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ORIGINAL ARTICLE

Is blood neutrophil-lymphocyte ratio an independent predictor of knee osteoarthritis severity?

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Abstract Knee osteoarthritis (OA) is one of the most common forms of joint disease, affecting an increasing number of people worldwide. Latest data suggests that inflammation plays a critical role in the pathogenesis of OA. There are a number of inflammatory markers like cytokins and cartilage degradation products that can be used as indicators in OA. Blood neutrophil-lymphocyte ratio (NLR) is a simple non-invasive and cost-effective marker of inflammation in various systemic diseases, but it has not been investigated in OA yet. The aim of the present study was to compare blood NLR levels in patients with severe - Kellgren and Lawrence (KL) grade 4 - knee OA and mild to moderate - KL grades 1–3 - knee OA. A total of 176 patients with knee OA were included in this cross-sectional study. KL grading was done according to the two-view (antero-posterior and lateral) plain radiography of both knees. Demographic characteristics, blood neutrophil, lymphocyte and platelet counts, erythrocyte sedimentation rate, and C-reactive protein were recorded. Blood NLR levels were calculated. In the severe knee OA group, blood NLR levels were found to be elevated as compared to the mild to moderate knee OA group. A blood NLR of ≥2.1 was taken as the cutoff based upon the receiver operating characteristics (roc). In the roc curve analysis, blood NLR ≥ 2.1 had 50 % sensitivity and 77 % specificity in predicting severe knee OA. In multivariate analysis, age and blood NLR ≥ 2.1 emerged as independent predictors of severe knee OA. The results of the present study, for the first time in the literature, suggests blood NLR as a novel and promising inflammatory marker indicating the severity of knee OA.

Keywords Inflammatory markers · Neutrophil-lymphocyte ratio · Osteoarthritis

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Introduction

Osteoarthritis (OA) is the most common joint disease, and the prevalence increases as the population gets older and fatter. It represents as an organ failure affecting not only the cartilage, but involving the entire joint. Knee OA is one of the most common forms of the disease [1].

There is an increasing body of evidence that inflammatory mechanisms play a role in the pathogenesis of OA. Macrophages and proinflammatory cytokines like IL-6, IL-8, IL-1, and TNF-α are recognized to have a part in the process. Moreover, OA also shares a similar inflammatory and biochemical profile with metabolic syndrome, and deserves attention as a systemic disease in the light of the recent literature [2–5]. Recently, C-terminal telopeptides of type I collagen (CTX I); CTX II; type III collagen N-propeptide; cartilage oligometric matrix protein (COMP); interferon-γ inducible protein 10 (IF-γ IP-10); matrix metalloproteinase-3 (MMP-3); MMP-2; adiponectin; interleukins like IL-8, IL-10, IL-15, IL-17; and TNF-α were suggested as biomarkers in osteoarthritis [6–8]. Nevertheless, a basic low-cost laboratory test that can be used as a marker of disease severity in OA has not been defined yet.

Recently, blood neutrophil-lymphocyte ratio (NLR) has emerged as a simple, cheap, and useful tool that represents

subclinical low-grade inflammation in many systemic circumstances [9–11].

Recognizing the absence of research investigating the relationship between blood NLR and OA, this study was undertaken to evaluate whether there is a correlation between the severity of knee OA and blood NLR levels or not.

Patients and methods

One hundred and ninety-five consecutive patients with knee OA were enrolled in this cross-sectional study. All patients were diagnosed with knee OA according to the American College of Rheumatology clinical criteria [12]. The participants who had post-infectious or post-traumatic arthropathy ($n=7$), systemic inflammatory or infectious diseases ($n=9$), and active malignancy ($n=3$) were excluded from the study. Thus, 176 patients (38 males, 138 females) were included into the study. The study was approved by the hospital ethics committee which was performed in accordance with the Helsinki Declaration, and informed consents were obtained from all participants.

Age, sex, height, weight, body mass index, neutrophil, lymphocyte and platelet counts, erythrocyte sedimentation rate, C-reactive protein, and Kellgren-Lawrence (KL) grading were recorded. Blood NLR levels were calculated. Patients were divided into two groups as patients with KL grades 1–3 (mild to moderate) knee OA and patients with a KL grade 4 (severe) knee OA.

The KL grading system was used for classifying radiographic osteoarthritis. It uses four radiographic features: joint space narrowing, osteophytes, subchondral sclerosis, and subchondral cysts. The severity of radiographic changes increases from grade 0 to 4 with grade 0 meaning no radiographic features of osteoarthritis whereas grade 4 means large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony deformity [13]. Although the KL grading of a separate patient's both knees was usually the same, if obvious difference was present between knees, the most severely affected one's grading was recorded.

Statistical analysis

Analyses were performed using SPSS. Continuous data were presented as mean ± SD. Categorical variables were summarized as percentages. Comparisons between groups were made using chi-square tests for categorical variables, independent-samples Student's t tests for normally distributed continuous variables and Mann-Whitney U tests when the distribution was skewed. A p value <0.05 was considered statistically significant.

Effects of different variables on severe knee OA were calculated in univariate analysis for each. Variables for which the unadjusted p value was <0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model using stepwise multivariate logistic regression analyses and eliminated potential markers using likelihood ratio tests. A p value <0.05 was considered statistically significant, and the confidence interval was 95 %. An exploratory evaluation of additional cut points was performed using receiver operating characteristics curve analysis.

Results

Of the 176 patients, 38 (21.6 %) were men and 138 (78.4 %) were women and mean age was 61.75 years (range 37 to 82 years). Mean BMI of the patients was 33.07 ± 4.58. All patients were grouped in two, those with KL grade 1–3 (mild to moderate) knee OA and those with KL grade 4 (severe) knee OA. The demographic and clinical characteristics of the patients according to the groups were presented in Table 1.

Receiver operating characteristics curves explored the relation between admission blood NLR and severe knee OA. For severe knee OA, area under the curve was 0.61 (95 % confidence interval 0.50 to 0.73). Using a cutoff point of 2.1, admission blood NLR predicted severe knee OA with a sensitivity of 50 % and specificity of 77 %. Levels of blood NLR ≥ 2.1 can be used as a marker of severe knee OA (Fig. 1).

Mean age ($p<0.001$), mean neutrophil count ($p=0.01$), blood NLR ≥ 2.1 ($p=0.001$), and mean blood NLR (0.023) of patients who had severe knee OA were significantly different from the patients who had mild to moderate knee OA (Table 1). Mean BMD ($p=0.45$) were similar in both groups (Table 1).

Besides, when the patients were divided into two groups as blood NLR ≥ 2.1 and blood NLR < 2.1, the ratio of patients with severe knee OA was significantly higher in the blood NLR ≥ 2.1 group (Fig. 2).

In univariate analysis, age ($p<0.001$) and blood NLR ≥ 2.1 ($p=0.001$) were significantly associated with severe knee OA (Table 2). In multiple logistic regression analysis, age ($p<0.001$) and blood NLR ≥ 2.1 ($p=0.01$) emerged as independent predictors of severe knee OA (Table 2).

Discussion

The findings of the present study demonstrate that a simple ratio (blood NLR) obtained from a universally available low-cost test (CBC with differential) provides relevant information regarding the radiographic severity of knee OA. According to our results, patients with severe knee OA have elevated blood NLR levels compared to patients with mild/moderate knee OA and blood

Table 1 Demographic and clinical characteristics and laboratory findings of knee OA patients according to knee OA severity

	Mild-moderate knee OA ($n=146$)	Severe knee OA ($n=30$)	p
Gender (%female)	78.76	76.66	0.79
Age	59.95 ± 9.69	70.50 ± 8.15	*< 0.001*
Height	158.92 ± 7.06	159.07 ± 10.1	0.94
Weight	80.90 ± 12.99	83.50 ± 12.88	0.48
BMI	31.69 ± 6.60	33.07 ± 4.68	0.45
Neutrophil count	3.94 ± 1.3	4.60 ± 1.63	*0.01*
Lymphocyte count	2.38 ± 0.75	2.35 ± 1.01	0.8
Platelet count	245.39 ± 61.66	256.71 ± 45.18	0.51
NLR	1.79 ± 0.8	2.18 ± 1.04	*0.023*
NLR ≥ 2.1 (%)	17.8	46.7	*0.001*
Sedimentation	10.80 ± 7.58	13.61 ± 10.53	0.23
C-reactive protein	0.79 ± 0.4	0.66 ± 0.3	0.72

Numbers in italics are significant at $p<0.05$

NLR neutrophil-lymphocyte ratio

NLR ≥ 2.1 is an independent variable predicting the severity of knee OA. In the light of the present study, blood NLR seems to be useful as a marker for knee OA severity.

It is known that there is an increased risk of OA from the age of 40. Approximately, 50 % of the population aged ≥65 years are affected by knee OA; nevertheless, it can affect young people too [14, 15]. Compatible with the literature, we also found age as an independent predictor of knee OA.

Though it is thought as a mechanical response to increasing load in years, OA is no longer accepted as a mechanically activated wear and tear process but instead a subclinical-low grade inflammatory condition in which mechanical stress and immunity acts simultaneously. The most popular hypothesis is that degraded cartilage fragments (generated from proteins, proteoglycans) or remnants of cellular breakdown, such as uric acid resulting from trauma, repetitive overuse, or normal aging, generate a sterile inflammatory response [16, 17]. This inflammatory response elicits upregulation of catabolic mediators such as proinflammatory cytokines, proteolytic enzymes, and chemokines and downregulation of anabolic mediators such as anti-inflammatory cytokines and growth factors [16]. Inflammatory cytokines involved into this process are IL-1β, TNF-α, IL-6, IL-15, IL-17, and IL-18, whereas the anti-inflammatory ones are IL-4 IL-10, and IL-13 [18–20]. Some of these cytokines and some cartilage degradation products are used as biological markers detecting OA. Unfortunately, the abovementioned markers of OA cannot be used practically in the clinic but instead for scientific investigations. Instead of these, an easy to access laboratory test for providing reliable information in clinical practice may be useful. In the present study, we investigated

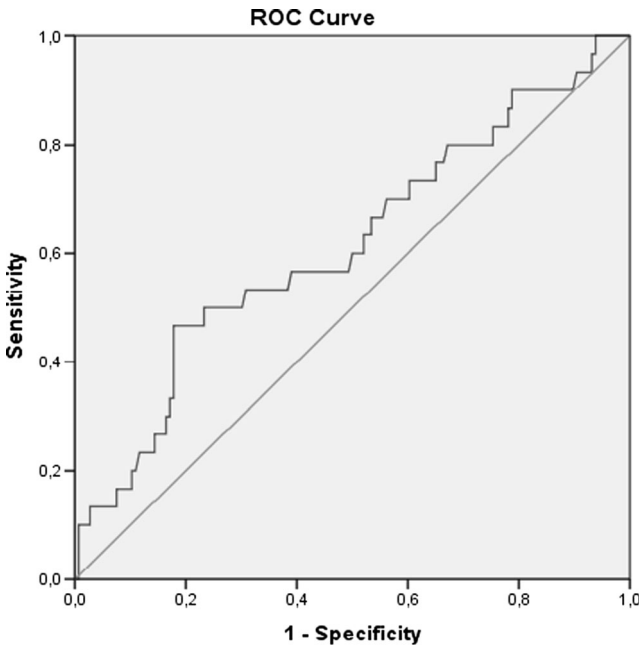

Fig. 1 Diagonal segments are produced by ties

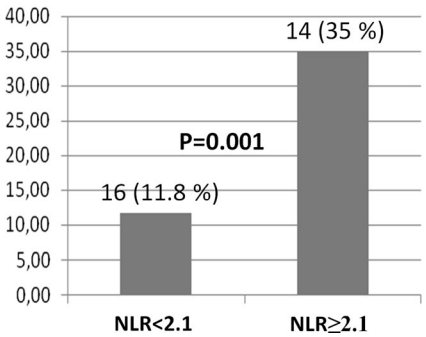

Fig. 2 Patients were divided into two groups as blood NLR ≥ 2.1 and blood NLR < 2.1, the ratio of patients with severe knee OA was significantly higher in the blood NLR ≥ 2.1 group

Table 2 Variables associated with OA severity by univariable and multivariable analysis

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	*p*	OR (95%CI)	*p*
Age	1.12 (1.07–1.18)	*<0.001*	1.12 (1.06–1.18)	*<0.001*
NLR ≥ 2.1	4.03 (1.75–9.29)	*0.001*	3.22 (1.25–8.28)	*0.01*
Gender[a]	0.88 (0.34–2.2)	0.79	1.78 (0.58–5.41)	0.30
Height	1.00 (0.93–1.08)	0.95		
Weight	1.02 (0.97–1.06)	0.48		
BMI	1.04 (0.94–1.15)	0.45		
Sedimentation	1.04 (0.97–1.11)	0.24		
C-reactive protein	0.89 (0.48–1.67)	0.73		

Numbers in italics are significant at $p<0.05$

NLR blood neutrophil-lymphocyte ratio, *BMI* body mass index, *OR* odds ratio, *CI* confidence interval

[a] Female

blood NLR as a basic inflammatory marker indicating the severity of knee OA.

Blood NLR is a recent indicator of systemic inflammation. It has been investigated in many systemic diseases on the basis of the increased neutrophil counts and decreased lymphocyte counts during stress responses and inflammation. Higher blood NLR values have been demonstrated to be associated with decreased survival rates in many cancer types [21–24]; increase in severity and higher disease activity in many systemic, neurologic, and rheumatologic diseases [25–28]; and poorer outcomes in cardiovascular diseases [10, 29, 30]. It can be easily calculated from the differential white blood cell counts, which is routinely performed on admission and universally available. Moreover, unlike many other inflammatory markers, blood NLR is inexpensive. There is no report showing the relationship of blood NLR with knee OA. To the best of our knowledge, for the first time in the literature, it is shown that blood NLR ≥ 2.1 is an independent risk factor for severe knee OA in our study.

The role of neutrophils in cartilage degradation has been extensively studied. Neutrophils release matrix metalloproteinase-8 and other cytokines such as IL-1 and IL-8, transforming growth factor beta 1 which take part in OA pathogenesis [31, 32]. Also, cellular infiltrates and synovial fluids with high amount of neutrophils and low amount of lymphocytes have been demonstrated in animal models of OA. It is believed that these acute inflammatory responses progress into a more chronic inflammation [33, 34]. Our study, demonstrating the relatively high neutrophil count compared to lymphocyte count (high blood NLR) in periferic blood also supports the role of neutrophils and chronic inflammation in OA pathogenesis.

Conclusions

In conclusion, OA is a public health problem with a growing incidence. Lots of biomarkers have been identified in numerous investigations mainly for scientific purposes. The present work for the first time in the literature has reported that blood NLR seems to be a useful biological marker predicting radiographic knee OA severity in the clinic. This study also points out the inflammatory mechanisms in OA pathogenesis. Future longitudinal studies are needed to shed light on the relation of blood NLR to OA progression.

Limitations

The most important limitation of the present study is the cross-sectional design which hides the cause and effect relationship. Also, this study cannot clarify the pathogenesis of elevated blood NLR in severe knee OA. Moreover, the use of a single blood sample does not allow assessment of the stability of blood NLR in an individual over time. So, longitudinal studies should be performed to evaluate the effects of blood NLR levels on OA progression and the part of blood NLR in OA pathogenesis. Besides, the number of patients included is relatively small for a highly prevalent disease, so larger patient groups representing the public population should be studied in order to generalize the results.

Compliance with ethical standards

Disclosures None.

References

1. Güler Uysal F, Başaran S (2009) Knee osteoarthritis. Turk J Phys Med Rehab 55(Suppl 1):1–7
2. Katz JD, Agrawal S, Velasquez M (2010) Getting to the heart of the matter: osteoarthritis takes its place as part of the metabolic syndrome. Curr Opin Rheumatol 22(5):512–9
3. Bondeson J, Bloom AB, Wainwright S, Hughes C, Caterson B, van den Berg WB (2010) The role of synovial macrophages and macrophage produced mediators in driving inflammatory and destructive responses in osteoarthritis. Arthritis Rheum 62(3):647–57
4. Franke S, Sommer M, Rüster C, Bondeva T, Marticke J, Hofmann G, Hein G, Wolf G (2009) Advanced glycation end products induce cell cycle arrest and proinflammatory changes in osteoarthritic fibroblast-like synovial cells. Arthritis Res Ther 11(5):R136
5. Huffman KM, Kraus WE (2012) Osteoarthritis and the metabolic syndrome: more evidence that the etiology of OA is different in men and women. Osteroarthr Cartil 20(7):603–4
6. Ishijima M, Kaneko H, Kaneko K (2014) The evolving role of biomarkers for osteoarthritis. Ther Adv Musculoskelet Dis 6(4): 144–53

7. Imamura M, Ezquerro F, Alfieri FM, Boas LV, Tozetto-Mendoza TR, Chen J, Özçakar L, Arendt-Nielsen L, Battistella R (2015) Serum levels of proinflammatory cytokines in painful knee osteoarthritis and sensitization. Int J Inflam 2015:329792. doi:10.1155/2015/329792
8. Mobasheri A (2012) Osteoarthritis year 2012 in review: biomarkers. Osteoarthr Cartil 20(12):1451–64
9. Uslu AU, Deveci K, Korkmaz S, Aydın B, Senel S, Sancakdar E, Sencan M (2013) Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? Biomed Res Int 2013:185317. doi:10.1155/2013/185317
10. Taşoğlu İ, Çiçek ÖF, Lafçı G, Kadiroğulları E, Sert DE, Demir A, Çavuş U, Çolak N, Songur M, Hodo B (2014) Usefullness of neutrophil/lymphocyte ratio as a predictor of amputation after embolectomyfor acute limb ischemia. Ann Vasc Surg 28(3):606–13
11. Galizia G, Lieto E, Zamboli A, De Vita F, Castellano P, Romano C, Auricchio A, Cardella F, De Stefano L, Orditura M (2015) Neutrophil to lymphocyte ratio is a strong predictor of tumor recurrence in early colon cancers: a propensity score-matched analysis. Surgery 158(1):112–20
12. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M (1986) Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 29(8):1039–49
13. Kellgren JH, Lawrence JS (1957) Radiological assessment of osteo-arthrosis. Ann Rheum Dis 16(4):494–502
14. Outerbridge RE (1961) The etiology of chondromalacia patellae. J Bone Joint Surg (Br) 43-B:752–7
15. Coleman S, Briffa NK, Carroll G, Inderjeeth C, Cook N, Mcquade J (2012) A randomised controlled trial of a self-management education program for osteoarthritis of the knee delivered by health care professionals. Arthritis Res Ther 14(1):R21
16. Orlowsky EW, Kraus VB (2015) The role of innate immunity in osteoarthritis: when our first line of defense goes on the offensive. J Rheumatol 42(3):363–71
17. Berenbaum F (2013) Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthr Cartil 21(1):16–21
18. Wojdasiewicz P, Poniatowski LA, Szukiewicz D (2014) The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm 2014:561459. doi:10.1155/2014/561459
19. De Lange-Brokaar BJ, Ioan-Facsinay A, van Osch GJ, Zuurmond AM, Schoones J, Toes RE, Huizinga TW, Kloppenburg M (2012) Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. Osteoarthr Cartil 20(12):1484–99
20. Liu Y, Peng H, Meng Z, Wei M (2015) Correlation of IL-17 level in synovia and severity of knee osteoarthritis. Med Sci Monit 21:1732–6
21. Shao N, Cai Q (2015) High pretreatment neutrophil-lymphocyte ratio predicts recurrence and poor prognosis for combined small cell lung cancer. Clin Transl Oncol. doi:10.1007/s12094-015-1289-8
22. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ (2005) Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol 91(3):181–4
23. Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH, Jamaris S, Taib NA (2015) Utility of pretreatment neutrophil-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer 113(1):150–8
24. Shimada S, Takiguchi N, Kainuma O, Soda H, Ikeda A, Cho A, Miyazaki A, Gunji H, Yamamoto H, Nagata M (2010) High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer 13(3):170–6
25. Celikbilek M, Dogan S, Ozbakır O, Zararsız G, Kücük H, Gürsoy S, Yurci A, Güven K, Yücesoy M (2013) Neutrophil-lymphocyte ratio as a predictor of disease severity in ulcerative colitis. J Clin Lab Anal 27(1):72–6
26. Buyukkaya E, Karakas MF, Karakas E, Akcay AB, Tanboga IH, Kurt M, Sen N (2014) Correlation of neutrophil to lymphocyte ratio with the presence and severity of metabolic syndrome. Clin Appl Thromb Hemost 20(2):159–63
27. Erkol İnal E, Sunar İ, Sarataş Ş, Eroğlu P, İnal S, Yener M (2015) May neutrophil-lymphocyte and platelet-lymphocyte ratios indicate disease activity in ankylosing spondylitis? Arch Rheumatol 30(2):130–7
28. Demirci S, Demirci S, Kutluhan S, Koyuncuoğlu HR, Yürekli VA (2015) The clinical significance of the neutrophil-to-lymphocyte ratio in multiple sclerosis. Int J Neurosci. doi:10.3109/00207454.2015.1050492
29. Demir M (2013) The relationship between neutrophil lymphocyte ratio and non-dipper hypertension. Clin Exp Hypertens 35(8):570–3
30. Muhmmed Suliman MA, Bahnacy Juma AA, Ali Almadhani AA, Pathare AV, Alkindi SS, Uwe WF (2010) Predictive value of neutrophil to lymphocyte ratio in outcomes of patients with acute coronary syndrome. Arch Med Res 41(8):618–22
31. Abbink JJ, Kamp AM, Nieuwenhuys EJ, Nuijens JH, Swaak AJ, Hack CE (1991) Predominant role of neutrophils in the inactivation of alpha 2-macroglobulin in arthritic joints. Arthritis Rheum 34:1139e50
32. Tortorella MD, Arner EC, Hills R, Easton A, Korte-Sarfaty J, Fok K et al (2004) Alpha2-macroglobulin is a novel substrate for ADAMTS-4 and ADAMTS-5 and represents an endogenous inhibitor of these enzymes. J Biol Chem 279:17554e61
33. Clements KM, Ball AD, Jones HB, Brinckmann S, Read SJ, Murray F (2009) Cellular and histopathological changes in the infrapatellar fat pad in the monoiodoacetate model of osteoarthritis pain. Osteoarthr Cartil 17(6):805–12
34. Ross TN, Kisiday JD, Hess T, McIlwraith CW (2012) Evaluation of the inflammatory response in experimentally induced synovitis in the horse: a comparison of recombinant equine interleukin 1 beta and lipopolysaccharide. Osteoarthr Cartil 20(12):1583–90