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Original Article

Is there a relationship between blood inflammation markers and the severity of knee osteoarthritis?

Nazlı Karaman[1], Aslıhan Ulusoy[2], Mehmet Karaman[3]

[1]Department of Physical Medicine and Rehabilitation, Balıkesir Bigadiç State Hospital, Balıkesir, Türkiye
[2]Department of Physical Medicine and Rehabilitation, Physical Medicine and Rehabilitation, İzmir Urla State Hospital, İzmir, Türkiye
[3]Department of Internal Medicine, Balıkesir Bigadiç State Hospital, Balıkesir, Türkiye

ABSTRACT

Objectives: This study aims to evaluate the monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP)-to-albumin ratio levels between individuals with mild to moderate knee osteoarthritis (OA) and those with severe knee OA.

Patients and methods: One hundred eighty-two participants (131 females, 51 males; mean age: 67.7±10.2 years; range, 43 to 91 years) affected by knee OA were involved in the cross-sectional retrospective study between January 2018 and January 2021. Kellgren and Lawrence (K-L) classification was performed in accordance with two-view (lateral and anteroposterior) plain radiograph examinations of each knee. The patients were grouped as follows: 98 patients had mild to moderate knee OA (K-L Grades 1-2), and 84 had severe knee OA (K-L Grades 3-4). Demographic data, neutrophil, monocyte, platelet, and lymphocyte levels, erythrocyte sedimentation rate, albumin, and CRP levels were documented. C-reactive protein-to-albumin ratio, NLR, MLR, and PLR levels were calculated.

Results: The MLR was significantly elevated in the severe knee OA group (p=0.047). A significant positive relationship was found with disease stage, MLR (r=0.206; p=0.005), and NLR levels (r=0.158; p=0.033). Receiver operating characteristic curve analyses for blood MLR demonstrated a sensitivity of 57% and specificity of 60%.

Conclusion: The study results suggest that while MLR and NLR may reflect the inflammatory response in knee OA, they are not highly diagnostic inflammatory markers that can be used to evaluate the severity or prognosis of the disease.

Keywords: Inflammatory markers, knee osteoarthritis, lymphocyte, monocyte, neutrophil, radiographic grading.

Osteoarthritis (OA) is a highly prevalent chronic and progressive joint disorder worldwide.[1,2] Osteoarthritis is not just a disease involving the mechanical degeneration of joint cartilage but also a complex inflammatory process that affects all joint structures, such as synovium, subchondral bone, meniscus, and ligaments.[3] Osteoarthritis can affect multiple joints in the body; however, it most commonly affects the knee, hip, hand, and foot joints.[4] Knee OA is the predominant type and is the primary cause of disability among elderly patients.[3] In a study, it was reported that symptomatic and radiographic knee OA in adults aged 75 years and older was 33%.[4] Additionally, symptomatic knee OA was detected in 13% of females and 10% of males aged 60 years and older.[5] Risk factors consist of age, the female sex, hereditary predisposition, obesity, muscle weakness, joint laxity, coagulation disorders such as hemophilia, major joint injuries, and infections.[4-7] Studies conducted to understand the impact of genetic factors on OA have shown that certain genetic features may increase the risk of OA and that these genetic features may cause inflammatory events.[8,9]

When pain and joint dysfunction are detected in knee OA, destruction begins around the joint cartilage.[10] Therefore, early diagnosis of knee OA is

Corresponding author: Nazlı Karaman, MD. Bigadiç Devlet Hastanesi, Fizik Tedavi ve Rehabilitasyon Kliniği, 10440 Bigadiç, Balıkesir, Türkiye
E-mail: naz_cakl@hotmail.com

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of critical importance for effective treatment of the disease.[10,11] The most commonly used diagnostic method in knee OA is radiographic evaluation. However, in mild to moderate knee OA, changes in imaging findings are often not obvious. In this case, a noninvasive and reliable diagnostic marker that facilitates early diagnosis of knee OA is needed.[10] Lymphocytes, neutrophils, and platelets contribute to inflammation regulation and are additionally linked to changes induced by inflammation. Monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP)-to-albumin ratio (CAR) have attracted attention as novel nonspecific inflammatory markers in recent years.[12]

Recent data suggest that OA is now considered an inflammatory disease. Investigating the inflammatory aspects of OA may be a crucial step in understanding the disease's progression and developing more effective treatment methods. The NLR, MLR, PLR, and CAR are noninvasive, straightforward, and economical markers for evaluating inflammatory conditions. However, studies investigating inflammation markers in patients with OA are limited. Therefore, our study aimed to investigate the significance and reliability of these inflammation markers for the early identification and assessment of OA severity.

PATIENTS AND METHODS

In this study, 352 consecutive patients who presented to the physical medicine and rehabilitation department at the Kütahya Health Sciences University, Faculty of Medicine between January 2018 and January 2021 with complaints of knee pain and were diagnosed with knee OA were retrospectively evaluated. All data were collected in the same facility by the same assessor. The inclusion criteria were being over 18 years of age and having routine blood parameters in the system, along with simultaneous radiography. Patients with cardiovascular, hematologic, rheumatologic, chronic liver, and kidney disease and a history of malignancy, orthopedic surgery, and active infection were excluded. Based on the clinical records, 170 patients were not eligible as they did not meet the inclusion criteria, and 182 patients (131 females, 51 males; mean age: 67.7±10.2 years; range, 43 to 91 years) were enrolled in the study (Figure 1). A written informed consent was obtained from each patient. The study protocol was approved by the Interventional Research Ethics Committee (date: 15.04.2021, no: 2021/07-22). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Age, sex, monocyte, lymphocyte, neutrophil, and platelet levels, 25-hydroxyvitamin D, erythrocyte

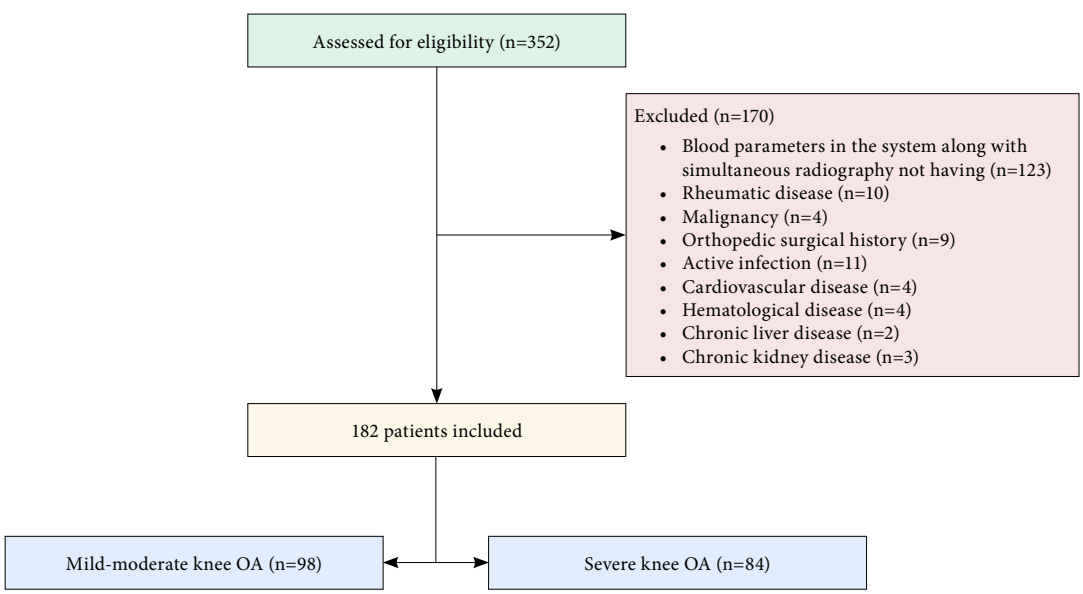

Figure 1. Study flow chart.
OA: Osteoarthritis.

sedimentation rate, CRP, and Kellgren-Lawrence (K-L) classification were documented. The MLR, NLR, PLR, and CAR were computed. The participants were categorized into two groups: those with K-L classification 1 and 2 were included in the mild to moderate knee OA group, and those with Grades 3 and 4 were included in the severe knee OA group. The mild to moderate knee OA group included 98 patients (66 females, 32 males), and the severe knee OA group consisted of 84 patients (65 females, 19 males).

The K-L classification system was employed to classify OA based on radiographs. Four radiographic characteristics were utilized: articular space reduction, osteophyte presence, subchondral cysts, and subchondral sclerosis. The degree of radiographic features varied from Grade 0 to Grade 4, with Grade 0 indicating no radiographic signs of OA, while Grade 4 signified large osteophytes, marked articular space reduction, significant sclerosis, and definite bony structural changes.[13] Kellgren-Lawrence classification of each knee was typically identical; however, if a significant disparity was found among the knees, the knee with the greatest severity was noted.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean ± standard deviation (SD). Nominal data were presented as frequency and percentage. For group comparisons, the chi-square test for nominal data and the Mann-Whitney U test for variables exhibiting skewed distributions were employed. The Shapiro-Wilk test was employed to evaluate the assumption of normality for the quantitative data. Nonparametric tests, specifically the Mann-Whitney U test and the Kruskal-Wallis test (with Dunn's test for pairwise group comparisons), were employed for data that did not conform to the normality assumption. The association among quantitative variables was examined using Spearman's rank correlation coefficient (Spearman's rho). A p-value <0.05 was considered statistically significant. Univariate analysis was conducted to evaluate the impact of each variable on severe knee OA. Predictors with p-values <0.10 in the logistic regression model were recognized as candidate risk indicators and were integrated for multiple analyses. The analysis employed stepwise multiple logistic regression, and candidate predictors were excluded based on likelihood ratio tests. Furthermore, an exploratory assessment of cutoff points was conducted via receiver operating characteristic (ROC) curve analysis.

TABLE 1
Demographic and laboratory findings of knee OA patients according to knee OA severity

	Mild-moderate knee OA (n=98)			Severe knee OA (n=84)			
	%	Median	Min-Max	%	Median	Min-Max	*p*
Age (year)		65.00	43-89		72.00	53-91	<0.001*
Sex							
Female	67.3			74.4			0.133
Monocyte count		0.45	0.20-0.88		0.48	0.26-0.79	0.071
Neutrophil count		4.29	2.03-8.31		4.41	2.07-13.40	0.958
Lymphocyte count		2.09	0.80-5.60		2.01	1.14-273.00	0.242
Platelet count		239.00	133-428		226.50	117-428	0.532
C-reactive protein		3.55	0.40-63.90		3.80	0.20-58.50	0.837
Albumin		4.10	1.07-5.00		4.10	3.00-5.10	0.732
Monocyte-lymphocyte ratio		0.22	0.10-0.96		0.24	0.00-0.63	0.047*
Neutrophil-lymphocyte ratio		2.12	0.78-8.28		2.16	0.01-7.14	0.400
Platelet-lymphocyte ratio		106.77	54.64-297.50		115.17	0.76-297.22	0.560
CRP-albumin ratio		0.91	0.09-16.82		0.89	0.05-14.27	0.812
25 hydroxyvitamin D		17.00	3-75		16.00	7-46	0.599
Sedimentation		11.00	2-67		14.00	2-79	0.070

OA: Osteoarthritis; CRP: C-reactive protein; * P value of <0.05 is considered statistically significant.

TABLE 2
Comparison of laboratory data of patients according to K-L grades

	Grade 1		Grade 2		Grade 3		Grade 4		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
Monocyte count	0.46	0.20-0.88	0.45	0.26-0.88	0.48	0.26-0.79	0.49	0.38-0.73	0.230
Neutrophil count	4.33	2.03-7.11	4.25	2.34-8.31	4.10	2.07-13.40	4.71	2.72-13.30	0.052
Lymphocyte count	2.26	1.22-3.71	2.08	0.80-5.60	2.12	1.14-273.00	1.94	2.28-4.70	0.131
Platelet count	245.00	171-428	228.00	133-395	216.50	117-428	245.50	140-368	0.141
C-reactive protein	3.10	0.40-30.80	3.70	0.60-63.90	3.50	0.20-58.50	3.91	0.77-19.90	0.793
Albumin	4.00	1.07-4.60	4.10	3.20-5.00	4.00	3.00-4.70	4.20	3.00-5.10	0.329
MLR	0.20	0.10-0.40	0.22	0.11-0.96	0.23	0.00-0.63	0.25	0.12-0.49	0.010*
NLR	1.82	0.78-4.11	2.16	1.00-8.28	1.95	0.01-7.14	2.64	1.10-4.49	0.027*
PLR	99.26	58.58-187.90	110.53	54.64-297.50	111.59	0.76-297.22	132.19	56.00-234.81	0.481
CRP-albumin ratio	0.70	0.09-7.70	1.07	0.14-16.82	0.93	0.05-14.27	0.88	0.19-5.85	0.840
25 hydroxyvitamin D	15.00	6-75	18.00	3-73	17.00	7-46	15.00	9-32	0.326

K-L: Kellgren-Lawrence; MLR: Monocyte-lymphocyte ratio; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; * P value of <0.05 is considered statistically significant.

A power analysis was performed with the G*Power version 3.1.9.4 software (Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany) to determine the required sample size. Significant differences between mild to moderate knee OA and severe knee OA groups on variables of interest were detected using the independent sample t-test. With 80% power, an alpha of 0.05, and considering a medium effect magnitude (d=0.50), the findings revealed the necessity of a minimum of 128 participants, with 64 individuals in each group.

RESULTS

The laboratory and demographic data are detailed in Table 1. When the data of patients with mild to moderate knee OA and severe knee OA were compared, a statistically significant variation was observed in terms of age (p<0.001) and MLR (p=0.047) across the groups.

Patient classification included in the study according to the K-L grading revealed that 17% were classified as Grade 1, 36.8% as Grade 2, 29.7% as Grade 3, and 16.5% as Grade 4. When correlations were examined to evaluate the relationship between laboratory parameter values and the progression of the disease phase, a significant positive relationship was detected linking disease stage and MLR levels (r=0.206, p=0.005), as well as NLR levels (r=0.158, p=0.033).

Comparison of the laboratory data for patients based on K-L stages revealed significant differences in NLR and MLR (Table 2). When pairwise comparisons were conducted, statistically significant differences were found between Grade 1 and each of the other grades in terms of age (p=0.003

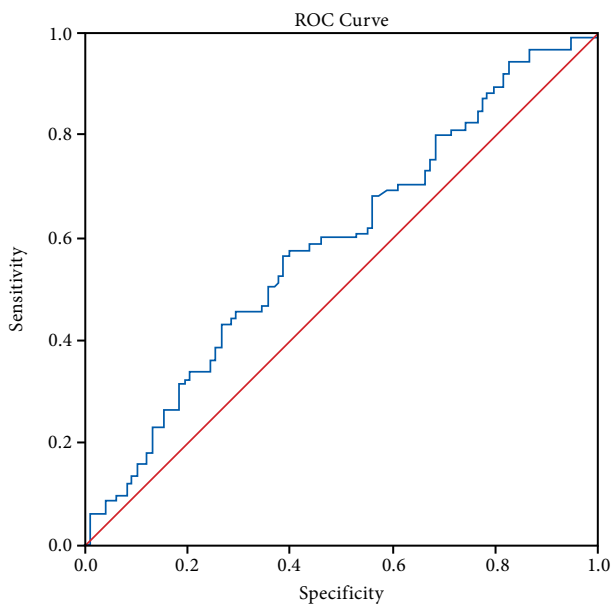

Figure 2. Receiver operating characteristic curve analysis (the red line represents the reference line; the blue line reflects the neutrophil-to-lymphocyte ratio).
ROC: Receiver operating characteristics.

for Grade 2, p<0.001 for Grade 3, and p<0.001 for Grade 4). Additionally, a significant difference was observed in Grade 1 compared to Grade 4 in terms of MLR (p=0.016) and NLR (p=0.011).

Multiple logistic regression was conducted to explore predictors of severe knee OA. Accordingly, it was determined that MLR was not an independent predictor for severe knee OA (p=0.332, odds ratio [OR]=4.157), but age was a significant predictor for severe knee OA (p=0.001, OR=1.057).

The diagnostic efficacy of MLR for knee OA was calculated using a ROC curve. The area under the ROC curve of MLR was 0.58 (95% confidence interval 0.503-0.668, p=0.047), with an optimal threshold of 0.22. The sensitivity and specificity were 57 and 60%, respectively (Figure 2).

DISCUSSION

In our study, we investigated the correlation between the degree of radiographic findings in OA of the knee and the MLR, NLR, PLR, and CAR, which are economical and noninvasive markers reported in different systemic inflammatory conditions. A significant positive association was identified between MLR and NLR as knee OA progressed. However, MLR's diagnostic value in knee OA was low, with 57% sensitivity and 60% specificity, indicating that it is not a sufficiently reliable prognostic marker. Additionally, MLR could not be used to predict severe knee OA. The study's findings demonstrated that inflammation markers do not have high diagnostic and prognostic value in determining the severity of knee OA.

The risk of knee OA increases with age, and it is known that approximately 50% of the population over the age of 65 is affected by this disease.[14,15] Consistent with the literature, our study concluded that age independently predicts knee OA severity.

In OA, as observed in other rheumatological conditions such as gout, rheumatoid arthritis, and psoriasis, inflammation plays a significant role.[6,14,16] It has been demonstrated that joint degeneration progresses in OA through the generation of inflammatory agents and the excretion of enzymes that degrade cartilage.[5,6] Interest in understanding the role of inflammation in the development of OA is increasingly growing. In conducted studies, the presence of macrophages and B and T lymphocytes adjacent to blood vessels has been documented at the cellular level during both early and late stages of OA.[6,17] In comparison to late-stage OA, an increase in the release of inflammatory mediators and the presence of CD68-positive and CD4-positive cells within the synovial tissue has been detected in patients with early-stage OA.[6,17,18]

Monitoring this inflammatory process in patients with knee OA is important for assessing disease progression and treatment response. As known, the counts of lymphocytes, neutrophils, monocytes, and platelets change markedly in generalized inflammation.[10] The NLR, MLR, and PLR are calculated by dividing the absolute number of neutrophils, monocytes, and platelets obtained from the complete blood count by the number of lymphocytes.[19-21] These are inexpensive and easily obtainable clinical markers used as indicators of immune activation in various medical conditions, including ankylosing spondylitis, rheumatoid arthritis, endometrial cancer, colorectal cancer, acute ischemic stroke, and COVID-19 (coronavirus disease 2019).[21-26] During a 2023 study, elevated levels of NLR and CRP were observed in patients with Parkinson's disease, characterized by chronic inflammation and tissue degeneration similar to OA, compared to healthy individuals. Additionally, as the stage of Parkinson's disease advanced, the thickness of distal femoral cartilage decreased.[27]

In the literature, there are publications similar to our study investigating the correlation between clinical markers and the severity of OA.[14,28,29] Taşoğlu et al.[14] reported that NLR levels increased in radiographically diagnosed individuals with severe OA of the knee compared to patients with mild knee OA. Büyükavcı et al.[28] reported that NLR levels could be a new inflammatory marker for predicting radiographic severity in knee OA. Shi et al.[29] reported no significant association between PLR and K-L grades among patients with knee OA, consistent with the results of our study. A study reported that both PLR and mean platelet volume could serve as inflammatory indicators for predicting the radiographic severity in hip OA.[30] Gao et al.[10] compared 119 individuals diagnosed with knee OA to 120 healthy volunteers and observed higher blood levels of MLR, NLR, and PLR in the knee OA group. It was demonstrated that the MLR has superior diagnostic efficacy compared to the PLR and NLR among individuals with knee OA.[10] In a study, MLR's diagnostic value in knee OA was determined to be 0.84.[16] In our study, this value was 0.58. However, its diagnostic value was limited due to its low sensitivity and specificity.

In a study examining the association between NLR and the indications of arthrosis in patients' hips, there was no difference in the blood NLR levels in patients with arthrosis affecting one or both hips.[6] In another study, Jaime et al.[31] found that natural killer cells in the peripheral blood and synovial fluid of patients with OA exhibit distinct phenotypes and cytotoxic activities. These findings indicate that the unique interactions among inflammatory cells have significant etiological relevance in individuals with OA.[6]

The CAR is another inflammatory marker with prognostic significance in inflammatory processes such as stroke and cardiovascular diseases. It has been found to be more sensitive in indicating inflammation compared to CRP levels alone.[32] In the literature, it is stated that the CAR is a useful marker for monitoring disease activity in rheumatological diseases such as psoriatic arthritis and rheumatoid arthritis.[32-34] Yiğit et al.[35] found that the CAR had prognostic value in determining the risk of periprosthetic infection in total joint arthroplasty. However, the roles of inflammatory markers in diagnosing and monitoring the treatment of knee OA have not been sufficiently clarified. In the literature, we did not find any other study similar to our study that investigated the relationship between disease severity and CAR in OA. In this context, the results of our study will shed light on future research. Similar to our study, Mermerci Başkan et al.[36] reported that serum 25-hydroxyvitamin D levels had no relationship with the progression of knee OA. It was observed that age, sex, and body mass index were the most important determinants of pain severity and functional status.

The limitations of the study include a small sample size, the inaccessibility of certain demographic data related to knee OA, such as body height and weight, the absence of healthy volunteers without OA, and a predominantly female sample. The strengths of the study include that all radiographs were evaluated by the same observer, and the evaluation of inflammatory biomarkers was performed simultaneously with radiography.

In conclusion, the results suggest that while MLR and NLR may reflect the inflammatory response in knee OA, they are not highly diagnostic inflammatory markers that can be employed for diagnosing and prognosing the progression of knee OA.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept or design of the study, drafting of the manuscript: N.K., A.U., M.K.; Acquisition of data: N.K., M.K.; Analysis or interpretation of data: N.K., A.U; Critical revision for important intellectual content: N.K.

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