated with a lower mortality rate by minimizing neutrophil-to-lymphocyte ratio value on T2 than general anesthesia.

Keywords: Hip fractures; Geriatrics; Neutrophils; Lymphocytes; Anesthesia; Coronary artery disease

CORRESPONDANCE

Mahmut Alp KARAHAN1
Harran University Faculty of Medicine,
Department of Anesthesiology and Reanimation,
Sanliurfa, Turkey.

Mobile: +905327808997
e-mail: mahmutalp_k@yahoo.com

Received: 24/04/2019
Accepted: 26/06/2019

[1] Harran University Faculty of Medicine,
Department of Anesthesiology and
Reanimation, Sanliurfa, Turkey.

ARAŞTIRMA

KALÇA PROTEZİ AMELİYATI GEÇİREN KORONER ARTER HASTALIĞINA SAHİP YAŞLI HASTALARDA SPİNAL ANESTEZİK TEKNİĞİN NÖTROFİL LENFOSİT ORANI VE POSTOPERATİF MORTALİTE ÜZERİNE ETKİSİ

Öz

Giriş: Bu çalışmada, kalça protezi ameliyatı geçiren koroner arter hastalığına sahip yaşlı hastalarda anestezi tekniklerinin nötrofil-lenfosit oranı ve postoperatif mortalite üzerine etkisini belirlemek amaçlanmıştır.

Gereç ve Yöntem: Retrospektif kohort çalışmamızda, Ocak 2015-Eylül 2017 tarihleri arasında kalça protezi ameliyatı geçirmiş koroner arter hastası olan geriatrik hastaların tıbbi kayıtlarını inceledik. Hastaların demografik özellikleri, uygulanan anestezik teknikleri; ameliyat süresi; ameliyat sonrası komplikasyonlar; ve postoperatif 1 yıllık mortalite ile ameliyat öncesi (T0; taban çizgisi), ameliyat sonrası 1. günde (T1) ve ameliyat sonrası 2. günde (T2) nötrofil-lenfosit oranı ölçüldü.

Bulgular: 14'ü (% 34,1) erkek, 27'si (% 65,9) kadın; yaş ortalaması 77.8 ± 7.89 (dağılım, 65–95) olan toplamda 41'i hasta çalışmaya dahil edildi. Bazal nötrofil-lenfosit oranı (T0) 6.22 ± 3.8 idi, T1'de 10.66 ± 11.47'ye ve T2'de 8.75 ± 7.81'e yükseldi. Genel anestezi alan hastalarda T2'deki nötrofil-lenfosit oranı , spinal anestezi alanlara göre anlamlı derecede yüksekti (p = 0.032). Ameliyattan sonraki 1 yıllık mortaliteye bakıldığında, spinal-epidural anestezi alan bir hasta ve genel anestezi alan 6 hasta (p = 0.044) olmak üzere yedi (% 30.6) ölüm rapor edildi. T2'deki nötrofil-lenfosit oranı eğrisi altındaki alan 0.79 , optimum cut-off değeri ise 5.18 (% 95 CI, 0.625-0.955; p = 0.017) idi.

Sonuç: T2'deki nötrofil-lenfosit oranı, kalça protezi ameliyatı geçiren koroner arter hastalığı olan yaşlı hastalarda 1 yıllık mortalite için risk faktörüdür. Spinal anestezinin, genel anesteziden ziyade T2'deki nötrofil / lenfosit oranını en aza indirerek düşük mortalite oranı ile ilişkili olduğu gözlendi.

Anahtar sözcükler: Kalça kırığı; Geriatri; Nötrofil; Lenfosit; Anestezi; Koroner arter hastalığı

INTRODUCTION

With improvements in living standards, the prolongation of human life has resulted in a rapidly growing aging population. Emergent conditions such as systemic diseases, reduction in reflexes, and cerebrovascular events may cause greater exposure to environmental trauma in the elderly population. In addition, the reduced bone mass in the elderly increases the incidence of fracture (1); the most commonly occurring extremity fractures are now viewed as a geriatric epidemic. The incidence of hip fractures (HF), which are usually associated with low-energy trauma, has increased with the growing aging population. Surgery is the best treatment option for elderly patients to regain functional abilities. Because HF occurs predominantly in elderly patients, a high prevalence of underlying coronary artery disease (CAD) can be expected (2). The adaptive capacity of elderly patients is low; moreover, concomitant diseases, particularly cardiovascular diseases (CVD), are often present. Therefore, hip replacement surgery may cause increased morbidity and mortality in elderly patients. The incidence of perioperative myocardial ischemia in elderly patients undergoing HF surgery has been reported to be 35%-2% (3). In recent systematic reviews, mortality within 1 year following HF surgery has been shown to increase from 8.4% to 36% (4,5).

Hip replacement surgery is widely performed in the elderly patients; however, there are controversies regarding the ideal anesthetic technique, particularly in elderly patients with CVD (6). The use of local anesthesia may be the key anesthetic technique to decrease the risk of postoperative complications in patients undergoing hip replacement surgery. The most notable outcomes associated with neuraxial anesthesia include avoidance of intubation and mechanical ventilation and a decrease in blood loss and postoperative analgesia use. However, general anesthesia may offer better hemodynamic stability than neuraxial anesthesia (7).

The neutrophil-to-lymphocyte ratio (NLR) is a popular hematological parameter used as an indicator for subclinical inflammation. NLR is an inexpensive and widely used independent biomarker of morbidity and mortality caused by CVD, particularly CAD. In addition, NLR has been shown to be a risk factor for postoperative mortality and cardiovascular complications in patients undergoing HF repair (8).

This study aimed to investigate the effects of anesthetic techniques on NLR and determine their impact on postoperative mortality in elderly patients with CAD who underwent hip replacement surgery.

MATERIALS AND METHOD

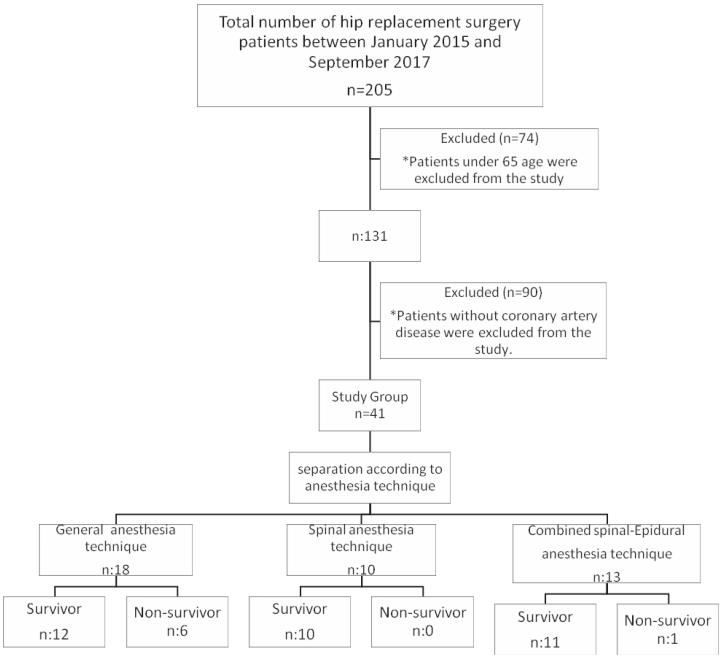
Study plan

In this retrospective cohort study, we reviewed the medical records of 41 elderly patients with CAD who underwent hip replacement surgery between January 2015 and September 2017. The following data were evaluated for each patient: demographic characteristics, laboratory parameters, anesthetic techniques, surgery duration, postoperative complications, and 1-year mortality. The follow-up period was completed in October 2018. Approval for the study was granted by University Medical Faculty Ethics Committee (Approval No. 11; date, February 1, 2018).

Aims of the study and Patient selection

Primarily, we aimed to investigate the effect of anesthetic techniques on NLR in elderly patients with HF and a history of CAD who underwent hip replacement surgery. Our secondary aim was to determine the effect of these techniques on postoperative 1-year mortality and to evaluate the survival period, which was measured from the date of the hip surgery to the last follow-up. The patients included in the study were aged ≥65 years, underwent hip replacement surgery and had a history of CAD (Figure 1).

Figure 1. Consort diagram



Laboratory assessment

Blood samples were obtained from each patient in our bioclinical laboratories preoperatively (T0; baseline) and on postoperative days 1 (T1) and 2 (T2). The blood samples were processed in a blood analyzer (CELL-DYN Ruby hematology analyzer, Abbott, USA) to detect differential whole blood cell and leukocyte counts based on ethylenediaminetetraacetic acid anticoagulants. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Survival status

The survival status of each patient (alive or dead) and the date of death (if any) were retrieved from the Turkish Central Civil Registration System (MERNIS) using the national ID numbers of the patients. However, the cause of death was unavailable in the system.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp). Continuous variables were expressed as mean±standard deviation (SD); categorical variables were expressed as frequencies and percentages. The normal distribution of data was determined using histograms, the Kolmogorov–Smirnov test and Shapiro-wilk test. As the NLR value showed nonnormal distribution, Friedman test was performed to compare time-dependent changes in these parameters. The groups were compared using Kruskal-Wallis H test. Kruskal-Wallis H test was applied to non-parametric data with a 95% confidence interval and p level of <0.05 was accepted significant. In the presence of a significant difference between the data sets, two groups were compared using Mann-Whitney U test to determine whether the differences between the groups were significant.

Relationship between the choice of anesthetic technique and mortality was analyzed using Chi-square test.

Correlations between continuous variables were determined using Spearman's Correlation Coefficient. The receiver-operating characteristic (ROC) curve analysis was performed to identify the sensitivity and specificity of NLR to predict 1-year mortality. A two-tailed test was applied, and a p value of <0.05 was considered to be significant.

RESULTS

Patient characteristics

In total, 41 ASA III patients with CAD who underwent cemented total hip replacement because of unstable trochanteric fracture were included in the study; of these, 14 (34.1%) were men and 27 (65.9%) were women, and their mean age was 77.8±7.89 (range, 65–95) years. In terms of the adequacy of the number of patients, power analysis was performed. We calculated the sample size according to the results of the seven patients in the study. From these differences and assuming a two-tailed α value of 0.05 (sensitivity 95%) and a β value of 0.20 (study power: 80%, effect size: 0.8), we determined that at least 30 patients were required for our study (G Power 3 power analysis programme) (9). We decided that we have enough patients for the study.

The mean durations of surgery, intensive care unit (ICU) stay, and hospitalization were 136.3±41.5 min, 1.2±2.4 days, and 8.2±2.7 days, respectively. The demographic and clinical characteristics of the patients are summarized in Table 1. The duration of ICU stay was positively correlated with the age of the patient (p=0.006, r=0.422) and the baseline NLR (p=0.018, r=0.368). Predictably, the duration of hospitalization was positively correlated with the duration of ICU stay (p=0.002, r=0.473).

Anesthetic technique

General, combined spinal-epidural, and spinal anesthesia were administered in 18 (43.9%), 13 (31.7%), 10 (24.4%) patients, respectively. Complications occurred in 25 (61%) of the patients during anesthesia or surgery; bleeding

Table 1. Baseline demographic and clinical characteristics of the patients

	n (%)
Gender	
Female	27 (65.9)
Male	14 (34.1)
Type of prosthesis	
Total	9 (22)
Partial	32 (78)
Type of anesthesia	
General	18 (43.9)
Spinal	10 (24.4)
Combined spinal-epidural	13 (31.7)
Complication	
Embolism	1 (2.4)
None	16 (39)
Bleeding	16 (39)
Hypotension	6 (14.6)
Delirium	2 (4.9)
Transfusion	
0	14 (34.1)
1	21 (51.2)
2	5 (12.2)
3	1 (24)

(39%) followed by hypotension (14.6%) were the most common complications. The prevalence of complications was lower in the spinal anesthesia group than in other groups. Moreover, the duration of ICU stay was the lowest in the spinal anesthesia group and highest in the general anesthesia group (p=0.016). Furthermore, the requirement for blood transfusion was the lowest in the spinal anesthesia group.

One-year mortality

Within one year after surgery, seven (30.6%) deaths were reported, including one patient who received spinal-epidural anesthesia and six patients who received general anesthesia (p=0.044; Table 2). In our study, in-hospital mortality occurred in only one patient who received general anesthesia because of postoperative pulmonary embolism. With regard to 1-year mortality, a significant difference was observed among the patients who received spinal, combined spinal-epidural anesthesia, and general anesthesia. NLR of >5.18 was determined to be the optimal cutoff level. The ROC curve analysis and the area under the ROC curve indicated a specificity of 85.7% and a sensitivity of 94.8% for the baseline NLR for predicting 1-year mortality. A significant association was observed between mortality and NLR on T2 (p=0.017) (Figure 2).

NLR

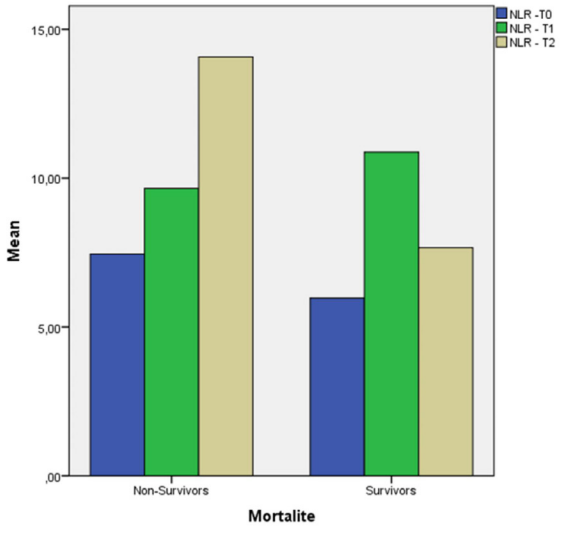
The baseline NLR (T0) was 6.22±3.8 and increased to 10.66±11.47 on T1 and 8.75±7.81 on T2. The increase in NLR from T0 to T1 (p=0.006) and the decrease from T1 to T2 (p=0.033) was statistically significant; however, no significant difference was observed in NLR between T0 and T2 (p=0,241). Moreover, no significant difference was observed in NLR between genders and types of prosthesis (p=0.142). However, a rapid increase in NLR on T2 was observed among the survivors and nonsurvivors (Figure 2).

Table 2. Mean Comparison of the demographic data between the surviving and non-surviving patients.

	Non- Surviving	Surviving	p
	Median (min-max) / n (%)		
Age (years)	75 (65-93)	80 (65-95)	0.245
Gender			
Female	4 (57.1%)	23 (67.6%)	0.594
Male	3 (42.9%)	11 (32.4%)	
Type of prosthesis			
Total	3 (42.9%)	6 (%17.6%)	0.142
Partial	4 (57.1%)	28 (82.4%)	
Anesthetic techniques			
General	6 (85.7%)	12 (35.3%)	0.044*
Spinal	-	10 (29.4%)	
Combined spinal-epidural	1 (14.3%)	12 (35.3%)	
Duration of surgery (min)	135 (100-260)	132.5 (55-240)	0.614

* Chi- square test

Figure 2. NLR values based on the survival status of 41 patients aged over 64 years following hip replacement surgery



No significant difference was found among the NLR values in each of the general anesthesia, spinal anesthesia, and combined spinal-epidural anesthesia groups (p=0.223, p=0.122, and p=0.292, respectively). However, a significant difference was found between general anesthesia and spinal anesthesia with regard to NLR values at T0, T1, and T2 (p=0.0013, p=0.0017, and p=0.004, respectively). Similarly, a significant difference was found between spinal anesthesia and combined spinal-epidural anesthesia with regard to NLR values at T1 (p=0.016) (Table 3). Furthermore, a positive correlation was observed between the baseline NLR and the duration of ICU stay (p=0.018; r=0.368).

DISCUSSION

In this study, we hypothesized that anesthetic techniques may have an effect on NLR and influence mortality rate in elderly patients with CAD who underwent hip replacement surgery. Our results showed that NLR on T2 was significantly higher in the general anesthesia group than in the spinal anesthesia group and that NLR predicted 1-year mortality. Moreover, a significant association was observed between mortality and NLR on T2; furthermore, NLR of >5.18 was determined to be an optimal cutoff level. To our knowledge, this is the first study investigating the effect of anesthetic techniques on NLR and mortality rates in elderly patients with CAD who underwent hip replacement surgery.

CVD is the most common cause of overall mortality in the general population (5,8). More than half of the patients who die because of CVD are aged ≥65 years. The prevalence of CAD, a major CVD, increases with age, particularly in the elderly population (8). CAD requires surgical intervention in half of the elderly patients aged ≥65 years. Furthermore, hip replacement surgery, which is associated with impaired mobility and increased morbidity and mortality in elderly patients, is prevalent is elderly patients with CAD (5). Therefore, an increasing number of elderly patients with CAD who undergo hip replacement surgery are encountered in anesthesia practice.

The "stress response" to surgery leads to the activation of the sympathetic nervous system and various endocrine, immunological, and hematological alterations, thereby resulting in adverse events such as increased oxygen consumption, hypertension, tachycardia, arrhythmia, myocardial ischemia, hemodynamic instability, catabolism, and immune dysfunction. Additionally, stress response has been associated with poor postoperative prognosis and clinical outcomes in patients with cardiovascular diseases, infection, and immunosuppression and in patients with a known diagnosis of endocrine, metabolic, and immune disorders (10, 11).

NLR provides information regarding the association between systemic inflammatory response and physiological stress (12). NLR, is a

Table 3. The effect of anesthetic techniques on NLR.

Anesthetic Technique	NLR T0	NLR T1	NLR T2	P*
	Mean ± SD	Mean ± SD	Mean ± SD	
General	7.33±3.67	14.79±15.70	11.89±9.67	0.223
Spinal	3.50±1.38	5.79±4.21	5.14±3.83	0.112
Combined spinal-epidural	6.77±4.39	8.70±5.16	7.18±5.83	0.292
P**	0.015a	0.021b	0.032c	

*Freidman test; ** Mann Whitney-U test (Kruskal-Wallis test was applied to non-parametric data with a 95% confidence interval and p level of <0.05 accepted significant. In the presence of a significant difference between the data sets, two groups were compared using Mann-Whitney U test to determine whether the differences between the groups were significant), a . Compared to general and spinal Anesthetic Technique (p = 0.0013) ,b. Compared to general and spinal Anesthetic Technique (p = 0.0017), Compared to spinal and combined spinal-epidural Anesthetic Technique (p = 0.016), c. Compared to general and spinal Anesthetic Technique(p = 0.004)

parameter indicating both elevation of neutrophils reflecting acute inflammatory response and reduced lymphocytes reflecting physiological stress. Moreover, NLR has been shown to be a simple predictive marker of clinical outcomes in patients with stable coronary artery disease (13).

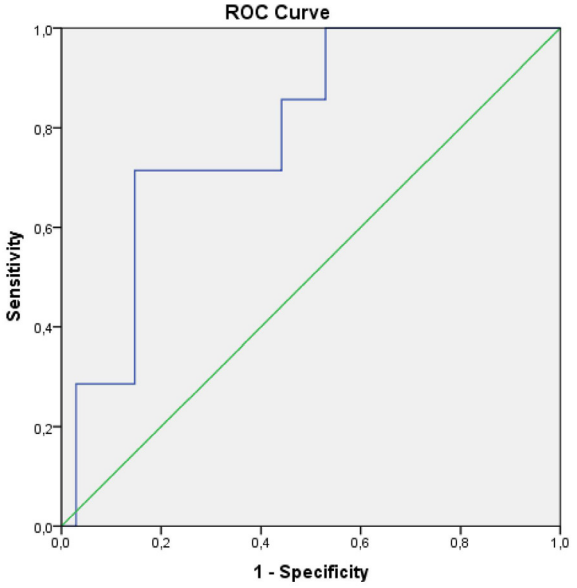
Pain, anesthesia, and surgery are the major stresses in elderly patients with HF. NLR may reflect the persistent status of stress in elderly patients because of The stress-induced hormonal changes involve cortisol secretion, which increases the number of neutrophils through vascular demargination and decreases the number of lymphocytes through a possible central medullary effect (3).

A systematic review by Tan et al. discussed the effects of NLR on mortality and morbidity in patients undergoing cardiovascular surgery (14). The results of the study confirmed a known association between increased NLR and increased mortality following myocardial infarction, chronic ischemic heart disease, and percutaneous coronary intervention. In another study, NLR was shown to be significantly increased in elderly patients with acute myocardial infarction compared with their younger spouses (<60 years); NLR of 9.41 was accepted as the optimal cutoff value for predicting in-hospital mortality (15).

The reduction and modulation of the stress response to surgery is associated with significantly decreased postoperative complications and morbidity. However, this achievement is largely dependent on the choice of an ideal anesthetic technique. Accordingly, previous studies indicated that the choice of anesthetic technique affects intraoperative stress response and thus has a significant effect on the clinical outcomes, morbidity, and the reduction of postoperative pain in patients undergoing surgical treatment. In turn, the choice of anesthetic technique is dependent on various factors including the characteristics of the disease, general condition of the patient, type and severity of the surgical procedure, and the availability of anesthetic equipment and services (10).

NLR is affected not only by the stress response to surgery but also by the choice of anesthetic technique. The formed responses are affected by factors such as direct pharmacological effect of anesthetic material and the type, duration and depth of anesthesia. The neuroendocrine alterations caused by anesthetic techniques are known to affect NLR and to have an indirect effect on postoperative complications; therefore, they are likely to affect the choice of anesthetic technique (16).

Figure 3. Performance analysis of NLR for one-year mortality in 41 patients aged over 64 years following hip replacement surgery. The area under the curve (AUC) for the NLR at T2 was 0.79 [95% CI, 0.625–0.955] (p=0.017, AUC=0.79) with an optimal cut-off value of 5.18. (specificity 85.7% ,sensitivity 94.8%)



The effects of general and regional anesthesia on proinflammatory and anti-inflammatory cytokines have been extensively shown in previous studies. (17, 18)Regional anesthesia has been shown to have several advantages over general anesthesia such as inhibition of metabolic and hormonal responses to surgery, reduced incidence of postoperative pain, accelerated peristalsis following abdominal surgery, reduced incidence of deep vein thrombosis, and shorter hospitalization periods. These advantages are attributed to spinal anesthesia blocking the sensory afferent nerve impulses originating from the surgical trauma and also to the blocking of the efferent and afferent pathways of the sympathetic and somatic nervous system that inhibits activation of the neuroendocrine axis during surgical procedures (10).

Our knowledge, no comprehensive study has reported regarding the effects of inhaled, spinal, or combined spinal-epidural on NLR in elderly patients undergoing specific surgeries. There are only limited studies regarding the effect of anesthetic techniques on NLR (16, 18-19). A previous retrospective study evaluating the relationship between NLR and the choice of anesthetic technique in patients undergoing cesarean section and reported that the postoperative NLR values were significantly lower in patients that underwent spinal anesthesia compared to general anesthesia (18). Another study evaluated the relationship between NLR and the choice of anesthetic technique in patients undergoing infraumbilical surgery and revealed that both postoperative total leukocyte count and NLR values were significantly higher in patients that underwent general anesthesia compared to spinal anesthesia (16). In our study, NLR in all time periods was significantly higher in the general anesthesia group than in the spinal anesthesia group.

In a retrospective analysis of 247 patients aged >65 years who had undergone surgery for HF, Forget et al. evaluated 1-year mortality based on perioperative NLR. General anesthesia was administered in most patients (98.4%), and the results indicated that NLR measured at postoperative day 5 was a risk factor for postoperative mortality and cardiovascular complications (3). Another study by the same authors estimated the mortality score in elderly patients with HF using a discrete 0–4 scoring system based on NLR and an NLR cutoff value of 4.9. The authors concluded that the scoring system could predict mortality in elderly patients within the first year after surgery. Nevertheless, details regarding the anesthetic technique used in the study were unavailable (20).

Fisher et al. examined the short-term outcomes of NLR in orthogeriatric patients and observed significant associations among the presence of

HF, postoperative complications, and NLR. NLR of >5.1 was associated with an increased risk of fractures, developing postoperative myocardial injury (troponin I increase), and a high inflammatory response/infection (21). Moreover, NLR of ≥5.1 and >8 could predict postoperative myocardial injury and in-hospital mortality, respectively. However, details regarding the anesthetic technique used in the study were unavailable.

In our study, the NLR cutoff value was 5.18, which was similar to that in previous studies (3,20). However, the increased NLR on T2 was revealed to be a prognostic factor for 1-year mortality. Furthermore, the incidence of 1-year mortality was observed to be higher in patients receiving general anesthesia than in those receiving other types of anesthesia; the lowest mortality rate was observed in the spinal anesthesia group. Similarly, the effect of spinal anesthesia on NLR on T2 was lower than that of general anesthesia.

Our study is a retrospective analysis of single-center for this reason a limitation of our study was the nonhomogeneous study design with regard to patients' ages associated with an increased risk of mortality (i.e., 65–95 years). Another limitation was that the study did not provide information regarding the nutritional status of the patients, although malnutrition is known to be a risk factor following HF and is typically associated with lymphopenia. Therefore, there is no nutritional data and it has been excluded from the scope of the study.

In conclusion, our study indicated that NLR measured on T2 and general anesthesia are associated with a high risk of mortality in elderly patients with CAD who underwent surgery for HF. Moreover, spinal anesthesia was observed to be associated with a lower mortality rate by minimizing NLR value on T2 than general anesthesia.

FUNDING

This research received no external funding.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

REFERENCES

1. Koç M, Saçan Ö, Gamlı M, et al. Retrospective Evaluation of Anaesthesia Techniques for Hip Replacement Operations. Turk J Anaesthesiol Reanim 2014 ;42(3):133-9. (PMID: 27366407)
2 Matot I, Oppenheim-Eden A, Ratrot R, et al. Preoperative cardiac events in elderly patients with hipfracture randomized to epidural or conventional analgesia. Anesthesiology 2003;98(1):156-63.(PMID: 12502992)
3 Forget P, Moreau N, Engel H, et al. The neutrophil-to-lymphocyte ratio (NLR) after surgery for hip fracture (HF). Arch Gerontol Geriatr 2015;60(2):366-71. (PMID: 25488015)
4 Petersen MB, Jørgensen HL, Hansen K, Duus BR. Factors affecting postoperative mortality of patients with displaced femoral neck fracture. Injury 2006 ;37(8):705-11. (PMID: 16765352)
5 Vidán M, Serra JA, Moreno C, Riquelme G, Ortiz J. Efficacy of a comprehensive geriatric intervention in older patients hospitalized for hip fracture: a randomized, controlled trial. J Am Geriatr Soc 2005;53(9):1476-82. (PMID: 16137275)
6 Van Waesberghe J, Stevanovic A, Rossaint R, Coburn M. General vs. neuraxial anaesthesia in hip fracture patients: a systematic review and meta-analysis. BMC Anesthesiol 2017 28;17(1):87. (PMID: 28659127)
7 Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA. Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. Anesthesiology 2012 ;117(1):72-92. (PMID: 22713634)
8 Piepoli MF, Hoes AW, Agewall S, et al. [2016 European guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of

the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts. Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation]. G Ital Cardiol (Rome) 2017;18(7):547-612. (PMID: 28714997)

9 Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-91 (PMID: 17695343)

10 Milosavljevic SB, Pavlovic AP, Trpkovic SV, Ilić AN, Sekulic AD. Influence of spinal and general anesthesia on the metabolic, hormonal, and hemodynamic response in elective surgical patients. Med Sci Monit. 2014;20(6):1833-40.(PMID: 25284266)

11 Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stres responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000;21(1):55-89. (PMID: 10696570)

12 Kovar FM, Endler G, Wagner OF, Jaindl M. Basal haemoglobin levels as prognostic factor for early death in elderly patients with a hip fracture—A twenty year observation study. Injury 2015;46(6):1018-22. (PMID: 25704141)

13 Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F. Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. Clin Chim Acta. 2008;395(1-2):27-31. (PMID: 18498767)

14 Tan TP, Arekapudi A, Metha J, Prasad A, Venkatraghavan L. Neutrophil-lymphocyte ratio as predictor of mortality and morbidity in cardiovascular surgery: a systematic review. ANZ J Surg 2015;85(6):414-9. (PMID: 25781147)

15 Guo TM, Cheng B, Ke L,et al. Prognostic Value of Neutrophil to Lymphocyte Ratio for In-hospital Mortality in Elderly Patients with Acute Myocardial Infarction. Curr Med Sci 2018;38(2):354-59. (PMID: 30074197)

16 Nethra SS, Chaithali H, Sudheesh K, Devikarani D, Raghavendra Rao RS, Chethana GM. The effect of anesthetic techniques on neutrophil to lymphocyte ratio in patients undergoing infraumbilical surgeries. Korean J Anesthesiol. 2019 May 17. [Epub ahead of print] (PMID: 31096728.)

17 Buyukkocak U, Caglayan O, Daphan C, Aydinuraz K, Saygun O, Agalar F. Similar effects of general and spinal anaesthesia on perioperative stress response in patients undergoing haemorrhoidectomy. Mediators Inflamm. 2006;2006(1):97257.(PMID: 16864910)

18 Erbaş M, Toman H, Gencer M, Şahin H, Kiraz HA, Şimşek T, et al. The effect of general and spinal anesthesia on neutrophil to lymphocyte ratio in patients undergoing cesarian section. Anaesth Pain Intensive Care 2015; 19: 485–8

19 Kim WH, Jin HS, Ko JS,et al. The effect of anesthetic techniques on neutrophil-to-lymphocyte ratio after laparoscopy-assisted vaginal hysterectomy. Acta Anaesthesiol Taiwan 2011;49(3):83-7. (PMID: 21982167)

20 Forget P, Dillien P, Engel H, Cornu O, De Kock M, Yombi JC. Use of the neutrophil-to-lymphocyte ratio as a component of a score to predict postoperative mortality after surgery for hip fracture in elderly subjects. BMC Res Notes 2016 26;9:284. (PMID: 27230508)

21 Fisher A, Srikusalanukul W, Fisher L, Smith P. The Neutrophil to Lymphocyte Ratio on Admission and Short-Term Outcomes in Orthogeriatric Patients. Int J Med Sci 20165;13(8):588-602. (PMID: 27499691)