



Neutrophil to Lymphocyte Ratio as a Marker of Disease Activity in Patients with Knee Osteoarthritis

Galala Mohamed Amin Qader^{1*}, Dashty Abbas Albustany²

Abstract

Background: Knee osteoarthritis is a debilitating inflammatory disease that affects the quality of life of people, especially the elderly. One of the markers is the neutrophil lymphocyte ratio (NLR) which can be used to monitor disease activity and determine inflammatory disease progression and treatment effectiveness. Therefore, this study was performed to evaluate the neutrophils lymphocytes ratio as an marker of disease activity in patients with osteoarthritis of the knee.

Method: This study is a cross-sectional study that was performed in October 2021 to April 2022 on 100 patients with knee osteoarthritis referred to the Rheumatology Clinic of Rizgari Teaching Hospital in Erbil. Data were collected using a questionnaire that included three sections: demographics, medical history, and test results for inflammatory markers.

Descriptive and linear regression tests were used to analyze the data.

Result: Examination of patients' clinical status showed that 99 (99%) people have knee pain, In terms of limb involvement and limb pain, 22% reported pain in the right leg. Also 22% reported pain in the left leg and 56% reported pain and involvement in both legs. The mean of NLR = 2.045 (1.373) CI 95%, 1.770 - 2.31 was obtained. The results of linear regression the relationship between NLR and pain intensity in patients has been reported directly.

Conclusion: According to the findings of the present study, it seems that the neutrophil to lymphocyte ratio (NLR) can be used as a marker in assessing the severity and activity of osteoarthritis (OA).

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Key Words: Knee Osteoarthritis, Neutrophil to Lymphocyte Ratio, Disease Activity, inflammatory Markers.

DOI Number: 10.14704/nq.2022.20.8.NQ44448

NeuroQuantology 2022; 20(8): 4156-4162

Introduction

Knee osteoarthritis (KOA), also recognized as degenerative joint disease, is usually the result of wear and tear and progressive loss of articular cartilage [1]. It is commonest in elderly women and men [2]. Knee osteoarthritis is usually a progressive disease that may eventually lead to disability [3]. The intensity of the clinical symptoms could vary from each individual. But they typically become more severe, more frequent, and more debilitating over time. The rate of progression also varies for every individual [4]. Common clinical symptoms include knee pain that's gradual in onset and worse with activity, knee stiffness and swelling, pain after

prolonged sitting or resting, and pain that worsens over time [4, 5].

Knee osteoarthritis (KOA) affects about 15 to 18% of people worldwide and reduces the quality of life of patients, increases the burden of health care, disrupts social and professional activities, increases costs and economic burden [6, 7]. Depending on the source, roughly 13% of women and 10% of men 60 years and older have symptomatic knee osteoarthritis [4]. Among those older than 70 years of age, the prevalence rises to as high as 40%. The prevalence of knee osteoarthritis in males is less than in females [2, 8].

Corresponding author: Galala Mohamed Amin Qader

Address: ¹Department of Rheumatology and Medical Rehabilitation, Rzgari Teaching Hospital, Erbil, Kurdistan Region, Iraq;

²Assistant Professor, Dean of College of Medicine, Hawler Medical University, Erbil, Kurdistan Region, Iraq.

E-mail:

¹galala.mohammed@gmail.com



Diagnosis of OA is usually made based on clinical signs and physical examination [9, 10]. Diagnostic tests such as X-rays, CT and MRI are also used to confirm the diagnosis [9]. Nowadays, the use of laboratory data is also very important due to its cheapness and simplicity, including tests used to diagnose OA can be used for complete blood count (CBC) analysis, mean platelet volume (MPV) and distribution width Red blood cells (RDW) noted [11, 12]. In case of inflammation, there is a change in the number and composition of blood cells [13]. Therefore, the characteristics of circulating blood cell components can be used to assess inflammatory activity [11, 14]. The researchers believe that the ratio of neutrophils to lymphocytes (NLR), which is obtained from a routine whole blood count (CBC) test, is a more sensitive indicator [15]. NLR is a useful tool for assessing inflammatory activity in chronic inflammatory disorders [16]. It is calculated as a simple ratio between neutrophil count and lymphocyte and has been evaluated as an indicator of systemic inflammation in the study of various diseases. The use of NLR to diagnose cardiovascular disease, malignancy, hypertension and ischemic stroke has been successful and has been introduced as an independent and inexpensive predictor of these diseases as well as many inflammatory diseases [17-20]. Given the importance of using this ratio, this study was performed to investigate the relationship between NLR as a marker of disease activity and KOA.

Methods and Materials

This study was a cross sectional study that was carried out in Rheumatology Consultancy Clinic of Rizgari Teaching Hospital in Erbil city during a period of six months from October 2021 to April 2022. A sample of 100 patients with symptoms and signs of knee osteoarthritis presented were selected after eligibility to inclusion and exclusion criteria. Inclusion criteria included Adults (age \geq 50 years), Patients who had not received any antibiotic treatment within 3 months before admission). Exclusion criteria included Younger age (age < 50 years), Patients complicated with tumors, Cardiovascular and cerebrovascular diseases, Autoimmune diseases, Patients with physical disabilities and who could not take care of themselves, Patients with hematological disease. The data was collected through direct interview from patients whom they fulfill all criteria of OA of the knee joint.

The study tool was a researcher-made questionnaire consisting of three sections: demographic information, medical history, clinical examination results and laboratory markers of inflammation. In the demographic information section, variables such as age, sex, marital status, living area, weight, height, education and occupation are mentioned. In the medical history section, there is a history of diseases such as blood pressure, diabetes, asthma and other diseases. As well as history of smoking and activity level status is mentioned. In the clinical examination section, there are the results of clinical examination in terms of knee pain, morning stiffness, cryptosis of the knee with active movement, bone tenderness, knee bone enlargement, palpable warmth, duration of the disease. In the Laboratory Results section, there are radiographic results, severity of knee osteoarthritis, classification of primary and secondary osteoarthritis, and the results of laboratory markers such as lipid level, ESR level, CRP, Neutrophils, Lymphocyte, and NLR.

After receiving the necessary permits from the university, the researcher went to the research environment and prepared it in the hospital where the research was conducted. The study process was such that patients with osteoarthritis of the knee who met the inclusion criteria met the inclusion criteria. After explaining the objectives of the study and how to do it for patients, they were informed. A clinical file was created for each patient, which included a clinical examination sheet and application forms for radiography and lipid, ESR, CRP, neutrophil, and lymphocyte tests. The radiographic results and tests requested were interpreted by the researcher and recorded in a questionnaire. Also, in the mentioned questionnaire, demographic information and the results of clinical examinations performed by the researcher were recorded for each patient.

Descriptive tests for determining the mean and frequency were used to analyze the data according to the objectives. Also, linear regression was used to evaluate the factors affecting pain intensity in patients and the effective factors were determined. All information was confidential; informed consent was obtained from patients to participate in the study.

Results

The total number of patients or patients with osteoarthritis was 100. Demographic information, clinical status or clinical examinations of patients



and to determine the ratio of neutrophils to lymphocytes were also recorded. Patients' ESR and CRP were also measured as inflammatory markers. The pain intensity scale was completed using the Severity of KOA guidelines, and finally the type of knee osteoarthritis was determined and classified as primary and secondary.

The study of demographic variables (Table 1) in patients with osteoarthritis of the knee showed that the mean age of these people in the present study is 61.34 (8.813) CI 95%, 59.591 - 63.088 years. The average height of the subjects in the study is 165.75 (6.912) CI 95%, 164.418 - 167.161 and the mean weight in these individuals was 80.23 (12.401) kg CI 95%, 77.769 - 82.690. The mean BMI of the participants in the study was 29.26 (kg / m²) BMI 29.26 (6.697) CI 95%, 28.33 -30.19.

Table 1.Evaluation of demographic variables (quantitative variables) in patients with knee osteoarthritis

Variable	Mean (SD)	Min	Max	CI:95%
Age	61.34 (8.813)	51	83	59.591 - 63.088
Height	165.75 (6.912)	150	186	164.418 - 167.161
Weight	80.23 (12.401)	56	121	77.769 - 82.690
BMI	29.26 (6.697)	19	42	28.33 -30.19

Evaluation of demographic variables (qualitative variables) in patients with knee osteoarthritis showed that 40 (40%) of the participants in the study were male, 59 (59%) had heavy work. the results showed that 93 (93%) people live in urban areas showed that 3 (3%) were single, 96 (96%) were married and 1 (1%) was a deceased spouse. Also 70 (70%) people are literate. In the study of previous medical history of the participants in the study 34 (34%) people had a history of hypertension. 14 (14%) people had history of diabetes. Fifteen people shared blood pressure and diabetes. 35 people had no history of any disease and 2 (2%) people had a history of other diseases. In the study of smoking status, it was shown that 16 (16%) people smoke and the rest 84 (84%) non-smokers. Also 25 (25%) people have physical activity and 75 (75%) people do not have any physical activity.

Examination of patients' clinical status showed that 99 (99%) people have knee pain. In terms of limb involvement and limb pain, 22 patients (22%) reported pain in the right leg. Also 22 patients (22%) reported pain in the left leg and 56 (56%)

reported pain and involvement in either legs. clinical status or clinical examinations of patients show in (table 2).

Table 2.Evaluation of clinical status in patients with osteoarthritis of the knee

Variable		Frequency	Percent
Knee pain	Yes	99	%99
	No	1	%1
Direction	Right	22	%22
	Left	22	%22
	Both Knee	56	%56
Morning stiffness	less than 30 minutes	100	%100
	more than 30 minutes	0	0
Crepitus on active joint motion	Yes	93	%93
	No	7	%7
Bony Tenderness	Yes	90	%90
	No	10	%10
Bony enlargement of the knee on examination	Yes	39	%39
	No	61	%61
Palpable warmth	Yes	0	0
	No	100	%100
Duration of the disease	(1-3) year	31	%31
	(4-6) year	37	%37
	≥ 6 year	32	%32

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The severity of the disease was classified based on the method of classifying radiological images of Kelgren and Lawrence. Examination of radiological images (X-ray) showed that the severity of the disease in 31 patients (31%) is in the first phase of the disease. The severity of the disease in 38 patients is in phase two of the disease. The rest of the patients 30 (30%) and 1 (1%) other patients are in phase three and four diseases, respectively. In this study, the status of hematological variables and markers of infection in patients with knee osteoarthritis was investigated. The results showed that the mean ESR of the participants was ESR = 6.44 (5.594) CI 95%, 5.329 - 7.550. Maximum and minimum ESRs of 29 and 1 were also obtained. Mean CRP = 1.914 (0.729) CI 95%, 1.767 - 2.056. Mean neutrophils and lymphocytes were 4.346 (5.594) CI 95%, 4.026 - 4.666 and 4.346 (5.594) CI 95%, 2.335 - 2.750, respectively. The mean of NLR = 2.045 (1.373) CI 95%, 1.770 - 2.31 was obtained. Also, the minimum and maximum of this ratio were 0.55 and 10.04, respectively (Table 3).

Table 3.Evaluation of hematology variables and markers of infection in patients with knee osteoarthritis



Variable	Mean (SD)	Min	Max	CI:95%
ESR	6.44 (5.594)	1	29	5.329 - 7.550
CRP	1.914 (0.729)	1	8.20	1.767 - 2.056
Neutrophil	4.346 (5.594)	1.80	10.84	4.026 - 4.666
Lymphocyte	2.543 (1.047)	0.60	6.30	2.335 - 2.750
NLR	2.045 (1.373)	0.55	10.04	1.770 - 2.317

Pain assessment based on KOA index, which is classified into three groups of mild, moderate and severe, showed that 33 patients were in the group of mild pain intensity. 37 patients are in the moderate pain intensity group and 30 patients are in the group of severe pain. The results showed that in the classification of patients based on the type of primary and secondary osteoarthritis, 70 patients (70%) have primary osteoarthritis and 30 patients (30%) have secondary osteoarthritis.

In this study, the effect of study variables on patients' pain intensity was evaluated based on linear regression. Based on the un adjusted variables model, variables: Age = OR (0.037) (P-Value ≤ 0.001, CI 95%, 0.021 - 0.053), Occupation = OR (-0.401) (P-Value ≤ 0.005, CI 95%, -0.678 - -0.123), Past medical history = OR (-0.081) (P-Value ≤ 0.016, CI 95%, -0.146 - 0.016), Physical activity = OR (0.011) ((P-Value ≤ 0.016, CI 95%, -0.057 - 0.079) have a significant relationship with patients' pain intensity. This relationship is directly related to age, so that the severity of pain has increased with age. For physical activity, this direct relationship has been obtained, so that with no physical activity, the intensity of pain has also increased. The results of linear regression for the type of occupation showed that occupations that are associated with sitting have a reducing effect on pain intensity and its relationship has been shown to be protective. There is also this protective link to the history of previous illnesses, as the absence of a previous illness has reduced pain and exacerbated the complications of the illness.

Based on the adjusted model, variables Age = OR (0.042) (P-Value ≤ 0.001, CI 95%, 0.026 - 0.058), Occupation = OR (-.0445) (P-Value ≤ 0.005, CI 95%, -0.756 - -135), Residency = OR (.0376) (P-Value ≤ 0.03, CI 95%, 0.038 - 0.715), Education = OR (-.110) (P-Value ≤ 0.003, CI 95%, -0.180 - -0.040), NLR = OR (0.131) (P-Value ≤ 0.024, CI 95, 0.018 - 0.244) have a significant relationship with patients' pain intensity. This relationship is a direct relationship for age, so that the intensity of pain increases with age. This is also a direct relationship for the place of residence, so that the intensity of pain increases with living in urban areas. The results for the type

of occupation showed that this relationship was obtained in a protective way, so that occupations that are associated with sitting have a reducing effect on pain intensity. The relationship between education and pain intensity has also been protective, and having an education has not been a protective factor for pain intensity in patients. Also, the relationship between NLR and pain intensity in patients has been reported directly, to the extent that with increasing NLR ratio, pain intensity and disease complications in patients increase (Table 4).

Table 4. Factors affecting pain intensity in patients with osteoarthritis of the knee

Variable	Unadjusted		Adjusted	
	B	P-Value, (CI 95%)*	B	P-Value, (CI 95%)**
Age	0.037	0.001, 0.021 - 0.053	0.042	0.000, 0.026 - 0.058
Sex	0.238	0.146, -0.085 - 0.561		
Occupation	-0.401	0.005, -0.678 - -0.123	-.0445	0.005, -0.756 - -135
Residency	-0.175	0.535, -0.733 - 0.383	.0376	0.03, 0.038 - 0.715
Education	0.100	0.552, -0.232 - 0.432	-.110	0.003, -0.180 - -0.040
BMI	0.011	0.476, -0.020 - 0.043		
Marital status	0.237	0.355, -0.269 - 0.743		
Past medical history	-0.081	0.016, -0.146 - 0.016		
Physical activity	0.011	0.742, -0.057 - 0.079		
Smoking	-0.312	0.127, -0.714 - 0.090		
ESR	-0.006	0.636, -0.033 - 0.020		
CRP	0.080	0.417, -0.155 - 0.275		
NLR	0.078	0.159, 0.031 - 0.187	0.131	0.024, 0.018 - 0.244

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Discussion

Osteoarthritis is known as a chronic inflammation with degeneration and loss of articular cartilage and manifests itself in the form of structural lesions. It causes arthralgia, joint dysfunction and joint deformity, and affects patients' lives and normal functioning. A new clinical indicator for early screening that could be effective in diagnosing and treating the disease is being studied. Li et al. (2014) in their study showed that ADAMTS-4 may be a potential marker for osteoarthritis [21]. A study by Park et al. (2015) showed that BeadChip's determination of the presence of CTX-II in serum



and urine was of significant diagnostic value for the disease. This study showed a direct relationship between the studies of neutrophil to lymphocyte ratio (NLR) as a marker of disease severity in patients with knee osteoarthritis [22].

The clinical status of patients was evaluated according criteria according to textbook on rheumatic diseases (3rd edition 2018) [23]. The present study showed that almost all people had knee pain and it was common in all patients. The symptom of pain has been reported as the most obvious symptom in other studies, which is consistent with the present study [24]. Also in terms of examination and stiffness in the morning less than 30 minutes, the sound of the knee joint and (dryness) most people had a history of these symptoms and these symptoms are considered as important symptoms in osteoarthritis, a result that has been reported in other studies [2, 25, 26]. The results showed that one third of patients had knee bone size, also, organ heat was not seen in any disease, which is also seen in the studies of Ene et al. (2015) and Sofat et al. (2011) and is consistent with the results of the present study [27, 28]. Examination of the variable duration of the disease in patients showed that one third of the patients have a history of 1-3 years of the disease, one third of patients have a history of 4-6 years and the other third is more than 6 years old since they started their disease in a study by Tekeoglu et al. (2016), the results showed that most patients had more than three years of illness [29].

Examination of radiological images showed that most people are in phases 1 to 3 of the disease and except for one person who is in the severe (sever) stage of the disease, the rest of the people are in the pre-osteoarthritis to moderate stages. And compared to other studies where most people are in the severe stages of the disease, the people in the present study are in the early stages of the disease [24, 30, 31]. According to the objectives of the present study, it was shown that the ratio of neutrophils to lymphocytes in general in patients with osteoarthritis is higher than normal.

According to the results of the present study, there is a direct relationship between the ratio of neutrophils to lymphocytes (NLR) to the disease and the severity of pain, so that with increasing this ratio, the severity of the disease and subsequently the pain caused by the disease increases. From these results, it can be inferred that using this ratio as a new inflammatory marker is useful for the early detection and follow-up of rheumatoid

arthritis the results of various studies have also shown this relationship. The study of Özler et al. (2018) also showed that increasing the ratio of neutrophils to lymphocytes (NLR) is a risk factor for the disease and with increasing this ratio, this risk factor will increase [32]. Other studies have also shown a direct relationship between neutrophil to lymphocyte ratio (NLR) and the severity of osteoarthritis (OA). Overall, studies have shown that NLR levels can be used as an indicator of systemic inflammation, which supports the inflammatory hypothesis of the pathogenesis of osteoarthritis [16, 30, 33].

Previous studies have shown a direct and significant relationship between age and osteoarthritis (OA) [16, 30]. The results of this study showed that age is a risk factor for osteoarthritis (OA) and disease severity, so that with age, the risk of disease will increase and the severity of the disease will be higher. According to the unadjusted model, the occupation and history of previous diseases showed an indirect and significant relationship with the disease, while in physical activity this relationship was direct and significant. Based on the adjusted model, occupation and education showed an indirect and significant relationship, while the type of urban or rural housing showed a direct and significant relationship with the severity of the disease.

Also, according to the results, ESR and CRP are not related to the disease. In the study of Hassan et al. (2021), there was no statistically significant relationship between CRP and the severity of osteoarthritis (OA), but unlike the present study, neutrophils showed a direct relationship with the disease [30]. In the study of Taşoğlu et al. (2015), the results showed a significant relationship between neutrophil levels and ESR with disease, while CRP was not significantly associated with disease severity [33]. In the study of Shi et al. (2018), unlike the present study, there was no significant relationship between ESR and disease severity [34].

Cai et al. (2021) in their study concluded that the history of previous diseases is not directly related to the severity of the disease, while the results of this study showed an inverse relationship [35]. In the study of physical activity variables, the results of this study are consistent with the results of the study of Cai et al. (2021) and the results indicate a direct relationship between physical activity and disease severity, also the results showed that the duration of the disease is directly related to the



severity of the disease, but in the present study this relationship is not shown [35].

Limitations

In the present study, due to the limited sample size, many of the results, especially those obtained in multivariate analysis, show a degree of uncertainty.

Conclusions

According to the findings of the present study, it seems that the neutrophil to lymphocyte ratio (NLR) can be used as a marker in assessing the severity and activity of osteoarthritis (OA). Considering this finding of the present study and also the findings of similar studies on the existence of a relationship between the ratio of neutrophils to lymphocytes and osteoarthritis, this ratio can be considered as a promising marker for early diagnosis and treatment of osteoarthritis (OA). And it can be used routinely in clinics and laboratory wards to diagnose the disease.

Acknowledgement

We would like to thank all the parents of the patients who patiently helped in this research. The Vice Chancellor for Research of Erbil University is also thanked for the material and spiritual support of this project.

Author's contributions

All authors passed the criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

Funding/Support

This study was supported by a grant received from.....

Conflict of interest

The authors have no conflicts of interest to declare.

Data Availability

The authors guarantee that the data of this research will be provided at the request of other researchers.

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