ORIGINAL RESEARCH

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Inflammatory Markers and Severity of Osteoporosis in Older Adults

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Abstract

Objective: Osteoporosis is a chronic disease that is prevalent in older adults and characterized by an imbalance between bone formation and destruction. Recently, many studies have been conducted to reveal the relationship between inflammation and osteoporosis. Monocyte to lymphocyte ratio (MLR) and neutrophil to lymphocyte ratio (NLR) have been shown to be predictive factors for disease activity, prognosis and survival in various inflammatory and malignant diseases. We aimed to determine whether there is a relationship between inflammatory markers and the severity of osteoporosis.

Materials and Methods: The mean age of 1.048 patients included in the study was 72.7±6.7 years and 87.9% were female. Osteoporosis was diagnosed by dual energy X-ray absorptiometry (DXA) at the lumbar spine and left femur. Inflammation was assessed by blood tests including MLR, NLR, C-reactive protein, erythrocyte sedimentation rate (ESR) and uric acid.

Results: MLR, NLR, ESR, and the proportion of female gender were higher in the lowest T-score group. MLR and NLR were found to be independently related to severity of osteoporosis according to the multivariate binary logistic regression analysis [p=0.032, odds ratio (OR)=3.513, and p=0.046, OR=1.218, respectively].

Conclusion: In our study, we revealed the relationship between osteoporosis and inflammation through different inflammatory parameters. We have shown that the two easily accessible parameters, MLR and NLR, may help evaluate bone mineral density in elderly osteoporotic individuals.

Keywords: Osteoporosis, monocyte to lymphocyte ratio, neutrophil to lymphocyte ratio, inflammation, older adults

Introduction

Osteoporosis is a chronic disease characterized by decreased bone mineral density (BMD) and deterioration of bone microarchitecture (1). Lower BMD scores are related to higher incidence of fractures (2). Many factors play a role in the development of osteoporosis. Loss of the bone protective role of estrogen and increase in proinflammatory cytokine levels are responsible factors in the development of postmenopausal osteoporosis, which is the most common type of osteoporosis (3).

Inflammation leads to osteoporosis through two main mechanisms. One of these mechanisms is that activated T lymphocytes stimulate osteoclast maturation by producing substances such as receptor activator of nuclear factor-κB ligand, tumor necrosis factor alpha (TNF-α), and some interleukins. In addition, marrow stromal cell-derived macrophage colony-stimulating factor stimulates the osteoclastic precursor cells, a member of the monocyte/macrophage family, and leads to differentiation into osteoclasts (4).

TNF-α, interleukin-1 (IL-1), IL-6, IL-11, IL-15, and IL-17 produced by macrophages and lymphocytes have been shown to induce the formation and activation of osteoclasts (5). The role of these cytokines has been investigated in inflammatory diseases associated with osteoporosis, such as rheumatoid arthritis (RA) and inflammatory bowel disease (6-8).

Previous studies stated that the increase in neutrophil to lymphocyte ratio (NLR) and monocyte to lymphocyte ratio

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(MLR) can be used in the evaluation of disease activity in RA and inflammatory bowel disease, as well as distinguishing osteoporotic adults from non-osteoporotics (9-13).

In this study, we evaluated the relationship between the severity of osteoporosis and MLR and NLR in elderly individuals.

Materials and Methods

Participants

A total of 1.048 individuals aged 65 and over (793 osteoporotic and 255 non-osteoporotic) was included in this retrospective study. The files and hospital electronic record system data of the participants (including comorbidities, medications, and laboratory results) were examined.

Patients with a previous or newly diagnosed fracture, primary bone disease other than osteoporosis, primary or metastatic bone tumor, parathyroid disease, renal impairment, and an active infection were excluded.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Local Ethics Committee of Gaziantep University (no: 2020/422, date: 24.02.2021).

DXA Scan

DXA scans (using hologic scanners) were performed and BMD was measured for the left proximal femur and lumbar spine. A T-score of -2.5 or below at the femoral neck or lumbar spine was considered osteoporosis as stated by the World Health Organization. Participants were divided into 3 groups according to T-scores: A T-score of -3.5 and below (Group 1), a T-score between -2.5 and -3.5 (Group 2), and a T-score above -2.5 (Group 3).

Blood Sample

Blood samples were taken during the admission. Complete blood count including lymphocytes, neutrophils, monocytes, basophils, hemoglobin, platelets, median platelet volume, median corpuscular volume, median corpuscular hemoglobin concentration and biochemistry analysis including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), uric acid, albumin, alanine transaminase, aspartate transaminase, and glucose tests were performed.

Statistics

The variables were analyzed for the normality of their distribution using the Kolmogorov-Smirnov test. The independent samples t-test and Mann-Whitney U test was used to compare two independent groups of variables. The relationship between categorical variables was evaluated using the χ^2 test, the numerical variables using Spearman's rank correlation coefficient, and the significance of the difference between three or more non-normally distributed groups was evaluated using the Kruskal-Wallis H test. We used multivariate logistic regression to simulate a model to determine factors affecting the severity of osteoporosis. A p-value of <0.05 was accepted as statistically significant. SPSS version 22.0 (IBM, Armonk, NY) was used to analyze the data.

Results

The mean age of the 1.048 participants was 72.7±6.7 years and the proportion of female participants was 87.9%. Of the 793 patients with osteoporosis, 311 had a BMD T-score ≤-3.5. The proportion of female participants in the group with a T-score ≤-3.5 was higher than in the non-osteoporotic group (p=0.038).

There was no statistically significant difference between the groups in terms of the frequencies of rheumatic diseases, malignancy and glucocorticoid use. Group 1 had higher ESR levels than Group 2 (p=0.039). MLR and NLR levels were statistically significantly higher in Group 1 compared to Group 2 and 3 (p=0.028 and p=0.022 for MLR, p=0.002 and p=0.002 for NLR, respectively). Although MLR, NLR and ESR levels were found to be higher in Group 2 compared to Group 3, there was no statistically significant difference. The participants' socio-demographic characteristics, laboratory analysis results, and pairwise comparison results of numerical variables are shown in Tables 1 and 2, respectively.

A statistically significant weak negative correlation was found between MLR, NLR, and ESR levels and both the lumbar spine and the femur T-scores. MLR and NLR were found to be independently related to severity of osteoporosis according to the multivariate binary logistic regression analysis [p=0.032, odds ratio (OR)=3.513, and p=0.046, OR=1.218, respectively] (Table 3).

Discussion

The main finding of this study is that NLR and MLR are independent variables in predicting a lower T-score. Osteoporosis results from the imbalance between bone formation and bone resorption. It has been proven that many factors such as hormones, growth factors and interleukins, as well as inflammation, play a role in the etiopathogenesis of osteoporosis (14). MLR and NLR have been shown to be predictive factors for disease activity, prognosis and survival in various inflammatory and malignant diseases (15-19).

Although the predictive role of MLR in inflammatory diseases has previously been demonstrated, there are limited number of studies evaluating the relationship between MLR and osteoporosis. It has been shown that decreased lymphocyte to monocyte ratio (LMR) was associated with increased disease

Table 1. Participants' socio-demographic characteristics and laboratory analysis results

	Groups			Total (n=1048)	p
Variable	**Group 1 (n=311)**	**Group 2 (n=482)**	**Group 3 (n=255)**		
Gender					
Female	284 (91.3%)*	422 (87.6%)	215 (84.3%)*	921 (87.9%)	0.038*
Male	27 (8.7%)*	60 (12.4%)	40 (15.7%)*	127 (12.1%)	
Age†	73.2±7.3	72.1±6.2	73.3±7.0	72.7±6.7	0.063
Comorbidities					
Hypertension	138 (44.4%)	218 (45.2%)	126 (49.4%)	482 (46.0%)	0.440
Diabetes mellitus	72 (23.2%)	114 (23.7%)	71 (27.8%)	257 (24.5%)	0.362
Rheumatic diseases	47 (15.1%)	79 (16.4%)	53 (20.8%)	179 (17.1%)	0.175
Coronary artery disease	43 (13.8%)	66 (13.7%)	49 (19.2%)	158 (15.1%)	0.105
Asthma/COPD	31 (10.0%)	35 (7.3%)	25 (9.8%)	91 (8.7%)	0.320
Cancer	11 (3.5%)	20 (4.1%)	9 (3.5%)	40 (3.8%)	0.874
GC-use	41 (13.2%)	62 (12.9%)	41 (16.1%)	144 (13.7%)	0.456
MLR†	0.30±0.14	0.28±0.12	0.27±0.10	0.28±0.13	0.010*
NLR†	2.21±0.92	2.07±0.97	1.89±0.62	2.07±0.89	0.001*
CRP†	5.38±6.72	4.73±5.83	4.53±5.12	4.86±5.94	0.983
ESR†	26.0±17.4	22.9±16.1	22.5±13.1	23.7±15.9	0.042*
Serum creatinine (mg/dL)†	0.71±0.16	0.72±0.17	0.73±0.17	0.72±0.17	0.105
Uric acid (mg/dL)†	4.77±1.56	4.97±1.47	4.95±1.56	4.90±1.52	0.116

†Data are presented as mean ± standard deviation. *p≤0.05. Group 1, patients with a T-score ≤-3.5; Group 2, patients with a T-score between -2.5 and -3.5; Group 3, patients with a - score >-2.5.
COPD: Chronic obstructive pulmonary disease, GC: Glucocorticoid, MLR: Monocyte-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein (mg/dL), ESR: Erythrocyte sedimentation rate (mm/hr)

Table 2. Pairwise comparison results between numerical variables

Variable	Group 2/Group 3 (p)	Group 1/Group 3 (p)	Group 1/Group 2 (p)
NLR	0.132	0.002*	0.002*
MLR	1.000	0.022*	0.028*
ESR	1.000	0.272	0.039*

*p<0.05. MLR: Monocyte-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio, ESR: Erythrocyte sedimentation rate. Group 1, patients with a T-score ≤-3.5; Group 2, patients with a T-score between -2.5 and -3.5; Group 3, patients with a T-score >-2.5

Table 3. Multivariate logistic regression analysis results of the independent variables for T-score ≤-3.5

Variable		T-score ≤-3.5
Gender (male vs. female)	r (95% CI)	0.614 (0.366; 1.029)
	p	0.064
ESR	r (95% CI)	1.008 (0.999; 1.017)
	p	0.085
NLR	r (95% CI)	1.218 (1.017; 1.469)
	p	0.046*
MLR	r (95% CI)	3.513 (1.025; 10.046)
	p	0.032*

*p<0.05. MLR: Monocyte-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio: CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, CI: Confidence interval

activity in RA patients (20). Increased MLR was also found to be independently associated with the severity of the coronary lesion in patients with myocardial infarction in another study (21).

Gao et al. (13) has shown that MLR, NLR and platelet to lymphocyte ratio (PLR) were higher in individuals with osteoporosis than in healthy individuals, and stated that MLR had a higher diagnostic value for osteoporosis than other parameters. However, unlike our study, the predictive value of MLR was not evaluated according to the T-score levels in osteoporotic participants in this study, and the participants were younger. In our study, MLR was superior to NLR in the prediction of lower T-scores.

Another important finding of our study was that NLR was also higher in patients with a T-score ≤-3.5. A study has shown that osteoporotic older adults had higher NLR levels compared to osteopenic and healthy groups (22). According to other studies carried out on women with postmenopausal osteoporosis, high NLR has been found to be a risk factor for osteoporosis (23,24).

As in these studies, a decrease in T-score was found to be related to an increase in NLR in our study. Our study included participants of both genders. Although the proportion of female participants were higher in the lowest T-score group, there was no independent effect of gender on T-score levels.

Although inflammation parameters such as white blood cell count, CRP and ESR levels are easy accessible in clinical practice, their specificity is not high (25). CRP is the most widely used parameter in clinical practice to show inflammation, but the results of studies evaluating the relationship between osteoporosis and CRP show variability. A higher ESR level was associated with the presence of osteoporosis in a study, but NLR level was found to be more predictive (22). Our results showed that ESR was not an independent determinant for lower T-scores according to logistic regression analysis.

Our study is unique for its feature evaluating the relationship of inflammation with T-score and including only elderly individuals. We found that patients with high MLR and NLR levels respectively had a 3.5-fold and 1.2-fold increase in the risk of having a T-score ≤-3.5.

Study Limitations

Our study has some limitations. We measured CRP, ESR, uric acid, MLR and NLR levels to assess inflammation, other parameters including proinflammatory cytokines such as IL-1, IL-6, TNF-α might also be considered. Due to the retrospective nature of the study, patients without a suspected fracture may not have been radiographically evaluated. A subgroup analysis of male osteoporosis could be performed if more male participants had been included. The strengths of our study are that it only included individuals over the age of 65 and included a large number of participants, and there was no significant difference between the groups in terms of chronic and inflammatory diseases that could affect MLR and NLR levels. Grouping osteoporotic patients according to T-scores enabled us to analyze the effect of osteoporosis severity on inflammation parameters more clearly.

Conclusion

The fact that MLR and NLR are easily accessible and cheap, and especially MLR has higher predictive value for lower T-scores, suggests that they may help evaluate the bone health in elderly osteoporotic individuals. Further researches supporting our results will bring a different perspective to the diagnosis of osteoporosis.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Local Ethics Committee of Gaziantep University (no: 2020/422, date: 24.02.2021).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., G.Ç., E.Ö., Concept: S.G., E.M.E., E.Ö., Design: S.G., G.Ç., E.M.E., Data Collection or Processing: E.M.E., E.Ö., Analysis or Interpretation: G.Ç., E.M.E., Literature Search: S.G., G.Ç., E.Ö., Writing: S.G., E.Ö.

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