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ARAŞTIRMA / RESEARCH

Relation of complete blood count parameters and derivatives with radiologic staging of knee osteoarthritis

Diz osteoartriti radyolojik evrelemesi ile tam kan sayım parametreleri ve türevleri ilişkisi

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Abstract

Purpose: In this study, the relationship between radiologic progression and complete blood count parameters and derivatives, which have appeared as biomarkers for systemic inflammation in recent years, were evaluated in patients with knee osteoarthritis (OA).

Materials and Methods: This retrospective study included 209 consecutive patients 40 to 80 years of age diagnosed with knee OA according to 2010 American College of Rheumatology clinical criteria. Participants' demographic characteristics, complete blood parameters and derivatives were recorded. Blood platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and monocyte to neutrophil ratio (MNR) levels were calculated.

Results: The majority of patients with high-grade knee OA were determined to be females of an advanced agewith higher patellar tendon length (PTL). Their leukocyte (WBC), neutrophil, and NLR levels were significantly higher than others. When we compared this group of patients to four groups (grades 1-4), advanced age, female gender, PTL, Q angle, WBC, neutrophils, mean platelet volume (MPV), and NLR were significantly higher in patients with grade 4 knee OA.

Conclusion: In advanced knee OA, patellofemoral Q angle and PTL increased along with serum WBC, neutrophil, NLR, and MPV levels while RBC, Hb, lymphocyte, monocyte, basophil, and eosinophil levels were reduced. In the future, these parameters may be used as a guide to OA progression.

Keywords: Osteoarthritis, inflammation, inflammatory markers; complete blood count; neutrophil to lymphocyte ratio

Öz

Amaç: Bu çalışmada diz osteoartritli (OA) hastalarda, son yıllarda sistemik inflamasyon için biyobelirteç olarak ortaya çıkan, tam kan sayımı parametre ve türevleri ile radyolojik ilerleme arasındaki ilişki değerlendirildi.

Gereç ve Yöntem: Bu retrospektif çalışma 2010 Amerikan Romatoloji Koleji klinik kriterlerine göre diz OA tanısı konmuş 40 ila 80 yaşları arasındaki 209 ardışık hastayı içermektedir. Katılımcıların demografik özellikleri, tam kan parametreleri ve türevleri kaydedildi. Kan trombosit / lenfosit oranı (PLR), nötrofil / lenfosit oranı (NLR) ve monosit / nötrofil oranı (MNR) seviyeleri hesaplandı.

Bulgular: Yüksek dereceli diz OA'sı olan hastaların çoğunluğunun, ileri yaşta, artmış patellar tendon uzunluğu (PTL) olan kadın olduğu belirlendi. Lökosit (WBC), nötrofil ve NLR düzeyleri diğer hastalardan anlamlı derecede yüksekti. Bu hasta grubunu dört gruba (örn. evre 1-4 arası) ayırdığımızda, 4. evre diz OA'lı hastalarda ileri yaş, kadın cinsiyet, PTL, Q açısı; WBC, nötrofiller ortalama trombosit hacmi (MPV) ve NLR anlamlı olarak yüksek bulundu.

Sonuç: İleri diz OA olgularında patellofemoral Q açısı ve PTL, serum WBC, nötrofil, NLR ve MPV ile birlikte artmış; RBC, Hb, lenfosit, monosit, bazofil ve eozinofil düzeyleri azalmıştır. Gelecekte, bu parametreler hastalığın ilerlemesinde bir rehber olarak kullanılabilir.

Anahtar kelimeler: Osteoartrit, inflamasyon, inflamatuar belirteçler; tam kan sayımı; nötrofil lenfosit oranı

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INTRODUCTION

Osteoarthritis (OA), also referred to as a degenerative joint disease or degenerative arthritis, is the most common chronic condition of the joints. It can affect any joint, but often occurs in knees, hips, lower back, neck, small joints of the fingers, and the bases of the thumb and big toe. It is a multifactorial and progressive disease with no treatment as yet. Scales to be used for clinical follow-up of the disease are of limited value due to the long, asymptomatic, slowly progressing characteristics of OA and clinical-imaging incompatibility. In recent years, several studies have been initiated to find novel biochemical and genetic biomarkers to identify early OA changes and disease progression[1,2]. There is not enough data detailing the process, diagnosis, and prognosis of OA due to the long asymptomatic periods associated with the disease. Diagnosis is usually made by evaluating simple clinical symptoms and radiographic changes.

Complete blood count (CBC) parameters are simple non-invasive and cost-effective markers oftenly used in clinical practice. Sometimes, acute phase proteins such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are insufficient to show disease activity as they are effected by other conditions such as infection, malignencies etc... Recent years CBC parameters and derivates are used to be for the diagnoses, clinical severity and prediction of many diseases in different areas of medicine. Recent studies have revealed the role of inflammation in the pathogenesis of OA. Specific biomarkers are needed to make an early and accurate diagnosis and prognosis. Studies related to the radiologic and clinical progression of OA are lacking. There is no specific biomarker used for disease monitoring in OA yet [3-6]. Therefore, the aim of this study was to investigate the importance of CBC parameters and derivatives as biomarkers in conjunction with radiologic follow-up of knee OA.

MATERIALS AND METHODS

The study designed as retrospective and cross-sectional. Patients' data were obtained from hospital data at department of Physical Medicine and Rehabilitation at University Hospital. The study included 209 consecutive patients 40 to 80 years of age diagnosed with knee OA according to 2010 American College of Rheumatology clinical criteria. The OA diagnosis was evaluated by the same trained physician at outpatient clinic with clinical (a history of knee pain and difficulty in walking and going up stairs) and radiological signs (conventional radiography and/or magnetic resonance imagination). Exclusion criteria included a known history of prior orthopedic surgery, major knee trauma, inflammatory rheumatological disease, acute or chronic infection and malignancy.

Those who have risk factors that would affect the CBC parameters were excluded. Participants' demographic characteristics, CBC parameters, and derivatives, radiological data were recorded at the same time they apply to outpatient clinic. Derivates such as, blood platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and monocyte to neutrophil ratio (MNR) were calculated. Complete blood count parameters were analyzed using a Sysmex XN-3000 automatic hematology device (Sysmex, Kobe, Japan).

Measures

Radiologic staging was performed according to the Kellgren-Lawrence classification[7,8] using anteroposterior and lateral plain radiographs of both knees. Patella and patellar tendon length (PTL), patellofemoral Q angle, and Insall-Salvati ratio were measured by the same trained radiologist on conventional radiographs.

Kellgren-Lawrence classification system

The Kellgren and Lawrence system is a common method of classifying the severity of knee OA using five grades[7]. This classification was proposed by Kellgren et al. in 1957[8] and later accepted by WHO in 1961.

Grade 0: No radiographic features of OA are present
Grade 1: Doubtful joint space narrowing (JSN) and possible osteophytic lipping
Grade 2: Definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
Grade 3: Multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4: Large osteophytes, marked JSN, severe sclerosis and definite bony deformity

Patellofemoral Q angle

The Q angle was first defined by Brattstrom[9]. It is formed by the crossing of two imaginary lines. The first line extends from the anterosuperior iliac spine (ASIS) to the center of the patella. The second line is drawn from the tibial tuberosity (TT) to the center of

patella. The angle formed between these two lines represents the Q angle. Traditionally, the Q angle has been measured with the knee at or near full extension. Normally Q angle is 14 deg for males and 17 deg for females. There exists an association between patellofemoral pathology and excessive lateral tracking of the patella, assessing the overall lateral line of pull of the quadriceps relative to the patella is a meaningful clinical measure[9].

Insall salvatti ratio

The Insall-Salvati ratio is obtained by dividing patellar tendon length (TL), patella length (PL). This can be measured on a lateral knee X-ray or sagittal Magnetic Resonance Imagination (MRI). Ideally, the knee is 30 degrees flexed. The Insall-Salvati ratio (TL/PL) is considered normal between 0.8 and 1.2: patella baja: <0.8; patella alta: >1.2 [10].

Statistics analysis

Analyses were performed using SPSS version 17.0 for Windows. 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 and numeric variables were analysed by Student's t test, one-way ANOVA test and Kruskall Wallis test according to their distribution characteristics. The coherence of variables to normal contribution (normality) was analysed by Kolmogorov-Smirnov test and histogram graphics as the number of patients in study group is more than 30. The Spearman's correlation analysis was used to analyze the level of the correlation between the variables. A p value <0.05 was considered statistically significant.

An exploratory evaluation of additional cut points was performed using receiver operating characteristics curve analysis and the confidence interval was 95 %. The study was approved by the Regional Committee for Ethics (no:2018/81) in Medical Research and complied with Helsinki criteria. An informed consent form was taken from the participants.

RESULTS

A total of 37 male and 172 female patients (N = 209) were included in this study. According to Kellgren-Lawrence OA staging, grades 1 and 2 were classified as low-grade and grades 3 and 4 as high-grade. Data from both low- and high-grade groups are summarized in Table 1. Patients with high-grade knee OA were predominantly female (*P*=0.009), of an advanced age (*P*= 0.00), with higher PTL (*P*= 0.01).

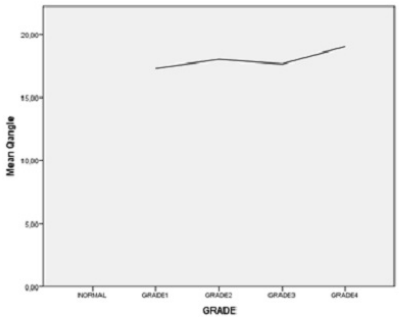

Figure 1. Q angle curve according to grade of knee OA.

When we compared this group of patients with four groups (KL grade 1-4), advanced age (*P*=0.00), female gender (*P* = 0.025), PTL (*P* = 0.08), Q angle (*P* = 0.026), WBC (*P* = 0.011), neutrophil (*P* = 0.04), mean platelet volume (MPV) (*P* = 0.009), and NLR (*P* = 0.004) were significantly higher in those with grade 4 knee OA. Conversely, lymphocyte (*P* = 0.03), monocyte (*P* = 0.002), basophil (*P* = 0.00), eosinophil (*P* = 0.025), erythrocyte (RBC) (*P* =0.03), and hemoglobin (Hb) (*P* = 0.01) values were significantly lower than others (Table 2). Of all the participants, 72.5% had normal patellae, 1.8% had patella baja, and 25.7% had patella alta. The incidence of patella alta was higher in patients with high-grade (3 or 4) knee OA (*P* = 0.009).

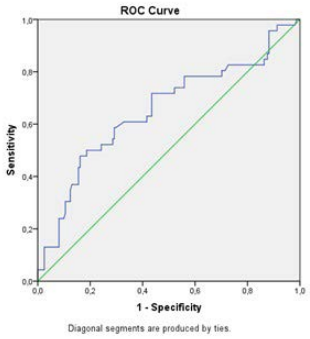

Figure 2. ROC curve analysis of the test (source of the curve green: reference line; blue: NLR value).

The stage of knee OA were positively correlated with PTL (*P*= 0.048), WBC (*P* = 0.026), neutrophil (*P* = 0.001), MPV (*P*= 0.012), and NLR (*P* = 0.003) levels,

but negatively correlated with RBC (P = 0.002), Hb (P = 0.000), and platelet distribution width (PDW) (P = 0.023) levels. The Q angle was positively correlated with patient age (Fig. 1) and negatively correlated with lymphocyte (P = 0.009), eosinophil (P = 0.030), and platelet (P = 0.045) levels. Patella length was positively correlated with WBC (P = 0.031) and neutrophil (P = 0.036), and negatively correlated with basophil (P = 0.001) and platelet distribution width (PDW) (P = 0.016).

The Insall-Salvati ratio was negatively correlated with basophile (P = 0.026). Receiver operating characteristics (ROC) analysis demonstrated that when the NLR cut-off value was set at 2.1, it could be used as a significance test for the diagnosis of severe OA (grade 4) with a sensitivity of 60% and a specificity of 71% (Fig. 2).

DISCUSSION

OA is presently one of the most common chronic diseases, and with the increase in life expectancy, both its prevalence and incidence is expected to rise. This condition is progressive and leads to functional decline and loss of quality of life, with important health care and society costs[11]. The etiopathogenesis of OA has not been entirely clarified. It is a heterogeneous disorder, and genetic as well as biomechanical, endocrine, and inflammatory effects may be involved in its origin[12]. An increased load due to an increase in body mass has been well established as a mechanical contribution to the pathophysiology of OA[13,14].

Table 1. Descriptive and analytic characteristic of the groups

	KL grade 1 and 2 (low grade OA)	KL grade 3 and 4 (high grade OA)	*P*
Age (year)*	53.3±10.4	65.6±10.3	0.00*
Gender (M/F)*	26/85	11/87	*0.009**
Patella length (PL) (cm)	4.1±0.5	4.1±0.38	0.48
Patellar tendon length (PTL) (cm)*	4.3±0.56	4.6±0.68	0.01*
Q angle (deg.)	16.9±9.9	18.2±11.3	0.38
İnsall salvatti ratio	1±0.17	1.1±0.19	0.13
Leucocyte*	7.4±1.9	8.2±2.2	0.008*
Neutrophil *	4.2±1.5	5.2±2.1	0.00*
Lymphocyte	2.2±0.71	2.2±0.92	0.47
Monocyte	0.52±0.35	0.71±0.91	0.052
Eosinophils	0.23±0.44	0.18±0.14	0.33
Basophil	0.05±0.09	0.08±0.197	0.29
RBC	4.7±0.43	4.6±0.81	0.87
Hb*	13.4±1.3	12.6±2	0.00*
MCV	83.4±8.1	84.1±6.6	0.53
RDW	14.8±4.6	15.2±4.9	0.58
Platelet	268.2±69.7	272.5±80.1	0.68
PDW	18.9±11.9	15.6±11.6	0.51
MPV	10.2±1.1	10.3±1.1	0.56
PLR	132.9±72.9	137±50.3	0.64
NLR*	2.1±1.5	2.9±2.4	0.009*
NMR	9±3.9	10±9.9	0.45

KL: Kellgren and Lawrence; RBC: red blood cells; Hb: Hemoglobine; MCV: mean corpusculer volume; RDW: red cell distribution witdh; PDW: platelet distribution witdh; MPV: Mean platelet volume; PLR: Platelet lymphocyte ratio; NLR: Neutrophil lymphocyte ratio; NMR: Neutrophil monocyte ratio *Independent student t test: statistically significant difference, P<0,05.

Disease progression has low X-ray sensitivity, thus radiography is usually considered a poor method to show the progression of joint damage at early diagnosis[15]. Imaging is used to assist differential diagnosis in suspicious cases. Conventional radiographs are traditionally the first imaging modality and are also used as an evaluation tool for treatment response[16-18].

Table 2. Comparison of characteristics among the groups

	KL 1 mean±std/ median	KL 2 mean±std/ median	KL3 mean±std/ median	KL4 mean±std/ median	P
Age (year)*	51.2±2.0	55.9±1.5	61.9±1.8	68.3±1.5	0.00*
Gender (M/F)*	14/32	12/53	8/44	3/43	0.025*
Patella length (PL)	4.20±0.07	4.11±0.06	4.10±0.05	4.32±0.06	0.167
Patellar tendon length (PTL)*	4.47±0.1	4.30±0.08	4.60±0.1	4.67±0.1	0.08*
Q angle*	15.63	17.46	16.11	21.12	0.026*
Insall Salvatti Ratio	1.07	1.06	1.13	1.09	0.203
WBC*	7.48	7.48	8.23	8.33	0.011*
Neutrophil*	4.34±0.35	4.30±27	5.01±0.23	5.54±0.46	0.04*
Lymphocyte*	2.26±0.08	2.30±0.1	2.33±0.09	2.07±0.19	0.03*
Monocyte*	0.59±0.11	0.49±0.017	0.75±0.18	0.68±0.04	0.002*
Eosinophil*	0.25±0.05	0.23±0.07	0.19±0.017	0.04±0.027	0.025*
Basophil*	0.05±0.003	0.07±0.017	0.11±0.039	0.04±0.07	0.00*
RBC*	4.84±0.085	4.75±0.05	4.8±0.55	4.36±0.29	0.03*
Hb*	13.6±0.25	13.3±0.20	12.8±0.30	12.3±0.28	0.01*
MCV	81.8	84.68	83.29	85.13	0.125
RDW	14.46	15.17	15.27	15.26	0.092
PLT	275.49±10.4	267.09±11.7	287.79±13.2	250.43±10	0.133
PDW	18.92	18.32	17.25	14.42	0.070
MPV*	9.98	10.44	10.09	10.78	0.009*
PLR	140	128.94	129.76	144.37	0.254
NLR*	2.29	2.09	2.53	3.44	0.004*

KL: Kellgren and Lawrence grade; RBC: red blood cells; Hb: Hemoglobine; MCV: mean corpusculer volume; RDW: red cell distribution width; PDW: platelet distribution width; MPV: Mean platelet volume; PLR: Platelet lymphocyte ratio; NLR: Neutrophil lymphocyte ratio; NMR: Neutrophil monocyte ratio *ANOVA or Kruskall wallis test. Statistically significant difference, P<0,05

A small number of inflammatory markers such as cytokines and cartilage degradation products have been used as markers for OA and in recent years, there have been many studies conducted to find more biomarkers for OA[1,19,20]. In the past year, several protein and non-protein biomarkers have been reported for diagnosis and qualification of OA[21,22]. Biomarkers that are soluble in serum, synovial fluid, and urine can be used as specific markers for joint inflammation and degeneration[23]. Ramonda et al[24] reported that C-reactive protein, collagen 2-1, and myeloperoxidase correlated with erosive OA disease severity. Also, hyaluronic acid is considered a marker for synovitis[24]. Zhang et al[25] reported C-reactive protein and cartilage oligomeric matrix protein as biomarkers for knee OA development. Taşoğlu et al[26] found that serum NLR values were significantly higher in patients with advanced knee OA, as well as a significant correlation between radiographic severity and PLR and MPV values in patients with hip OA[2]. Shi et al[27] found that NMR and PLR levels can be used as a guide for knee OA (correlated with severity and inflammation). Hanada et al[28] reported that serum C-reactive protein and sedimentation in patients with knee OA significantly correlated with clinical and radiologic findings of disease.

Similarly, we found high WBC, neutrophil, MPV, NLR and PTL, and low lymphocyte, eosinophil, basophil, RBC and Hb levels in patients with advanced knee OA. Comparable to the findings of Taşoğlu et al[2], we also support the idea of using NLR as a test for the diagnosis of advanced knee OA. A high number of neutrophils is associated with poor prognosis and an increased mortality rate. In recent years, studies have addressed the relationship between inflammation and neutrophils. It has been reported that NLR increases in response to various inflammatory diseases[29-33]. We have found that advanced radiologic stage in OA patients appears to be associated with high inflammation and disease activity.

Many studies have analyzed the effect of patellofemoral malalignment on patellofemoral instability. Patients with patellar cartilage lesions usually have an increased tendon/patella length ratio (Insall-Salvati ratio). The abnormal patellar length and chondral lesions are significantly correlated[34,35].

However, there is a limited number of studies showing the correlation between patellar cartilage defects and patellofemoral malalignment. The Q angle is also considered as an important factor in assessing knee joint function. An increase in Q angle beyond the normal range is considered as an indication of extensor mechanism misalignment and associated with patellofemoral pain syndrome, knee joint hypermobility, and patellar instability[9].

In our study, the PTL, patellar alta prevalence, and Q angle were found to be significantly higher in patients with high-grade knee OA. In addition, Q angle negatively correlated with lymphocyte, eosinophil, and platelets. Patella length was positively correlated with WBC and neutrophils. The PTL was negatively correlated with basophil and platelet distribution width. The Insall-Salvati ratio was negatively correlated with basophils. Various laboratory markers have a significant relationship with cartilage degeneration and patellofemoral alignment disorders in knee OA progression. Biomarkers in conjunction with radiologic results may guide us in early diagnosis and follow-up of patients with degenerative knee OA.

Advanced age is an unmodifiable risk factor associated with OA. It is predictable that radiologically advanced OA patients will be older than those with low grade OA; therefore, age-dependent alterations in patients' laboratory results (e.g., anemia which is associated with low RBC and Hb values) show concomitance with radiologic advanced stages. Sample size was also a limitation of this study.

OA is a progressive disease characterized by a slow course of development and long asymptomatic periods. Recent literature supports the supposition that OA is a low-grade systemic inflammatory disease accompanied by peripheral inflammation with various inflammatory mediators. In our study, we found significant differences in radiologic staging and patellar measurements and blood parameters and blood derivatives in patients with knee OA. Based upon these findings, we conclude that serum WBC, NLR, MPV, and neutrophil can be considered as important markers of severe OA.

Yazar Katkıları: Çalışma konsepti/Tasarımı: TTK, MB; Veri toplama: TTK, BFK; Veri analizi ve yorumlama: TTK; Yazı taslağı: TTK; İçeriğin eleştirel incelenmesi: TTK; Son onay ve sorumluluk: TTK, MB, BFK; Teknik ve malzeme desteği: MB; Süpervizyon: TTK; Fon sağlama (mevcut ise): yok.
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