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Red cell distribution width, eosinophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio can predict the development of infection and the number of antibiotics used in elderly patients undergoing revision total knee arthroplasty

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ABSTRACT

Introduction: We aimed to evaluate the relationship between complete blood parameters reported to be associated with inflammation and development of complications, length of hospital stays and the number of antibiotics used in elderly patients undergoing revision total knee arthroplasty (rTKA).

Material and Method: Our retrospective study was conducted in a single center and included 72 older patients who underwent rTKA operations. We recorded patients' firs day preoperative, first day postoperative and 45th day postoperative whole blood parameters.

Results: It was found that the development of postoperative infection and the number of antibiotics used were higher in patients with low preoperative Hb values and high platelet-to-lymphocyte ratio (PLR) rates. In patients with high RDW value and high eosinophil-lymphocyte ratio (ELR) one day after surgery, both the development of infection (P=0.002, P=0.002) and the number of antibiotics used during follow-up were found to be significantly higher (P<0.001, P<0.001). When the laboratory parameters were evaluated 45 days after the operation, it was determined that the RDW (P=0.001, P=0.001) and ELR (P=0.039, P<0.001) elevations continued in the patients who developed infection and used multiple antibiotics. CRP and ESR values one day and 45 days after surgery were also found to be significantly associated with the development of infection and the use of multiple antibiotics.

Conclusion: RDW, ELR and PLR parameters may be as important as CRP and ESR in predicting the development of infection and the number of antibiotics used in elderly patients undergoing rTKA.

Keywords: Eosinophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, red cell distribution width, revision total knee arthroplasty

INTRODUCTION

Total Knee Arthroplasty (TKA) has been widely used as a treatment for gonarthrosis in recent years. In parallel, revision total knee arthroplasty (rTKA) procedures are also increasing. Revision TKA is generally applied for infection, aseptic loosening, polyethylene wear, instability, pain/stiffness, osteolysis, and malposition/misalignment (1,2). According to the Canadian Institute for Health Information (CIHI), between 2012 and 2017, out of 84.770 operations (excluding 35.945 patella operations), the most frequent indication for rTKA was infection (3). It was also shown that infection was the most common reason for early TKA failures in a retrospective study of 781 patients who underwent rTKA (4).

Knee arthroplasty surgery, like other orthopedic surgeries and trauma, causes changes in blood parameters, mainly neutrophil and lymphocyte rates (5-7). Blood parameters such as platelet count, neutrophil count, mean platelet volume (MPV), red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), which are easily accessible, have been evaluated in several knee surgery studies. Platelet count, MPV, and NLR have been reported to be better markers than erythrocyte sedimentation rate (ESR) and

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C-reactive protein (CRP) in showing inflammation and joint infection (8,9). In a study, serum IL-6, TNF-a, NLR, and PLR were measured just before the operation and on the first and third days postoperative. Stress response was found to be higher in those with high preoperative NLR (10). RDW is a parameter that shows anisocytosis and is routinely calculated in whole blood tests. High RDW is associated with mortality in many internal and surgical diseases other than anemia (11-13). In patients who underwent revision arthroplasty, those with high preoperative RDW values were reported to have worse post-revision optimal results (14).

In our study, we compared the pre- and postoperative whole blood parameters of elderly patients who underwent rTKA in our clinic with the development of complications, especially infection, the number of antibiotics used, and the length of hospital stay. Our aim was to evaluate the relationship between whole blood parameters known to be associated with inflammation, especially RDW, NLR, PLR, eosinophil-lymphocyte ratio (ELR), and the development of postoperative complications, length of hospital stay, and the number of antibiotics in elderly patients undergoing rTKA. The current literature contains no studies of the rTKA patient group in this context.

MATERIAL AND METHOD

The study was carried out with the permission of the Aydın Adnan Menderes University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 15.09.2020, Decision No: 2020/165). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

This study is a single-center, retrospective study. The study was planned after obtaining the ethics committee approval from the institution. Seventy-two patients over 65 years of age were included. Patients who underwent total knee revision due to infection were included in the study. The operations were performed by a single physician.

Patients with iron, vitamin B12, folic acid deficiency and Hb value below 11 g/dL, and patients with malignancy, rheumatological disease, severe liver and kidney disease were not included in the study. Patients who developed complications during the operation and needed blood transfusion were excluded from our study.

In our routine revision procedure, infected total knee prostheses are removed and are replaced with antibiotic spacers. Antibiotic treatment is managed with CRP, ESR, and microbial culture follow-ups. Antibiotics are stopped when CRP falls below 10. A total knee prosthesis revision is performed in cases where the CRP level remains below 10 for at least two months. If there is evidence of infection after the operation, prophylactic antibiotics are started. Treatment is revised according to the results of the antibiogram, and combination treatments are used if necessary.

Postoperative complications were recorded in our study. We also recorded the number and type of antibiotics used to treat infections, as well as hospitalization time. If there was no bleeding, drainage, or other complications in the operation area, the patient was discharged after 3-4 days.

Method

Each patient's body mass index (BMI) was calculated and recorded. Venous blood samples taken for whole blood and biochemical tests were collected in VACUETTE tubes (Greiner Bio-One, Monroe, NC, USA). A complete blood count was performed within 60minutes and measurements were made with a Mindray Auto Hematology Analyzer BC - 6800 (Shenzhen Mindray Bio-medical Electronics, Shenzhen, China) using standard methods and reagents. ESR was measured by the Westergren method and CRP titers were measured using standard reagents on a Beckman-Coulter DXC 800 system analyzers. The normal reference range is 0-20 mm/h for ESR and 0-5 mg/dL for CRP.

We recorded patients' one-day preoperative, first day postoperative, and 45th day postoperative blood parameters: Hb, hematocrit (Hct), red blood cell (RBC), MPV, RDW, white blood cell (WBC), MPV, neutrophil, lymphocyte, monocyte, eosinophil, basophil, and thrombocyte results. NLR, MLR, PLR, ELR, and BLR were calculated. The average values and standard deviations of all blood parameters at the three different times of testing were calculated (**Table 1**). The parameters obtained from the blood tests were compared with complications, antibiotic use, and length of hospital stay.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) program, 22nd version. Quantitative data are presented as mean±standard deviation. Individuals were divided into two groups according to gender, three groups according to smoking and alcohol use, six groups in terms of having additional disease, three groups according to developing complications, three groups according to the anesthetic agent method applied, and four groups according to the anesthetic method. After testing the suitability of the quantitative data to normal distribution with the Kolmogorov-Smirnov method, a Spearman Correlation Test was conducted to determine the relationship between data that were not suitable for normal distribution. The Mann-Whitney U test was applied between quantitative data that did not show normal distribution and dichotomous data. During the statistical evaluation of normally distributed quantitative data, one-way analysis of variance (ANOVA) and then

Tukey honestly significant difference tests were used to examine the differences between groups. During the statistical evaluation of quantitative data that did not show normal distribution, the Kruskal Wallis method and then the Pairwise Comparisons test were used to examine the differences between groups. Pearson Chi-Square and Fisher Chi-Square tests of independence were used for categorical data. A P-value less than 0.05 was considered statistically significant.

Table 1. Pre- and postoperative whole blood parameters, CRP and ESR average values.

	Preoperative day one (Mean±SD)	Postoperative day one (Mean±SD)	Postoperative day 45 (Mean±SD)
Hemoglobin (g/dL)	11.799±1.915	10.239±1.479	10.211±1.876
Hematocrit (%)	37.04±5.586	32.247±4.315	31.968±5.230
RBC (m/uL)	4.497±0.6712	3.909±0.608	3.904±0.764
RDW (%)	15.407±2.258	15.81±2.940	15.858±2.311
WBC (mm^3)	11.295±5.610	8.475±2.871	9.147±4.407
Neutrophil (mm^3)	5.166±2.289	8.725±5.308	6.661±4.103
Lymphocyte (mm^3)	2.176±0.765	1.767±0.709	1.692±0.831
Monocyte (mm^3)	0.590±0.292	0.614±0.254	0.611±0.287
Eosinophil (mm^3)	0.186±0.149	0.164±0.294	0.163±0.230
Basophil (mm^3)	0.040±0.021	0.031±0.015	0.033±0.017
Thrombocyte (mm^3)	319.63±157.12	288.15±128.76	276.14±109.34
MPV (fL)	9.933±1.297	9.811±1.154	9.807±1.174
NLR	2.503±1.415	5.718±3.779	5.001±4.225
MLR	0.293±0.191	0.390±0.220	0.440±0.302
ELR	0.095±0.085	0.098±0.165	0.093±0.133
BLR	0.025±0.035	0.027±0.061	0.024±0.211
PLR	154.035±84.367	180.875±82.305	192.54±113.830
CRP (mg/L)	8.372±17.266	9.676±28.373	7.291±13.162
ESR (mm/h)	27.18±25.32	21.09±44.81	21.17±28.78

RBC: Reed blood cell, RDW: Red cell distribution widths, WBC: White blood cell, MPV: Mean platelet value, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, ELR: Eosinophil-to-lymphocyte ratio BLR: Basophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

RESULTS

Of the 72 patients included in the study, 54 were women (75%). The mean age of the patients was 69.99±4.82 years (range 65-81) and mean BMI was 30.49±3.64 kg/m^2 (range 24-38). Fifty-five of the patients (76%) had chronic diseases such as hypertension, diabetes mellitus, coronary artery disease or cerebrovascular disease. Out of 72 patients, 58 had no history of smoking or alcohol use (81%), while 14 had a history of smoking and/or alcohol use. The average hospital stay was 5.1±2.6 days. There were a variety of postoperative complications: seventeen patients developed infections and seven patients experienced embolic events (deep vein thrombosis in three patients, pulmonary embolism in two patients, myocardial infarction in one patient, and a cerebrovascular accident in one patient).

In patients with postoperative infections; ampicillin + sulbactam, ciprofloxacin, cefazolin sodium, sodium fusidate, cephalexin monohydrate, clindamycin, cefixime, gentamicin, rifambisin, trimethoprim + sulfamethoxazole, levofloxacin, metronidazole, and teicoplanin group antibiotics were used and revised according to culture results and follow-up.

The age, gender, BMI, smoking and/or alcohol use, anesthetic method, and anesthetic agent variables did not affect the length of hospital stays, the development of complications, or the number of antibiotics used. It was observed that the duration of hospitalization was longer in patients with one or more comorbidities (P=0.019). Comorbidities did not affect the development of complications, or the number of antibiotics used.

We separately evaluated the relationships between the duration of hospitalization, development of complications, and the number of antibiotics used to the whole blood parameters, ESR, and CRP values measured one day before, one day after, and 45 days after the operation.

Evaluation of whole blood parameters measured one day before the operation

When the laboratory parameters one day before the operation were evaluated, our data revealed that the postoperative infection development and the number of antibiotics used were both higher in those with low Hb values (P=0.046, P=0.008). In patients with high preoperative platelet counts and PLR rates, both postoperative infection development (P=0.014, P<0.001) and the number of antibiotics used (P=0.001, P<0.001) were observed to be higher. No significant relationship was found between any other parameters (**Table 2**).

Evaluation of whole blood parameters measured one day after the operation

When the laboratory parameters one day after the operation were evaluated, it was found that the development of infections and the number of antibiotics used in follow-up were both significantly higher in those with high RDW values (P=0.002, P<0.001). There were also positive correlations between eosinophil count and ELR, and both development of infection (P=0.001, P=0.002) and the number of antibiotics used (P=0.001, P<0.001, P<0.001). It was observed that the number of antibiotics

used was higher in those with high neutrophil counts and NLR (P=0.026, P=0.003). On the first postoperative day, it was observed that the development of infection (P=0.009, P=0.003) and the number of antibiotics used (P<0.001, P<0.001) were higher in patients with high ESR and CRP. No significant relationship was found between any other parameters (**Table 2**).

Evaluation of whole blood parameters measured 45 days after the operation

When the laboratory parameters were evaluated 45 days after the operation; RDW (P=0.001, P=0.001), eosinophil count (P=0.006, P<0.001) and ELR (P=0.039, P<0.001) parameters were still high in patients who developed infection and overused antibiotics. At day 45, CRP and ESR were also significantly positively correlated with the development of infection (P=0.023, P=0.016) and the number of antibiotics used (P=0.008, P=0.043) (**Table 2**).

DISCUSSION

Whole blood tests can be easily performed routinely in most centers. Various whole blood parameters have been shown to be useful in predicting and evaluating some postoperative problems. In this study, inflammation-related parameters such as CRP, ESR, NLR, PLR, MLR, ELR, BLR and RDW were evaluated in elderly patients undergoing total knee replacement revision surgery. The relationships between these parameters and the development of postoperative complications, the number of antibiotics used, and the length of stay in the hospital were evaluated. The relationship between the parameters in our study and inflammation has been evaluated in different patient groups in many previous studies. Our study is the first study evaluating these parameters in the rTKA patient group.

In several previous studies, the effect of age, gender, BMI, and duration of the operation was evaluated, and it was found that these parameters affect the development of complications (such as infection, prosthetic failure, and thromboembolism) after primary and revision knee surgeries (15-17). In other studies, age, gender, and BMI were not found to be related to operation time or the development of complications (18,19). Out of the factors that were evaluated in our study, age, gender, BMI, alcohol use, smoking, anesthetic method, and anesthetic agent were not found to be associated with the development of infections, number of antibiotics, or the length of hospital stays. It was observed that patients with comorbidities were hospitalized longer. These results are among the important findings of our study. The low number of patients without comorbidity may have caused the lack of a significant relationship with the other two factors. The high number of alcoholic/non-smoker patients may also have caused the absence of a significant relationship.

Table 2. Comparison of pre- and postoperative whole blood parameters, CRP, and ESR and length of hospitalization, infection and number of antibiotics used (p values).

	Preoperative day one p value			Postoperative day one p value			Postoperative day 45 p value		
	Hospital stay	Infection	Antibiotic count	Hospital stay	Infection	Antibiotic count	Hospital stay	Infection	Antibiotic count
Hemoglobin (g/dL)	0.178	0.046*	0.008*	0.982	0.820	0.952	0.605	0.835	0.629
Hematocrit (%)	0.062	0.114	0.367	0.998	0.581	0.276	0.682	0.929	0.244
RBC (M/mcL)	0.058	0.083	0.950	0.607	0.170	0.196	0.935	0.298	0.203
RDW (%)	0.083	0.066	<0.108	0.085	0.002*	<0.001*	0.260	0.001*	0.001*
WBC (mm³)	0.522	0.387	0.538	0.593	0.354	0.120	0.608	0.387	0.745
Neutrophil (mm³)	0.718	0.293	0.413	0.560	0.252	0.026*	0.643	0.372	0.603
Lymphocyte (mm³)	0.455	0.624	0.340	0.360	0.414	0.127	0.298	0.954	0.749
Monocyte (mm³)	0.058	0.072	0.114	0.276	0.243	0.286	0.191	0.262	0.524
Eosinophil (mm³)	0.990	0.388	0.145	0.955	0.001*	<0.001*	0.679	0.006*	<0.001*
Basophil (mm³)	0.188	0.312	0.200	0.987	0.083	0.181	0.095	0.062	0.343
Thrombocyte (mm³)	0.278	0.014*	0.001*	0.463	0.086	0.101	0.635	0.060	<0.091
MPV (fL)	0.589	0.062	0.436	0.792	0.435	0.058	0.752	0.886	0.090
NLR	0.989	0.229	0.096	0.605	0.213	0.003*	0.832	0.509	0.775
MLR	0.590	0.058	0.072	0.377	0.729	0.521	0.626	0.394	0.352
ELR	0.393	0.351	0.086	0.692	0.002*	<0.001*	0.653	0.039*	<0.001*
BLR	0.093	0.572	0.454	0.370	0.226	0.329	0.318	0.153	0.062
PLR	0.507	<0.001*	<0.001*	0.901	0.624	0.210	0.430	0.170	0.086
CRP (mg/L)	0.781	0.087	<0.121	0.509	0.003*	<0.001*	0.953	0.023*	0.008*
ESR (mm/h)	0.946	0.104	<0.234	0.504	0.009*	<0.001*	0.729	0.016*	0.043*

*$P<0.05$. RBC: Reed blood cell, RDW: Red cell distribution widths, WBC: White blood cell, MPV: Mean platelet volume, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, ELR: Eosinophil-to-lymphocyte ratio, BLR: Basophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

RDW is routinely measured during a complete blood count. Aali-rezaie et al. (14) investigated the relationship between preoperative RDW levels and mortality and length of hospital stays after hip and knee revision arthroplasty. They found a significant correlation between preoperative high RDW values and mortality, in-hospital complications, and re-hospitalization within 90 days. In our study, no significant correlation was found between the RDW values on the first day before the operation, the development of complications, the length of hospital stays and the number of antibiotics used. However, high RDW values on the first postoperative day, and 45 days postoperative were found to be significantly associated with both the development of infection and the number of antibiotics used. This significant relationship detected with high RDW value was also in parallel with high CRP and ESR values. These findings, which we found in rTKA patients, are among the important results of our study. With RDW follow-ups that will start immediately after the operation, the development of infection can be predicted and it can give an idea about the number of antibiotics that may be required. In addition, RDW can be as valuable an indicator as CRP and ESR in monitoring the treatment response to infection.

Previous studies suggest that, in patients undergoing total knee and hip revision surgery, platelet counts and MPV should be considered for the diagnosis of periprosthetic joint infection; high platelet counts are an important additional test for the diagnosis of deep surgical site infections after open internal fixation; and perioperative PLR and NLR may be important in predicting deep vein thrombosis (DVT) induced by total joint Arthroplasty (8,20). In our findings, it is seen that high platelet counts and high PLR detected preoperatively are important in predicting the development of postoperative infection. These results suggest that PLR may be more important than CRP and ESR. The development of infections, the number of antibiotics and the length of hospital stay were not significantly associated with MPV and NLR before and after surgery. When our findings are evaluated together with the findings of previous studies, the high PLR detected before the operation seems to be an important parameter in predicting the development of postoperative infection.

Chawla et al. (10) evaluated IL-6, TNF-alpha, NLR, and PLR values pre and postoperatively in 50 patients who underwent primary TKA. IL-6, NLR, and PLR values increased on the first postoperative day and decreased on the third day. They concluded that preoperative risk stratification can be done using preoperative IL-6 and NLR measurements and then appropriate measures can be taken to improve postoperative results. In our study, in which rTKA patients were evaluated and more patients were recruited; It has been determined that preoperative high PLR may be important in predicting the development of postoperative infection. There was no significant relationship between pre- and postoperative NLR. Studies in which more patients are evaluated in different patient groups can be planned.

In addition to whole blood parameters such as RDW, NLR, PLR and MPV, parameters such as ELR and BLR have been investigated in relation to many inflammatory clinical conditions and cancers (21-23). A study conducted by Kökoğlu et al. (24) evaluated whether there was a relationship between patient satisfaction and NLR, PLR, ELR, and BLR in patients who underwent septoplasty. They reported that ELR and BLR can be used to predict patient satisfaction and for patient selection after septoplasty and inferior conchae reduction. Akkececi et al. (25) evaluated the relationship between disease activity and whole blood parameters and inflammation markers in patients with Takayasu Arteritis. They detected significantly higher ESR, CRP, RDW, NLR, PLR, and MLR, and significantly lower MPV in patients with Takayasu arteritis. They found no significant relationship to lymphocytes, monocytes, eosinophil, basophil, ERL, or BLR. In the postoperative evaluations in our study, high eosinophil and ELR ratios were significantly associated with the development of infection and the number of antibiotics used. This result is one of the important findings of our study. As with RDW, follow-up of ELR immediately after surgery can predict the development of infection and give an idea of the number of antibiotics that may be required. In addition, ELR can be as valuable an indicator as CRP and ESR in monitoring treatment response to infection. A significant correlation was found between the number of antibiotics used and the patients with high NLR values on the first postoperative day. No significant relationship was found between NLR and the other two parameters. These findings can be evaluated in different patient groups with new studies involving more patients. In our study, no significant relationship was found between MLR and BLR and complications, number of antibiotics and length of hospital stay.

It was found that patients with low Hb values on the first day preoperatively had a higher rate of postoperative infection and required more antibiotics. This finding shows the importance of adequate preoperative erythrocyte replacement in geriatric patients with low Hb values.

Some whole blood parameters, which have been shown to be associated with inflammation in many previous studies, were evaluated for the first time in the elderly orthopedic patient group. The limitation of this study is that it was performed in a single center and it was retrospective. We thought that the high rate of post-operative infection and slightly longer hospital stay may

be due to the advanced age of our patient group and the high number of patients with comorbidities. The inclusion of patients who underwent revision due to infection in the study may also have caused this situation. In studies involving more patients in different orthopedic patient groups, the relationship of RDW, PLR, ELR, NLR, MLR, BLR whole blood parameters with the development of infection, the number of antibiotics used and the length of hospital stay can be evaluated.

CONCLUSION

In elderly patients who underwent revision knee surgery, high RDW and ELR values detected one day after the surgery may help to predict the development of infection and antibiotic use that may occur during follow-up. These parameters can be as valuable as CRP and ESR in monitoring treatment response to infection. In this patient group, high PLR detected one day before the operation is also an important parameter in predicting the development of postoperative infection.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Aydın Adnan Menderes University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 15.09.2020, Decision No: 2020/165).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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