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Relationship of hematological and biochemical parameters with WOMAC index to severity of osteoarthritis: A retrospective study

Hematolojik ve biyokimyasal parametreler ile WOMAC indeksinin osteoartrit şiddeti ile olan ilişkisi: Retrospektif bir çalışma

Kenan Özler [1]

Abstract

Aim: Our aim was to investigate whether any hematologic changes that could be detected easily in whole blood counts together with the Western Ontario and McMaster Universities Osteoarthritis score (WOMAC) had diagnostic value for predicting knee osteoarthritis severity.

Methods: A retrospective study including a total of 208 knee osteoarthritis patients (112 patients early and 106 patients late osteoarthritis) was carried out. Cut-off values for age, C-reactive protein, neutrophil leukocyte ratio and WOMAC index for osteoarthritis were calculated. A multivariate logistic regression model was used to identify the independent factors of late osteoarthritis.

Results: Compared with late osteoarthritis with early osteoarthritis, late osteoarthritis had significantly higher C-reactive protein, neutrophil leukocyte ratio and WOMAC index (p=0.019, p=0.028 and p=0.001, respectively). Area Under Curve was found to be 0.922, 0.533, 0.558 and 0.824 for age, C-reactive protein, neutrophil leukocyte ratio and WOMAC index, respectively. Multilogistic regression analysis was performed with C-reactive protein, neutrophil leukocyte ratio and WOMAC index to determine independent risk factors associated with late osteoarthritis. Odds ratios for neutrophil lymphocyte ratio, C-reactive protein and WOMAC index were found to be 1.317 (95% CI = 1.030-1.682, p = 0.034), 1.055 (95% CI = 1.004-1.108, p = 0.028) and 1.078 (95% CI = 1.056-1.100, p=0.001), respectively. Age, neutrophil leukocyte ratio, C-reactive protein and WOMAC index were statistically significant in predicting late osteoarthritis.

Conclusions: Our study suggests that increased neutrophil leukocyte ratio, C-reactive protein and WOMAC index are associated with independent risk factors for late osteoarthritis.

Key words: Neutrophil-lymphocyte ratio, C-reactive protein, WOMAC index, knee, osteoarthritis

Öz

Amaç: Amacımız, Western Ontario ve McMaster Üniversiteleri Osteoartrit skoru (WOMAC) ile birlikte kolayca saptanabilecek tam kanda herhangi bir hematolojik değişikliğin diz osteoartriti şiddetini öngörmede tanısal değere sahip olup olmadığını araştırmaktır.

Yöntemler: 208 diz osteoartrit hastasını (112 hasta erken ve 106 hasta geç osteoartrit) içeren retrospektif bir çalışma planlandı. Yaş, CRP, nötrofil lökosit oranı ve WOMAC index için cut-off değerleri hesaplandı. Geç osteoartrit için bağımsız faktörlerini tanımlamak için çok değişkenli lojistik regresyon modeli kullanıldı.

Bulgular: Erken ve geç osteoartrit karşılaştırıldığında, C-reaktif protein, nötrofil lökost oranı ve WOMAC indeksi anlamlı olarak geç osteoartrit olan grupta daha yüksekti (sırası ile; p=0,019, p=0,028 ve p=0,001). Yaş, C-reaktif protein, nötrofil lökosit oranı ve WOMAC index Area Under Curve değerleri sırasıyla 0,922, 0,533, 0,558 ve 0,824 olarak bulundu. Geç osteoartrit ile ilişkili bağımsız risk faktörlerini belirlemek amacı ile yapılan regresyon analizinde, nötrofil lökosit oranı için odds oranı 1.317 (95% CI = 1.030-1.682, p=0.034), C-reaktif protein için odds oranı 1.055 (95% CI = 1.004-1.108, p= 0.028) ve WOMAC index için odds oranı 1.078 (95% CI = 1.056-1.100, p=0.001) idi. Geç osteoartrit öngörüsünde yaş, nötrofil lökosit oranı, C-reaktif protein and WOMAC index istatistiksel olarak anlamlı idi.

Sonuç: Nötrofil lökosit oranı, C-reaktif protein düzeyleri ve WOMAC indeksinin, geç osteoartrit için bağımsız risk faktörleri ile ilişkili olduğu düşünülmektedir.

Anahtar Kelimeler: Nötrofil lenfosit Oranı, C-Reaktif Protein, WOMAC indeks, diz, osteoartrit

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Introduction

Osteoarthritis (OA) is a progressive degenerative joint disease associated with cartilage destruction, subchondral bone remodeling and synovium inflammation. OA is the leading cause of the lower extremity insufficiency especially in the elderly group. The incidence of OA is now increasing due to the aging population and increasing obesity [1]. OA is characterized with joint pain, pain in movements, short stiffness and crepitation in joints [2].

Although pathophysiology of OA has been proposed for many reasons, recent studies have also shown that inflammatory and anti-inflammatory mediators such as IL-1b, TNF-alpha, leukocyte inhibitory factor, IL- 1 receptor antagonist, matrix metalloproteinases, proteases, chemokines, nitric oxide, and prostaglandins and leukotrienes have been clearly understood to role in the development and progression of the symptoms of OA [3, 4]. Proinflammatory cytokines are altered together with some peripheral blood markers such as leukocytes, lymphocytes and neutrophils in inflammatory responses. Increased lymphocytes levels have been shown to be important in the prognosis of diseases such as over cancer [5], sepsis [6], pneumonia [7] and differentiation of benign and malignant ovarian masses [8]. Neutrophil lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) were positively correlated with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in rheumatoid arthritis, ankylosing spondylitis, and OA [9]. CRP is a pentameric protein with acute phase reactivity, elevated in serum in cases of inflammation, infection, and tissue damage. CRP can increase inflammation by accelerating leukocyte uptake and proinflammatory cytokine synthesis [10]. Studies have shown that serum CRP levels in OA patients are significantly increased compared to control groups [11, 12]. In clinical practice, the evaluation of knee OA is mainly based on clinical manifestation and radiographic changes. The Kellgren-Lawrence (KL) grading scale was traditionally used to grade the severity of knee OA on radiographs [13].

We aimed to determine levels of inflammatory markers levels such as NLR and CRP in OA patients and to investigate the predictive value of NLR and CRP levels in association with The Western Ontario and McMaster Universities Osteoarthritis score (WOMAC index) index used for severity of knee OA.

Materials and methods

A retrospective study using a prospectively held database was carried out between December 2016 and January 2018. Two hundred and eight patients diagnosed as OA were recruited consecutively from orthopedics outpatient clinics. The study protocol was performed according to the principles of the Declaration of Helsinki and approved by the local Ethical Committee of our hospital.

The diagnosis of knee OA determined by radiographic features, the KL scale was chosen by the World Health Organization as the accepted reference standard. The KL grading was used for classifying OA according to radiographic signs (joint space narrowing, subchondral sclerosis, osteophytes and subchondral cysts) and radiographically are graded from 1 to 4 [13]. Body mass index (BMI) was homogenized in patients with knee OA and BMI <30 kg/m^2 were included in the study.

Patients were excluded if any of the following disorders were present: septic arthritis, patients undergoing surgery with a diagnosis of OA, patients receiving local medication or systemic antibiotic therapy, malignant patients, patients receiving chemotherapy, radiotherapy or immunosuppression, patients with systemic acute infection, patients with chronic inflammatory disease, patients with acute surgery.

All participants included in the study were evaluated at the initial admission. Clinical examination was performed, X-ray images of the knee and anthropometric measurements as well as the previous surgery and medical history were recorded. KL grading of the mostly affected knee was performed for each patient through the evaluation of X-ray images. Blood samples were obtained at the same time with the X-ray images by venipuncture for complete blood count (white blood cell count [/mm^3], lymphocyte count, platelet count [/mm3], platelet lymphocyte ratio (PLR) and mean platelet volume (MPV) [femptolitre-fL]), C-reaktif protein (CRP) [mg/dl] and erythrocyte sedimentation rate (ESR) [mm/hour] measurements.

Patients were then divided into two groups as the patients with KL grades 1–2 (mild-moderate) knee OA and the patients with KL grades 3–4 (severe) knee OA. So, 112 patients were early stage (stage 1 and stage 2) knee osteoarthritis (EOA) and 106 patients were late stage (stage 3 and stage 4) knee osteoarthritis (LOA).

Knee functions were assessed by WOMAC index that is consisting of 24 parameters that include pain (score range: 0–20), stiffness (score range: 0–8), and functional impairment (score range: 0–68) [14].

All data with regard to demographic and clinical features including WOMAC index, laboratory findings and imaging features graded by X-ray images were recorded into the prospectively held database.

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 22 (SPSS Inc., Chicago, IL, United States). Data were shown as mean with 95% Confidence Interval (CI) or number of cases and percentage, where applicable. Continuous variables were tested for normality by the Kolmogorov– Smirnov test. Normally distributed data are presented as mean ± standard error. We used the independent samples t -test for parametric groups. Receiver operating curve (ROC) analysis was performed for age, CRP, NLR and WOMAC index and the correspondent AUC values with 95% CI was calculated in OA. Multivariate logistic regression analysis was used to determine the relationship of WOMAC index, CRP and complete blood count parameters with LOA. A p value less than 0.05 was considered statistically significant.

Results

A total of 218 participants were enrolled in the study. 112 were EOA and 106 were LOA. The baseline anthropometric and biochemical characteristics of EOA and LOA patients are given in Table 1. The patients in the LOA group were older than the EOA group (p=0.001). CRP and NLR levels were 3.65 ±

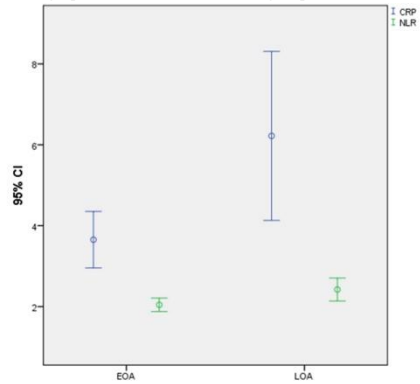
0.35 mg/dl and 2.04 ± 0.08 in the EOA group and 6.22 ± 1.05 mg/dl and 2.40 ± 0.14 in the LOA group, respectively. CRP and NLR were significantly higher in the LOA group than in the EOA group (p=0.019 and p=0.028) (Table 1, Figure1). The WOMAC index was 44.86 ± 1.28 in the EOA group and 64.08 ± 1.60 in the LOA group. The WOMAC index was significantly higher in the LOA group than in the EOA group (p=0.001) (Table 1).

Table 1: Baseline characteristics, clinic and laboratory parameters of EOA and LOA patients.

	EOA (n=112)	LOA (n=106)	p
Age (year)	52.19 ±7.12	67.33 ± 7.99	0.001
CRP (mg/dl)	3.65 ± 0.35	6.22 ± 1.05	0.019
ESR (mm/hour)	12.52 ± 2.60	16.48 ± 1.51	0.198
WBC (/mm^3)	7.53 ± 0.16	7.37 ± 0.22	0.556
Platelet counts (/mm^3)	247.56 ± 5.62	231.30 ± 7.68	0.086
Neutrophil counts	4.44± 0.129	4.69 ± 0.163	0.232
Lymphocyte counts	2.39 ± 0.074	2.27 ± 0.090	0.299
NLR	2.04 ± 0.08	2.40 ± 0.14	0.028
PLR	115.16 ±4.79	117.58 ± 6.34	0.759
MPV (femptolitre-fL)	10.09 ±0.96	11.05 ± 0.81	0.230
WOMAC index	44.86 ± 1.28	64.08 ± 1.60	0.001

Independent simple t test, mean ± standart error mean. CRP; C-reaktif protein, WBC; white blood cell, NLR; neutropil/lymphocyte ratio, PLR; platelet lymphocyte ratio MPV; mean platelet volume, ESR; Erythrocyte sedimentation rate, WOMAC index; Western Ontario McMasters Osteoartritis index.

Figure 1. CRP and NLR graphic from EOA and LOA groups



Counts for white blood cell, lymphocyte and platelet, levels of PLR and MPV, and ESR were not statistically different between EOA and LOA groups (Table 1).

We determined the cut-off level of 45 for age; this cut-off specificity was 83%, sensitivity 78% and AUC 0.897 (0.853-0.940) . The cut-off value for CRP was 5 mg/dL with specificity of 52%, sensitivity of 48% and AUC of 0.467 (0.390-0.544). For NLR, the cut-off level was 4.13 with specificity 48%, sensitivity48 % and AUC 0.558 (0.482-0.635). The cut-off level of WOMAC index was 54; specificity, sensitivity and AUC were 80%, 69% and 0.824 (0.771-0.877), respectively (Table 2, Figure 2).

All parameters were further evaluated with multivariate regression analysis to determine the independent risk factors in LOA (Table 3). Age, CRP, NLR and WOMAC index were found to be significantly associated with LOA (p=0.001, p=0.034, p=0.028 and p=0.001, respectively) (Table 3).

Table 2: The cut-off value, sensitivity, specificity and AUC (95% Cl) of CRP, NLR and WOMAC index in OA.

	Cut off value	Specificity	Sensitivity	AUC (95 % Cl)	p
Age (year)	45	83%	78%	0.922 (0.886-0.957)	0.001
CRP (mg/dl)	5	52 %	48 %	0.533 (0.456-0.610)	0.406
NLR	4.13	48 %	48 %	0.558 (0.482-0.635)	0.137
WOMAC index	54	80 %	69 %	0.824 (0.771-0.877)	0.001

CRP: C-reactive protein, NLR: neutrophil/lymphocyte ratio, WOMAC index: Western Ontario McMasters Osteoartritis index.

Figure 2. Age, CRP, NLR and WOMAC index ROC curve in OA

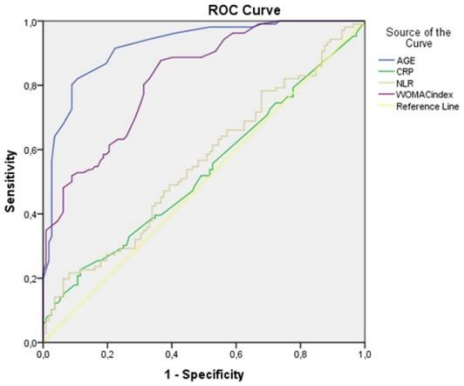


Table 3: Multivariate logistic regression analysis for prediction of LOA.

	Multivariable analysis	
	OR (95 % Cl)	p
Age (year)	1.300 (1.216-1.391)	0.001
CRP (mg/dl)	1.055 (1.004-1.108)	0.034
ESR (mm/hour)	1.010 (0.994-1.025)	0.235
WBC (/mm^3)	0.961 (0.842-1.096)	0.554
Platelet counts (/mm^3)	0.997 (0.993-1.001)	0.089
Neutrophil counts	1.113 (0.934-1.327)	0.232
Lymphocyte counts	0.846 (0.618-1.160)	0.299
NLR	1.317 (1.030-1.682)	0.028
PLR	1.001 (0.996-1.006)	0.758
MPV (femptolitre-fL)	1.153 (0.887-1.498)	0.288
WOMAC index	1.078 (1.056-1.100)	0.001

CRP: C-reactive protein, WBC: white blood cell, NLR: neutropil/lymphocyte ratio, PLR: platelet lymphocyte ratio, MPV: mean platelet volume, ESR: Erythrocyte sedimentation rate, WOMAC index: Western Ontario McMasters Osteoartritis index.

Discussion

In the present retrospective case-control study of knee OA, increased levels of NLR, CRP and WOMAC index were found to be associated with LOA. Knee OA is a chronic disease characterized by progressive chondrocyte degeneration that plays a role in proinflammatory processes. Studies have also shown that mononuclear cell infiltration is increased in synovial fluid of early and late stage OA patients [15]. Tascioglu et al. [16] showed that age, neutrophil, lymphocyte and platelet counts, MPV, PLR, and ESR were significantly higher in the late OA group than in the early OA group. Gundogdu et al. [17] determined that serum white blood cell count, CRP and NLR levels were not different between OA and healthy controls, but NLR was higher in stage 4 knee OA cases [17].

In the present study we found that age, NLR and CRP levels were significantly higher in EOA compared to LOA. Many studies have shown the relationship between serum CRP levels and OA [18]. At the same time, CRP is one of the

systemic markers showing synovitis [18]. BMI homogenized studies have also shown that CRP is an independent risk factor for OA [11]. Hanata et al. [19] determined that ESR increased in OA patients and was also significantly higher in grade 3-4 OA patients than in grade 1 OA patients. ESR and high-sensitivity CRP concentration were higher in knee OA and related to clinical features [19, 20].

Benito et al. [21] reported that the infiltration of CD4 and CD68 cells were increased in the synovial fluid and that TNF alpha and IL-1 beta levels in these cells were significantly higher in the early OA group than in the LOA group.

Radiography is used first to determine structural changes in OA [22]. However, the diagnostic value of radiographic imaging is limited to development of EOA and progression of OA. However, non-invasive methods such as magnetic resonance imaging and 3D ultrasonography are used to determine the progression of the OA disease by looking at joint morphology, but it is known that these tests show a low rate of progression in a large population [23]. In some studies, serum CD14 and CD163 macrophage markers have been shown to be associated with joint symptoms, severity and progression of radiological osteoarthritis [24

The limit of our study is patient count is low and proinflammatory markers are not working. The other limitation is that the four osteoarthritis stages are not evaluated separately.

In conclusion, we found that age, NLR and CRP levels were significantly higher in EOA compared to LOA. Also age, CRP, NLR and WOMAC index were found to be significantly associated with LOA in our study. We think that the progression of loss of cartilages can be independent risk factors by using clinical features (WOMAC index), inflammatory markers (NLR, CRP) and imaging features and these factors can be used in the detection of high-risk population for progression.

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