Research Article / Araştırma Makalesi

Effect of the Neutrophil-Lymphocyte Ratio and Red Blood Cell Distribution Width on Postoperative Prognosis

Preoperatif Nötrofil-Lenfosit Oranının ve Eritrosit Dağılım Genişliğinin İzole Kalp Kapak Ameliyatlarında Postoperatif Prognoza Etkisi

[1]Resul Ekici, [2]Dilek Çetinkaya, [3]Ferda Yaman, [4]Sadettin Dernek

[1]Eskişehir Osmangazi University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Eskisehir, Türkiye
[2] Eskişehir Osmangazi University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Eskisehir, Türkiye
[3] Eskişehir Osmangazi University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Eskisehir, Türkiye
[4] Eskişehir Osmangazi University, Faculty of Medicine, Department of Cardiovascular Surgery, Eskisehir, Türkiye

Abstract: It has been stated that red blood cell distribution width (RDW) and neutrophil-lymphocyte ratio (NLR) have prognostic value in cardiovascular surgery, as well as various clinical conditions. This study aimed to determine whether preoperative NLR and RDW values had an effect on postoperative mortality and morbidity in patients undergoing isolated heart valve surgery.
Methods: This study was retrospectively conducted by examining the medical records of patients who underwent isolated heart valve replacement surgery between 2016 and 2020. Preoperative RDW and NLR values, postoperative extubation, mechanical ventilation, intensive care unit stay, and hospital stay, presence of postoperative cerebrovascular disease (CVD) and new-onset atrial fibrillation (AF), and dialysis requirement were recorded. The data of 68 patients were evaluated. In all the patients, the mean preoperative NLR value was 4.67±3.67, and the mean preoperative RDW value was 15.06±2.19. The NLR and RDW values were determined as 4.91(p=0.756) and 15.48 (p=0.032); respectively in the patients that developed postoperative AF, 3.34 and 17.56, respectively in those that developed postoperative CVD, and 9.26 and 14.93, respectively in those that required dialysis. Although preoperative the NLR and RDW values were high among the patients undergoing heart valve replacement surgery, it is not possible to state that these two markers have prognostic value for postoperative adverse events in this patient population.
Keywords: Heart Valve Surgery, Neutrophil-Lymphocyte Ratio, Red Blood Cell Distribution Width

Özet: Kırmızı kan hücresi dağılım genişliği (RDW) ve nötrofil-lenfosit oranının (NLR), çeşitli klinik durumlar yanında kardiyovasküler cerrahide prognostik değere sahip olduğu belirtilmektedir. Bu çalışmada, izole kalp kapak ameliyatı geçiren hastalarda preoperatif NLR ve RDW değerinin postoperatif mortalite ve morbiditede etkisi olup olmadığını gözlemlemeyi amaçladık. Bu çalışma 2016-2020 tarihleri arasında izole kalp kapak replasman cerrahisi uygulanan hastaların tıbbi kayıtlarının geriye dönük incelenmesi ile oluşturulmuştur. Ameliyat öncesi RDW ve NLR değerleri, ameliyat sonrası ekstübasyon, mekanik ventilasyon, yoğun bakım kalış ve hastanede kalış süreleri, ameliyat sonrası serebrovasküler hastalık (SVH) ve yeni başlayan atriyal fibrilasyon (AF) varlığı ve diyaliz gereksinimi kaydedildi. Toplam 68 hastanın verileri değerlendirildi. Tüm hastaların ameliyat öncesi ortalama NLR değeri 4,67±3,67, ameliyat öncesi ortalama RDW değeri ise 15,06±2,19 idi. NLR ve RDW değerleri postoperatif AF gelişen hastalarda sırasıyla 4,91(p=0.756) ve 15,48 (p=0.032); postoperatif SVH gelişen hastalarda sırasıyla 3,34 ve 17,56; diyaliz gerektiren hastalarda sırasıyla 9,26 ve 14,93 olarak belirlendi. Kalp kapak replasman ameliyatı geçiren hastalarda ameliyat öncesi NLO ve RDW değerleri yüksek olmasına rağmen bu iki belirtecin bu hasta popülasyonunda ameliyat sonrası istenmeyen olaylar açısından prognostik değere sahip olduğunu söylemek mümkün değildir.
Anahtar Kelimeler: Kalp Kapak Ameliyatı, Nötrofil-Lenfosit Oranı, Kırmızı Kan Hücresi Dağılım Genişliği

ORCID ID of the authors: RE. 0000-0002-0061-9239, DÇ. 0000-0002-9320-7005, FY. 0000-0001-6847-1720, SD. 0000-0002-0865-7694

Received 19.07.2024 ***Accepted*** 25..09.2024 ***Online published*** 27.09.2024

Correspondence: Dilek ÇETİNKAYA- Eskişehir Osmangazi University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Eskisehir, Türkiye
e-mail: drdceyhan@gmail.com

1. Introduction

Inflammation and immune response are the essential components in the pathogenesis of many diseases. Red blood cell distribution width (RDW) and neutrophil-lymphocyte ratio (NLR) are considered to have prognostic value in a variety of clinical situations, for example type 2 diabetes and acute kidney injury (1,2). RDW is a measure of changes in circulating red blood cell volume and traditionally used to differentiate causes of anemia. Increased RDW, which represents greater heterogeneity in circulating erythrocyte size (anisocytosis), has been reported to be strongly associated with adverse outcomes in patients with chronic heart disease (3). NLR, a marker of host inflammation calculated by dividing the number of neutrophils by lymphocytes, has also been suggested to have the potential to predict survival in various cancers (4).

During cardiac surgery, acute systemic inflammatory response develops due to cardiopulmonary bypass, cardiac arrest, and surgical trauma, and this increased response is known to increase the risk of postoperative complications (5). It has also been reported that NLR and RDW are prognostic in predicting 1 year mortality when used together with traditional factors in patients undergoing percutaneous coronary intervention (6). In light of this information, we planned the current study to determine whether preoperative NLR and RDW values had an effect on postoperative mortality and morbidity in patients undergoing isolated heart valve surgery.

2. Materials and Methods

After obtaining approval from the local ethics committee (2020/43), this study was retrospectively conducted by examining the files of patients aged over 18 years, who underwent elective isolated heart valve surgery from January 1, 2016, through January 1, 2020. Patients with an ejection fraction (EF) below 20%, pulmonary artery pressure (PAP) above 50 mmHg, and diagnosis of atrial fibrillation (AF) or iron deficiency anemia were excluded from the study.

The patients' gender and age, body mass index (BMI), comorbidities [diabetes mellitus, hypertension, and chronic obstructive pulmonary disease (COPD)-asthma], EF, cross-clamp time, extubation time, mechanical ventilation (MV) requirement, length of stay in the intensive care unit (ICU) and hospital, number of valves replaced, presence of postoperative cerebrovascular disease (CVD) and new-onset AF, and postoperative dialysis requirement were recorded from the patient files, anesthesia records, and perfusion charts, and the preoperative NLR and RDW values were calculated.

Statistics: All the statistical analyses were performed using IBM SPSS v. 25.0. Descriptive statistics in the analyses were expressed as frequency (f) and percentage (%) values. First, the phenotypic characteristics of the patients were examined. Then, the clinical findings of the patients were included in the evaluation. Finally, the relationship between the patients' clinical findings and quantitative variables was examined with the Pearson correlation analysis. The statistical significance level was accepted as $p < 0.05$.

3. Results

A total of 68 patients who met the inclusion criteria were included in the study. The mean age of the patients was 56.88 ± 10.04 years. Of all the patients, 40 (58.8%) were male and 28 (41.2%) were female. The mean BMI was 28.21 ± 2.09, the mean EF percentage was 54.29 ± 10.48, and the mean PAP was 38.09 ± 10.04. When the comorbidities were evaluated, 16 (23.5%) of the patients had diabetes mellitus, 40 (41.2%) had hypertension, and 15 (22.1%) had COPD-asthma (Table 1). The mean preoperative NLR value was 4.67 ± 3.67, and the mean preoperative RDW value was 15.06 ± 2.19.

The mean number of valves replaced was 1.54 ± 0.63. Mitral valve replacement was performed in 20 patients, aortic valve replacement in 16, aortic and mitral valve replacement in 27 and aortic and mitral valve replacement together with tricuspid valve intervention in five. The mean cross-clamp

time of the patients was 117.31 ± 34.59 minutes, mean MV time was 12.54 ± 28.36 hours, mean extubation time was 11.25 ± 11.87 hours, mean length of ICU stay was 75.49 ± 36.51 hours, and mean length of hospital stay was 9.44 ± 3.74 days.

In the postoperative period, 18 (26.48%) patients developed new-onset AF, three (4.42%) patients developed CVD, three (4.42%) patients required dialysis, and 16 (23.53%) patients required MV support for longer than six hours. The preoperative NLR and RDW values of these patients are given in Table 2.

Of the patients who postoperatively developed new-onset AF, nine were female and nine were male. The RDW value of the patients with new-onset AF development was statistically higher compared to the remaining patients (15.48 ± 3.21, p =0.032). The NLR value was also higher in the patients with new-onset AF development, but this was not statistically significant (4.91 ± 4.06, p=0.756). The mean age (63.5 ± 9.54, p=0.013) and PAP value (40.7 ± 10.23, p=0.132) of these patients were higher than the remaining patients. A strong correlation has been proven between increasing age and postoperative atrial fibrillation, which was also found in this study. PAP value was not statistically significant. However, the mean number of operated valves and the cross-clamp times were found to be statistically similar between the patients with and without new-onset AF (Table 3).

The length of ICU stay had a positive and moderately significant correlation with preoperative RDW ($p < 0.05$) but was not significantly correlated with preoperative NLR ($p > 0.05$). There was no statistically significant correlation between the preoperative NLR and RDW values and postoperative bleeding.

Table 1. Demographic and clinical data of the patients

n=68		**Mean ± SD, n-%**
Age (year)		56.88 ± 10.04
Gender	Male/Female	40 (58.8%)/28(41.2%)
BMI (kg/m^2)		28.21 ± 2.09
Comorbidity	DM	16 (23.5%)
	HT	40 (58.8%)
	COPD-Asthma	15 (22.1%)
EF (%)		54.29 ± 10.48
PAP (mmhg)		38.09 ± 10.04
MV time (hours)		12.54±28.36
Extubation time (hours)		11.25±11.87
ICU stay time (hours)		75.49±36.51
Hospital stays time (days)		9.44±3.74

SD: standard deviation, BMI: body mass index, DM: diabetes mellitus, HT: hypertension, COPD: chronic obstructive pulmonary disease, EF: ejection fraction, PAP: pulmonary artery pressure, MV: mechanical ventilation, ICU: intensive care unit

Table 2. Postoperative adverse complications

	Preoperative NLR Mean (min-max)	**Preoperative RDW Mean (min-max)**
New-onset AF (n = 18)	4.91 (1.67-16.6)	15.48 (12.7-20)
CVD (n = 3)	3.34 (2.6- 4.5)	17.56 (12.7- 20)
Dialysis requirement (n = 3)	9.26 (3.4-16.6)	14.93 (14.4 -15.3)
Prolonged ventilation requirement (longer than six hours) (n = 16)	4.62 (2- 14.1)	15.31 (13.4- 20.8)

NLR: neutrophil/lymphocyte ratio, RDW: red blood cell distribution width, AF: atrial fibrillation, CVD: cerebrovascular disease

Table 3. Comparison of the patients with and without new-onset AF development

	Patients with new-onset AF (n = 18)	Patients without new-onset AF (n = 40)	P value
RDW	15.48 ± 3.21	14.91 ± 2.02	0.032
NLR	4.91 ± 4.06	4.59 ± 3.52	0.756
Age (year)	63.5 ± 9.54	52.42 ± 10.23	0.013
EF	54.5 ± 10.35	52.22 ± 11.09	0.580
PAP	40.7 ± 10.23	36.68 ± 11.02	0.132
Cross-clamp time (min)	110.27 ± 7.65	119 ± 8.35	0.149
Number of valves replaced	1.39 ± 0.71	1.58 ± 0.67	0.679

RDW: red blood cell distribution width, NLR: neutrophil/lymphocyte ratio, EF: ejection fraction,

4. Discussion

Previous data have shown that a high leukocyte count is associated with a worse outcome in coronary heart disease (7), and more prognostic information can be obtained by evaluating the NLR values of patients (8). It has also been suggested that NLR values may reflect the long-term consequences of increased perioperative myocardial damage (7). However, a similar mechanism has not been demonstrated in patients undergoing heart valve replacement surgery. In a previous study investigating the predictive value of NLR in patients with calcific aortic stenosis in which inflammation and calcification are active, the incidence of major adverse cardiac events was reported to be higher among those with an NLR value of >2, and thus the authors concluded that NLR could be used in risk classification in these patients (9). Similarly, in the current study, the NLR value was above 2 in the patients who developed adverse events postoperatively. This value even reached 9.26 among those that required postoperative dialysis.

It has been suggested that RDW is an indicator of the patient's physiological reserve or the ability of cells to defend against strong hypoxia stress. An increased RDW value reflects a low physiological reserve (10). It is, therefore, not surprising that a low reserve increases the risk of complications in cardiac operations involving high stress. In a study evaluating the prognostic role of RDW in patients undergoing cardiac rehabilitation after myocardial revascularization and/or heart valve surgery, it was determined that the cardiovascular death rate increased at RDW values above 13.9% and even tripled at those above 15 (11). Consistently, we determined that the RDW value was higher in the patients with postoperative adverse events.

In the current study, the rate of AF development after cardiac surgery was recorded as 48.8% after heart valve surgery. It is known that many factors (inflammation, previous cardiac status, age, gender, etc.) are effective in the pathogenesis of AF (12). Although postoperative AF often occurs in the first week after surgery, the highest incidence is seen on the second day. Therefore, it can be stated that the risk of postoperative AF development is high in patients with high preoperative inflammation and oxidative stress. RDW, an indicator of high oxidative stress and inflammation, can be considered as a predictor of postoperative AF (13). In the literature, studies investigating the relationship between high preoperative RDW values and postoperative AF have shown that a high RDW value is an independent factor of AF development (13-15). In our study, the preoperative RDW value was higher in the patients who postoperatively developed new-onset AF, but the mean age of these patients was also higher compared to the remaining cases. Since advanced age is a major risk factor for the development of postoperative AF, it does not seem possible to consider RDW alone as a predictor of postoperative AF in our patients.

There are publications reporting that patients with high RDW values have a higher incidence of stroke, and high RDW values have also been associated with a worse prognosis in patients with an acute stroke

(16,17). Although the exact pathogenesis remains unclear, it has been suggested that high RDW causes impaired microcirculation (18). Duchnowski et al. observed high RDW values in patients who had a stroke after elective heart valve surgery and concluded that a high RDW value was associated with perioperative stroke/transient ischemic attack and mortality (18). In another study investigating the relationship of the preoperative NLR value with 30-day mortality, it was found that patients with NLR > 3.23 had higher postoperative creatinine values, prolonged intubation time and ICU stay, and a higher rate of new-onset neurological conditions. Therefore, the authors stated that NLR might be useful for perioperative risk assessment in patients undergoing cardiac surgery (20). According to our evaluation, three patients had a new-onset stroke and three had kidney failure requiring dialysis. The mean NLR value of the patients that had a stroke was 3.34, which is higher than reported by Haran et al (20). In addition, the mean RDW value of our patients with a stroke was 17.56. While the NLR value was found to be very high in the three patients with kidney failure requiring dialysis, the RDW values were above the cut-off value determined by Lazzeroni et al (11). Similarly, the length of ICU stay increased with high RDW values, but no such relationship was observed for high NLR.

Our study has certain limitations, including the single-center and retrospective design, small sample size, and the evaluation of only preoperative values.

In conclusion, we determined the preoperative NLR and RDW to be high in the patients that underwent heart valve replacement surgery. However, it is not possible to state that these two inflammatory markers have prognostic value for postoperative adverse events in this patient population.

REFERENCES

1. Assulyn T, Khamisy-Farah R, Nseir W, Bashkin A, Farah R. Neutrophil-to-lymphocyte ratio and red blood cell distribution width as predictors of microalbuminuria in type 2 diabetes. *J Clin Lab Anal*. 2020;34(7):e23259
2. Zhu J, Zeng C, Zhang L, Shu S, Liu Y, Chen G, et al. Red blood cell distribution width and neutrophil-to-lymphocyte ratio in predicting adverse outcomes of acute kidney injury in hospitalized patients. *Kidney Dis (Basel).* 2020:6:371-381
3. Yamada S, Yoshihisa A, Kaneshiro T, Amami K, Hijioka N, Oikawa M, et al. The relationship between red cell distribution width and cardiac autonomic function in heart failure. *J Arrhythm.* 2020;36:1076-1082
4. Arıman A, Merder E. The prognostic importance of neutrophil-to-lymphocyte ratio in testicular cancer. *Urologia.* 2021;88:200-205
5. 5. Weedle RC, Da Costa M, Veerasinggam D, Soo AWS. The use of neutrophil lymphocyte ratio to predict complications postcardiac surgery. *Ann Transl Med.* 2019;7:778
6. Huo LK, Chen KY, Tse G, Liu T. Association of inflammatory markers based on routine blood with prognosis in patients underwent percutaneous coronary intervention. Medicine (Baltimore) 2004;103 (19):e38118.
7. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI,Gibson G, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J*. 2007;154:995-1002
8. Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al. Which white blood cell subtypes predict increased cardiovascular risk? *J Am Coll Cardiol.* 2005;45:1638-1643
9. Cho KI, Cho SH, Her AY, Singh GB, Shin ES. Prognostic utility of neutrophil-to-lymphocyte ratio n adverse clinical outcomes in patients with severe calcific aortic stenosis. *PLoS One*. 2016;11:e1061530
10. 10. Hunziker S, A Cell L, Lee J, Howell MD. Red cell distribution width improves the simplified acute physiology score for risk prediction in unselected critically ill patient. *Crit Care*. 2012;16:89
11. Lazzeroni D, Moderato L, Marazzi PL, Pallegrino C, Musiari E, Castiglioni P, et al.

Red blood cell distribution width as a novel prognostic marker after myocardial revascularization or cardiac valve surgery. *Sci Rep.* 2021;11:7889
12. Qureshi M, Ahmed A, Massie V, Marshall E, Harky A. Determinants of atrial fibrillation after cardiac surgery. *Rev Cardiovasc Med*. 2021;22:329-341
13. Xin L, Chenghao C, Shuwen H, Shenglin G, Chenggxin Z. Association of red blood cell distribution width with post-operative new-onset atrial fibrillation following cardiac valve replacement surgery: a retrospective study. *Biomarkers*. 2022;27: 286-292
14. Ertaş G, Aydin C, Sönmez O, Erdoğan E, Turfan M, Tasal A, et al. Red cell distribution width predicts new-onset atrial fibrillation after coronary artery bypass grafting. *Scand Cardiovasc J.* 2013;47:132-135
15. Kılıcgedik A, Naser A, Gurbuz AS, Kulahcioglu S, Bakal RB, Unkun T, et al. Red cell distribution width with CHADS2 and CHA2DS2-VASc score is associated with post-operative atrial fibrillation after coronary artery bypass grafting. *The Heart Surgery Forum.* 2018;21 :E170–E174
16. Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. *J Neurol Sci*. 2009;277:103-108
17. Kim J, Kim YD, Song TJ, Park JH, Lee HS, Nam CM, et al. Red blood cell distribution width is associated with poor clinical outcome in acute cerebral infarction. *Tromb Haemost.* 2012;108:349-356
18. Patel KV, Mohanty JG, Kanapuru B, Hesdorffer C, Ershler WB, Rifkind JM. Association of the red cell distribution width red blood cell deformability. *Adv Exp Biol.* 2013;765:211-216
19. Duchnowski P, Hryniewiecki T, Kusmierczyk M, Szymanski P. Red cell distribution width is a pronostic marker of perioperative stroke in patients undergoing cardiac valve surgery. *Interact Cardiovasc Thorac Surg*. 2017;25:925-929
20. Haran C, Gimpel D, Clark H, McCormack DJ. Preoperative neutrophil and lymphocyte ratio as a predictor of mortality and morbidity after cardiac surgery. *Heart Lung Circ.* 2021;30(3):414-418

Ethics

Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Ethics Committee (43/2020).
Informed Consent: This study did not require informed consent.
Authorship Contributions: Consept, Design, Data Collection or Processing, Analysis, Literature Search: RE, DÇ. Writing: DÇ FY, Surgical and Medical Practices: SD
Copyright Transfer Form: Copyright Transfer Form was signed by all authors.
Peer-review: Internally peer-reviewed.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.