The relationship of monocyte to high density lipoprotein-cholesterol ratio and complete blood count parameters with radiologic staging of knee osteoarthritis

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ABSTRACT

Aim: To evaluate the predictive ability of bioindicators derived from complete blood count (CBC) parameters and monocyte-high density lipoprotein-cholesterol ratio (MHR) in the diagnosis of radiological stage of knee osteoarthritis (OA) in this study.

Method: This cross-sectional retrospective study was carried out between November 2017 and June 2021, in our physical therapy and rehabilitation clinics. 65 patients knee x-rays and routine laboratory results were included in the study. Each knee x-rays were assigned a grade from 0 to 4 (Kellgren-Lawrence Classification System (KL)). Patients were divided into two groups according to severity of the knee OA as follows. Group 1: Mild-moderate OA (KL Grade1-2), Group 2: Severe OA (KL Grade 3-4).

Results: Independent T test and Mann Whitney U test were used to assess whether there was a difference in CBC parameters and their derivatives between two groups. Platelet lymphocyte ratio (PLR), red cell distribution width (RDW) to platelet ratio (RPR) and platelet (PLT) counts indicated statistically significant differences between the groups, p-values were 0.04, 0.03 and 0.04 respectively. There were no significant differences in terms of MHR score between the groups.

Conclusions: We could not find a relationship between MHR and radiological degree of knee osteoarthritis. However, there is a correlation between radiological stage of knee osteoarthritis and hemogram parameters like PLT and their derivatives such as PLR and RPR.

Key words: Knee, osteoarthritis, monocyte, high density lipoprotein, cholesterol, platelet, lymphocyte, red cell distribution.

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Introduction

Osteoarthritis (OA) is the most common cause of arthritis, characterized by progressive degeneration and destruction of joint cartilage. Genetic factors, old age, trauma, high body mass index (BMI), and deterioration of biomechanical properties are the main conditions that accelerate the process of osteoarthritis development. OA may remain silent for a long time or manifest slow progression. The disorder most commonly affects the knee joint symptomatically. Symptoms of OA include pain, joint dysfunction, and deformities. Knee OA is detected in approximately 80% of patients over 65 years old on plain radiographs; however, only one in three of these patients has
symptoms [1]. Early diagnosis of the disease and estimation of the clinical course and prognosis is difficult due to long asymptomatic periods. Recent studies have focused on discovering reliable biomarkers in the diagnosis and progression of OA [2,3]. Until recently, OA was accepted as a degenerative disease caused by joint abrasion and degeneration of periarticular soft tissue due to aging and increased mechanical load. Novel studies have proven that OA is associated with low-grade chronic inflammation [4-7]. Low-grade inflammation contributes to the pathogenesis of OA by inducing the production of pro-inflammatory cytokines. This process involves mononuclear cell (monocytes, macrophages, and activated T and B lymphocytes) infiltration in joint space and the release of pro-inflammatory mediators, such as IL-1β and TNF. These mediators stimulate the production of matrix-metalloproteinases (MMPs), prostaglandin E2 (PGE2), nitric oxide (NO), and some other cytokines (IL-6, IL-8, IL-15, IL-17, IL-21). IL-1, IL-6, and TNF, which are key cytokines involved in the inflammatory process, may also lead to platelet activation. Platelets release inflammatory mediators and growth factors during hemostasis, inflammation, and tissue repair [8,9]. Monocytes and neutrophils contribute to inflammatory process steps and oxidative stress by releasing pro-inflammatory and pro-oxidative cytokines [10]. In recent years, various hematologic parameters, including mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-high density lipoprotein-cholesterol ratio (MHR), have been evaluated as indicators of inflammation [11,12]. Previous studies have shown that high density lipoprotein-cholesterol (HDL-C) has anti-inflammatory, anti-oxidant effects and protects endothelial cells [13,14]. Parameters such as MHR and NLR and red cell distribution width-platelet ratio (RPR) can be utilized by routine laboratory tests. These ratios can be computed by using complete blood count (CBC) results and biochemical profiles easily and inexpensively.

These parameters have been evaluated as indicators of inflammation and oxidative stress for systemic inflammatory diseases and cardiovascular disorders [15].

NLR has been introduced as a marker of inflammation in irritable bowel syndrome, ulcerative colitis, thyroiditis, and type 2 diabetes mellitus [16-19]. PLR has also been increased in various inflammatory conditions, including malignancy [20].

There is a paucity of research about the clinical and radiological progression of OA. Therefore, we aimed to assess the predictive ability of bioindicators derived from CBC parameters and the MHR ratio in the diagnosis of the radiological stage of knee OA in this study.

**Materials and methods**

**Ethics statement**

This cross-sectional retrospective study was carried out between November 2017 and June 2021, in our physical therapy and rehabilitation clinics. The study protocol was approved by our Institutional Review Board (Ethics Committee Approval Date and Number: 08.06/2021-148) and conducted in accordance with the Declaration of Helsinki.

**Study design and population**

**Inclusion criteria**

Patients with primary knee OA according to the clinical criteria of the American College of Rheumatology (ACR) and between the ages of 40-80 were included in the study. If OA wasn’t unilateral, only the patients with an equal degree of OA on both knees were included.
All diagnostic decisions were made by the same physician. 65 patients with standing, weight bearing anteroposterior and lateral knee x-rays and routine laboratory results were included in the study. Each knee x-rays was assigned a grade from 0 to 4 (Kellgren-Lawrence Classification System (KL)). Demographic information and body mass index of the patients with knee OA were recorded. Patients were divided into two groups according to severity of the knee OA as follows. Group 1: Mild-moderate OA (KL Grade1-2) Group 2: Severe OA (KL Grade 3-4)

Kellgren-Lawrence classification system
The Kellgren-Lawrence system is applied specifically to classify the severity of knee OA using five grades and originally described using AP knee radiographs. This classification system was accepted by WHO in 1961. Below is the original description.
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

Exclusion criteria
Participants with hematologic disorders which may affect blood parameters, patients with diagnosis of diabetes mellitus, acute decompensation and organ failure, inflammatory diseases, rheumatic diseases, acute or chronic infection, cardiovascular diseases, secondary osteoarthritis, oncologic diseases, patients who are receiving intra-articular steroid or hyaluronic acid treatment, patients with history of severe knee trauma or operation last 6 months, patients during the pregnancy and lactation period were excluded from participation.

Laboratory analysis
While low density lipoprotein cholesterol [LDL-C] (mg/dL), and high density lipoprotein cholesterol [HDL-C] (mg/dL) levels were obtained from biochemical analysis (Architect CI4100, Chicago, USA), white blood cell (WBC) (K/uL), neutrophil (K/uL), lymphocyte (K/uL), monocyte (K/uL), hemoglobin (Hb) (g/dL), red blood cell distribution width (RDW), platelet (K/uL) (PLT) and mean platelet volume (MPV) (fl), platelet distribution width (PDW) values were acquired from CBC analysis using an XT1800İ Kobe, JAPAN hematology analyzer. On the basis of these test results, NLR, PLR, LMR and MHR were calculated as dividing by different parameters. All assays were performed according to the manufacturer’s’ instructions.

Statistical analyses
The data obtained in the study were analyzed on SPSS statistical package (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Mean values, standard deviation values were calculated for all parameters. Kolmogorov-Smirnov test is used to assess normality of the variables. Independent T tests were used to compare the means between the groups for normally distributed data. Chi-square test is performed to understand the relationship of categorical variables. A p-value less than 0.05 is considered statistically significant.

Results

Demographic characteristics
Overall, 65 patients between the ages of 40-80, including 35 with mild-moderate OA and 30 with severe OA, were assigned to our study. Patients ranged in age from 44 to 80, with a mean age of 65.7±9.4. Most participants were
female (64%). Demographic characteristics were similar between the two groups (P > 0.05). Most patients (72%) were admitted to our outpatient clinics, and the remaining patients were hospitalized. Detailed information about the demographics of the participants is available in Table 1.

**Prediction of OA grade according to hemogram parameters and MHR**

Independent T test and Mann Whitney U test were used to assess whether there was a difference in CBC parameters and their derivatives between the two groups. PLR, RPR ratios, and PLT counts indicated statistically significant differences between the groups; p-values were 0.04, 0.03, and 0.04, respectively. The area under the curve for PLR and RPR was computed as 0.644 and 0.374, respectively (Figure 1). There were no significant differences in terms of MHR score between the groups; p-values were 0.07. The rest of the factors did not show a statistically significant difference between the groups (Table 2).

#### Table 1: Demographic information.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (Mild-Moderate Osteoarthritis)</th>
<th>Group 2 (Severe Osteoarthritis)</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean ± SD</td>
<td>62.5±8.6</td>
<td>69.4±9.1</td>
<td>65.7±9.4</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>46-77</td>
<td>44-80</td>
<td>44-80</td>
</tr>
<tr>
<td>Gender</td>
<td>Female (n, %)</td>
<td>21 (60%)</td>
<td>21 (70%)</td>
<td>42 (64%)</td>
</tr>
<tr>
<td></td>
<td>Male (n, %)</td>
<td>14 (40%)</td>
<td>9 (30%)</td>
<td>23 (35%)</td>
</tr>
<tr>
<td>Admission status</td>
<td>In-patient (n, %)</td>
<td>11 (31%)</td>
<td>7 (23%)</td>
<td>18 (28%)</td>
</tr>
<tr>
<td></td>
<td>Out-patient (n, %)</td>
<td>24 (67%)</td>
<td>23 (77%)</td>
<td>47 (72%)</td>
</tr>
</tbody>
</table>

SD: standard deviation, Min: minimum, Max: maximum

**Discussion**

The major findings of our study, in which we evaluated the predictive performance of bioindicators like blood parameters and MHR in the diagnosis and staging of knee osteoarthritis, were as follows:
A significant difference was detected in terms of PLT, PLR and RPR values.

There were no significant differences in terms of MPV, MHR, NLR score between the groups.

There were no significant differences in terms of HDL and LDL levels between the groups.

Previous studies showed that hemogram parameters and their derivatives, such as MPV, NLR, and PLR, could indicate systemic inflammation in various etiologies [21-23].

MPV is one test run during the CBC; NLR and PLR can be easily calculated by dividing neutrophil or platelet count by lymphocyte count. In the literature, there seem to be limited studies on the relationship between OA and PLT parameters. PLT indices may reflect subclinical inflammation in OA and disease activation. What is known about the PLT activation process is not only that the number of PLT increases, but also that to reach a larger surface area, their morphology changes from discoid to spherical patterns [24]. Also, larger
platelets are likely to be more active at releasing pro-inflammatory and thrombotic mediators, and increased demand is seen during acute phase response [25].

Several studies have been conducted on the diagnostic and prognostic ability of CBC parameters and their derivatives, such as MPV, RDW, and RPR, during infectious and inflammatory disorders [26,27]. It has been proposed that there is a link between high MPV and RDW values and mortality or morbidity due to vascular events affecting the heart and kidneys, resulting in infectious disease [28-30]. Although many attempts have been made to assess the relationship between MPV and systemic inflammatory disorders, the results are contradictory [31,32]. It has been reported that MPV values in patients with active rheumatoid arthritis (RA) or ankylosing spondylitis (AS) are lower than in healthy controls. However, it is recommended to be careful when interpreting the MPV values, because this ratio is not consistently related to disease activity indexes, and tests may be influenced by technical settings [33,34]. Balbaoglu et al. compared patients with a diagnosis of OA, patients with synovitis related to OA, and a control group; there was no statistically significant difference detected between all groups. On the contrary, MPV values in patients with synovitis related to OA were lower than in the other groups [31].

Koca et al. reported that MPV value was increased in patients with severe osteoarthritis [32]. Despite the Koca et al. findings, a recent study conducted by Atar et al. found that NLR, PLR, and MPV values were similar between 92 knee OA patients and 52 healthy controls [32,35]. Our results share a similarity with Atar et al.’s findings; no significant correlation was observed between MPV values and OA grades. PLR, which is calculated as absolute platelet count dividing by absolute lymphocyte count, is another principal factor with an influence on systemic inflammatory response pathogenesis [36].

In contradiction with earlier findings, we found a relationship between PLR ratio, knee osteoarthritis degree, PLT, and RPR levels in patients with advanced knee osteoarthritis [35]. NLR, as a marker of systemic inflammation, may reflect the neutrophil & lymphocyte balance and immune system status of the patient [37].

Tasoglu et al. compared NLR ratios of 176 patients with OA according to the Kellgren-Lawrence classification and found higher NLR values in patients with severe OA (grade 4). They suggest that the NLR ratio can be used as a predictor tool to estimate the radiological grade of knee OA [3]. Büyükavcı et al. proposed using blood platelet distribution width (PDW) and NLR to predict the severity of knee OA in clinical practice [38]. Atar et al. did not find a significant correlation between NLR ratio and radiological severity of knee osteoarthritis [3,35-38]. Similar to Atar et al.’s study, we did not find a relationship between the radiological stage of knee OA and NLR [35]. Contradictory results may be explained by local inflammation without systemic response. Future studies with larger populations should concentrate on this topic.

To the best of our knowledge, this is the first study in the literature evaluating the association between the MHR ratio, which is a novel bioindicator recently used as a marker of inflammation, and knee osteoarthritis. The mononuclear phagocyte system plays a fundamental role in the inflammatory response during the development and progression of atherosclerosis. In the premature steps of the process, circulating monocytes migrate to the subendothelial matrix of the arterial wall, mature into macrophages, and internalize
oxidized LDLs and other lipids. Subsequently, these cells transform to foam cells, which release immunoregulatory cytokines, trigger inflammation, and invite T-lymphocytes, platelets, and further monocytes [39]. However, HDL-C disrupts monocyte functions, interferes with the conversion of monocytes to macrophages, and removes cholesterol from them, which reduces the inflammatory response [40]. Therefore, it is appropriate to utilize the combination of both parameters (MHR) in a single index as a pro-inflammatory marker. Previous studies recommended using MHR as a predictive marker of cardiovascular disease due to its ability to demonstrate systemic inflammation [41]. Demirbaş et al. showed a significant decrease in MHR, monocyte to lymphocyte ratio (MLR), and NLR levels after colchicine treatment [42]. Sirin et al. revealed that the Psoriasis Area and Severity Index score (PASI) was associated with C-reactive protein, serum amyloid A, and MHR in their study of 60 psoriasis vulgaris patients and 50 healthy controls. Our findings do not support previous studies, and we did not find a relationship between MHR and radiological grade of knee osteoarthritis [43]. The retrospective design of the study and the limited number of participants may be the reason for this concordance.

Recently, it has been thought that osteoarthritis may be a metabolic disease and lipid metabolism defects may be one of the underlying mechanisms [44,45]. Schwager et al. investigated the effects of serum cholesterol, low-density lipoprotein, and high density lipoproteins on the risk of knee osteoarthritis. As a result, they reported that they did not find a significant relationship between HDL, LDL and total cholesterol levels, and cartilage loss or worsening pain. [46]. Irshad et al. reported that serum cholesterol and triglyceride levels were associated with osteoarthritis, but there was no relationship between serum HDL and LDL levels and osteoarthritis [47]. Like these studies, no significant correlation was found with HDL and LDL levels in our study.

Advanced age is a non-modifiable risk factor associated with OA. It is predictable that radiologically advanced OA patients will be older than those with low-grade OA; hence, age-dependent alterations in patients’ laboratory results show concomitance with radiologic advanced stages.

We know our study may have a few limitations. The first is that the retrospective design of the study may have influenced the assessment of the clinical presence of inflammation. Another limitation is that there was no control group to compare the results with patients. The small sample size is also a limitation of this study.

**Conclusions**

The evidence from our study suggests that there is a correlation between the radiological stage of knee osteoarthritis and hemogram parameters like PLT and their derivatives such as PLR and RPR. However, we could not find a relationship between NLR, MHR, MPV, and radiological degree of knee osteoarthritis. Further work needs to be carried out in a larger patient group with more clinical evaluation parameters.

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Ethical statement:** This study protocol was approved by Bolu Abant Izzet Baysal University Clinic Review Board (Date and Number: 08.06/2021-148), and conducted in accordance with the Declaration of Helsinki.
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