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The Association of Neutrophil-Lymphocyte Ratio with the Severity of Primary Knee Osteoarthritis in a Sample of Iraqi Patients

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Abstract

Background: Osteoarthritis is increasingly recognized as a disease with a significant inflammatory component. Blood neutrophil-lymphocyte ratio level is simple, non-invasive, cheap and was introduced as a novel marker to determine inflammation in other diseases. Objective: To evaluate the association between severity of knee osteoarthritis and neutrophil-lymphocyte ratio. Patients and methods: This was a case-control study conducted during a period of 10 months included 126 Iraqi patients with knee osteoarthritis and 126 apparently healthy subjects as a control group. X-rays of both knee joints in anterior-posterior view and laboratory investigations were performed. Neutrophil-lymphocyte ratio was calculated and compared. Results: Neutrophil-lymphocyte ratio was significantly higher in knee osteoarthritis patients than controls. On regression analysis, only older age and higher neutrophil-lymphocyte ratio were significantly associated and predictors of severe knee osteoarthritis, odds ratio (OR) for age was 2.45 (range: 1.31 – 16.70), P-value = 0.014) and for neutrophil-lymphocyte ratio the OR = 1.45 (range: 1.18 – 7.63), P-value = 0.039). Receiver operating characteristics (ROC) curve analysis revealed that neutrophil-lymphocyte ratio was a weak predictor for severity of knee osteoarthritis. Conclusions: Knee osteoarthritis patients had higher neutrophil-lymphocyte ratio compared to healthy population. Higher neutrophil-lymphocyte ratio was weakly associated with severity of knee osteoarthritis and it was a poor predictor of severity of knee osteoarthritis.

Keywords:
Osteoarthritis, pathophysiology, epidemiology, predictors, neutrophil-lymphocyte ratio

1 INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis (1). It is a leading musculoskeletal cause of disability in elderly people all over the world and a major cause of physical limitations and reduced quality of life. It is a chronic multifactorial disease characterized by progressive joint degeneration accompanied by sub-chondral bone sclerosis which can lead to the formation of bone cysts and marginal osteophytes. Besides these intrinsic changes of the joints, other signs such as decreased knee flexibility, pain, joint effusion, crepitus, deformities, and loss of function are often present (2). Knee osteoarthritis (KOA) knee is one of the most frequently affected sites and the most common parts to be affected are the tibio-femoral and patella-femoral compartments (3). Osteoarthritis is a strongly age-related disorder. It is uncommon before the age of 40, but its prevalence rises rapidly with age thereafter, such that most people over the age of 70 have the pathological changes of OA in some of their joints (although they may remain asymptomatic)(3). About 13% of women and 10% of men aged 60 years and older have symptomatic KOA. The proportions of people affected with symptomatic knee osteoarthritis are likely to increase due to the aging of the population and the rate of obesity or overweight in the general population (4). Many persons with x-ray evidence of OA have no joint symptoms and the symptomatic KOA which have radiographic evidence of KOA is more common in women than in men, female to male ratio is 1.7:1(5-6).

The major elements of the diagnostic evaluation are the history, physical examination, imaging studies and in some cases where special questions arise, laboratory testing should be done (7). Radiographic features of OA include, plain x-rays particularly the most symptomatic joints. X-rays generally reveal marginal osteophytes, narrowing of the joint space, increased density of the subchondral bone, subchondral cyst formation, bony remodeling and joint effusions (8). Radiological osteoarthritis was assessed by means of the grading system proposed by Kellgren and Lawrence grading system.

The goals of treatment include alleviation of pain and improvement of functional status. The treatment can be divided into the following; lifestyle modification and physical therapies (9, 10), Medications such as non-steroidal anti-inflammatory drugs(NSAIDs),

opioids , joint injections of glucocorticoids (11,12). Also colchicine combined withacetaminophen have a greater beneficial symptomatic effects and longer duration of action (13) Another recent study in 2016 showed that simvastatin effective in treatment of KOA symptoms (14) Joint replacement surgery is an option when OA affects the quality of life and conservative management is ineffective (15).

Osteoarthritis is increasingly recognized as a disease with a significant inflammatory component (16) Previous studies suggested that up to 90% of subjects with KOA have evidence of synovial thickening on magnetic resonance imaging (MRI)(17). Macrophages and pro-inflammatory cytokines are recognized to have a part in the process (18-20) C-terminal telopeptides of type I collagen (CTXI), CTXII, type III collagen N –propeptide, cartilage oligometric matrix protein (COMP), interferon-gamma inducible protein 10 (IF-γ IP-10), matrix metalloproteinase-3 (MMP3), MMP-2, adiponectin, interleukins (IL) like IL-8, IL-10, IL15, IL-17 and TNF-α were suggested as biomarkers in osteoarthritis (21-24). 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. 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 (25-27).

2 | PATIENTS AND METHODS

This was a case-control study conducted during a period of 10 months included 126 patients with knee osteoarthritis (KOA) diagnosed according to the American College of Rheumatology clinical criteria (28). Additionally, 126 apparently healthy subjects were almost age and gender matched to the patients were recruited as control group.

Inclusion criteria :

1. Patients with KOA diagnosed according to the American College of Rheumatology clinical criteria (28).
2. Patients were recruited regardless their age or gender.

Exclusion criteria:

Patient with one or more of the following criteria was excluded from the study:

1. History of knee trauma and post traumatic arthropathy.
2. Post infection arthropathy.
3. Malignancy.
4. Systemic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE).

Data were collected using a pre-constructed data collection sheet, including the age, gender, height, weight, body mass index (BMI), smoking history , duration of pain ,time since diagnosis and the side of KOA (left, right or both) . Clinical and laboratory data including radiological findings of both knee joints. Additionally, the laboratory results for hemoglobin (HGB), white blood cells count (WBC count), neutrophils count, lymphocytes count, platelets count, ESR and C-reactive protein were reported. Neutrophil-lymphocyte ratio for each participant was calculated.

The severity of KOA was assessed according to the Kellgren-Lawrence (KL) grading system 11). The severity of radiographic changes graded from 0 to 4 with grade 0 meaning no radiographic features of OA while grade 4 means large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony deformity (29). However, patients were categorized according to their KL grading system ; those with grade 1- 3 considered to have mild to moderate KOA and those who had grade 4 considered to have severe KOA.

Statistical analysis performed using the statistical package for social sciences (SPSS) version 24, statistical tests and procedures were applied according to the variable types under level of significance of 0.05.

3 | RESULTS

There were 126 patients with primary knee osteoarthritis and 126 controls enrolled in this study. No statistically significant differences had been found between the studied groups in Socio-demographic variables, P. value >0.05 (Table 1).

The mean values of hematological parameters where the only significant difference between KOA patients versus controls was reported in NLR; patients with KOA had significantly higher NLR than controls, the mean NLR were (2.19 ± 0.72) and (1.97 ± 0.88), respectively, (P-value =

0.036). The differences between KOA patients and controls in other parameters; hemoglobin (HGB), platelets (PLTs), white blood cell (WBC) count, neutrophils count and lymphocytes count didn't reach the statistical significance, (P-value >0.05), (Table 2). The mean C- reactive protein (CRP) of the patients was (5.9 ± 3.4) ranged (0 – 13) where it was not detected in some patients. The mean duration of pain and duration of disease since diagnosis was (31 ± 24) months and (23 ± 22) months, respectively, (Table 3).

Regarding the distribution of the KOA patients according to their KL grading scale, 23 patients (18.3%) had grade 1, 47 (37.3%) patients grade 2, 29 patients (23%) grade 3 and 27 (21.4%) patients had grade 4, (Table 4). Furthermore, the distribution of the patients according to severity of KOA revealed that 99 patients (78.6%) had mild-moderate knee osteoarthritis and 27 patients (21.4%) had severe KOA, (Figure 1). The association between severity of KOA and other patients demographic, clinical and laboratory variables was demonstrated in (Table 5), among these variables, age, duration of pain and duration of disease since diagnosis NLR were significantly different. Patients with severe KOA were older than those with mild-moderate KOA, the mean age (63.0 ± 7.4) and (56.6 ± 9.9), respectively, (P-value =0.002). On the other hand, patients with severe KOA had longer duration of pain and duration of disease since diagnosis, (P-value <0.001). The NLR was significantly lower in patients with mild-moderate KOA than those with severe KOA, the mean NLR was (2.11 ± 0.60) and (2.47 ± 1.04), respectively, (P-value = 0.022) (Figure 2). Further analysis was performed for the association between severity of KOA and the variables that showed significant association on univariate analysis using the binary multiple logistic regression analysis (Table 6), which revealed that age and higher NLR were significantly associated with severe KOA. However, old age was stronger predictor than NLR; odds ratio (OR) for age was 2.45 ((range: 1.31 – 16.70), P-value = 0.014) and for NLR OR = 1.45 ((range: 1.18 – 7.63), P- value = 0.039), these findings indicated that older patients were about 2.5 folds more likely to have severe KOA, (OR = 2.45) than younger age patients. Those with higher NLR were about 2 folds (OR=1.92) more likely to have severe KOA than those with lower NLR. However, regression test indicated that older age and higher NLR were independent risk factors for severe KOA.

Furthermore, to assess the validity of neutrophil-lymphocyte ratio as a predictor for the

severity of knee osteoarthritis, receiver operating characteristics (ROC) curve analysis was performed for NLR against severity (Figure 3). ROC curve revealed that NLR was a weak and moderately valid predictor for severity of KOA, area under the curve (AUC) = 0.531. Using a cutoff point of 2.1, the sensitivity of NLR in prediction of severe KOA was (38 %), specificity (41%) and accuracy (39%), these validity parameters were low (Table 7).

4 DISCUSSION

Up to the best of our knowledge this is the first case control study that looked for the association of NLR with the severity of KOA in a sample of Iraqi patients. The demographic data of the patients in the current study were similar to the clinical picture of KOA documented previously, where the mean age was (58.3 ± 9.7) years and females were the dominant gender (66.7%), moreover, majority of the patients, (86.5%) were overweight and obese and there was no relation with smoking (P-value=0.33). Previous epidemiological studies on KOA documented that incidence of KOA increased by age and further increased with longer lifetime and higher average weight. In these studies female gender found to be significantly associated with OA particularly above the age of 55 years while smoking was not associated with KOA as we found in our study (30,31). Despite that there were very few studies available about the association between NLR and OA, our findings were consistent with that reported in these studies; Tasoglu ,et al. (32) reported in 2016 that the mean NLR of Turkish patients with mild to moderate KOA was (1.79 ± 0.8) and the mean in those with severe KOA patients was (2.18 ± 1.04) , however, Tasoglu ,et al. did not include a control group to compare with in his study (36).A recent Turkish study in 2017 was conducted by Hira and Tamam (33) found that the mean NLR was significantly higher in OA group than controls, (2.15 ± 1.12) and (1.79 ± 0.97), respectively.

There were many previous studies that had shown the NLR can be used as an indicator of systemic inflammation (34-36) (38-40). However other studies showed there were no associations between NLR and chronic inflammatory diseases (37).This reveals there was inconsistency about the predictive role of NLR in diagnosis, prognosis or as a marker for

disease activity for other diseases.

There were previous studies considered osteoarthritis as an inflammatory disease Though traditionally considered “wear and tear” disease, the pathogenic mechanisms of osteoarthritis have not yet been elucidated (38-40). This may explain the significant association between sever KOA and higher NLR in our study.

The increasing number of articles demonstrating the influence of inflammatory factors in the onset and progression of the disease currently raises great debate about the importance of each of the factors involved in the disease .Even the choice between the terms “Osteoarthritis” and “Osteoarthrosis” generates controversy, since the first term implies the presence of inflammation as the key generator of the disease and the latter denotes a degenerative/mechanical causal factor and OA is no longer accepted as a mechanically activated wear and tear process but a subclinical-low grade inflammatory condition in which mechanical stress and immunity acts simultaneously (3, 16, 38-41). Jawad et al reported in their study that IL-6 was the most detectable interleukin in sera of patients with KOA and this may related to the role of IL-6 in induction of acute phase reactions in response to inflammation(42). All the previous mentioned studies reported the role of inflammatory process in KOA.

It is worth mentioning that many previous studies documented the association of nodal generalized osteoarthritis (NGOA) with autoimmune process; and showed that increased frequency of rheumatoid factors in NGOA may reflect an autoimmune diathesis (43,44). On the other hand Lawrence et al. (45) reported increased frequency of HLAA1B8,Brodsky et al (46) an increase in HLA-B8 and at the same time other previous studies showed no associations with NGOA.This may suggest a relationship between KOA and auto immune inflammatory process as KOA may accompany NGOA (46-51). The previous mention informations documented that KOA may be a part of NOGA where inflammatory process could have a role which will explain the elevation of NLR. Multivariate analysis and binary logistic regression analysis for the association between severity of KOA and the variables that showed significant association on univariate analysis, revealed that older age and higher NLR still significantly associated with severe KOA. However, old age was stronger predictor than

NLR; severe KOA was still significantly associated with older age (OR = 2.45, P=0.014) and higher NLR (OR = 1.92, P-value = 0.039), on the other hand duration of pain and duration of disease since diagnosis showed insignificant association.

Previous studies mentioned that old age is a significant risk factor of OA and associated with severe KOA, our findings are comparable to previous studies in this field (30-32, 41). The explanation of this association between aging and severity of KOA could be attributed to the fact that the general incidence and prevalence of KOA has been reported to increase by almost ten times in older age population than younger ones, particularly above the age of 65 years who are commonly affected by KOA, with the increase in age there is progressive sedentary behavior, changes in lifestyle patterns, diet routine and other factors. Additionally, the aging changes observed in the cells and extracellular matrix of joint tissues increase the susceptibility of older adults to OA when other OA risk factors are also present. OA is characterized by an imbalance between catabolic and anabolic activity in the joint and aging likely contributes to this imbalance. Aged chondrocytes respond poorly to growth factor stimulation and so are unable to maintain homeostasis in the articular cartilage. A loss of chondrocytes due to an increased susceptibility to cell death appears to be important as well (41,52).

In the present study, we assessed the validity of NLR as a predictor for the severity of KOA, using two methods of analysis; the first method used a cut-off value for NLR of 2.1 and the second method used the ROC curve, both analyses revealed that NLR had low sensitivity, low specificity and low accuracy, (38 %),(41%) and (39%), respectively, on the other hand, the ROC curve revealed that NLR was a weak independent predictor of severity of KOA.

The previous findings did not supported the recently published study from Turkey (2016) in which Tasoglu et al (32), suggested that NLR was a novel and promising inflammatory marker indicating the severity of KOA. Additionally, they found that NLR had higher sensitivity and specificity than our study, (50%) and (77%) respectively. Other finding of the Turkish study showed that NLR ≥ 2.1 can be used as a marker of severe KOA which is inconsistent with our finding when used the 2.1 NLR as a cutoff, where in our study when this cutoff used there was low accuracy ROC curve analysis (AUC = 0.531) which was very close to (0.5) (the value below

which the diagnostic test considered failed predictor) (53). These differences possibly due to difference in demographic features between the two studies as well as the sample size.

5 CONCLUSIONS

Knee osteoarthritis patients had higher neutrophil-lymphocyte ratio compared to healthy population. Higher neutrophil-lymphocyte ratio was weakly associated with severity of knee osteoarthritis. So, Neutrophil-lymphocyte ratio was a poor predictor of severity of knee osteoarthritis. Age was a strong predictor of severity of knee osteoarthritis, and neutrophil-lymphocyte ratio alone may not be dependent as a marker or predictor of severity of knee osteoarthritis. However, further studies with larger sample size included other markers are highly suggested recommended in order to generalize the results.

Ethical Issue:

All ethical issues were approved by the author, in accordance with Ethical Principles of Declaration of Helsinki of the world Medical Association, 2013, for research involving human subjects

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