Sultan Qaboos University Med J, November 2022, Vol. 22, Iss. 4, pp. 508–514, Epub. 7 Nov 22
Submitted 5 Jul 21
Revision Req. 29 Aug 21; Revision Recd. 16 Sep 21
Accepted 13 Oct 21
https://doi.org/10.18295/squmj.11.2021.145

CLINICAL & BASIC RESEARCH

Inflammatory Markers as a Predictor of Postmenopausal Osteoporosis

Cross-sectional study from Sultan Qaboos University Hospital

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abstract: ***Objectives:*** Postmenopausal osteoporosis is a progressive metabolic bone disease resulting from oestrogen deficiency. Due to the silent nature of the disease, there is an urgent need for a simple, early predictive marker. This study aimed to assess the potential of three factors—neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR)—as inflammatory markers of bone mineral density (BMD) loss. ***Methods:*** A retrospective cross-sectional study was conducted among 450 postmenopausal Omani women undergoing dual-energy X-ray absorptiometry at the Sultan Qaboos University Hospital, Muscat, Oman, from January 2017 to December 2019. The participants were allocated to groups based on lumbar spine BMD t-score values. A receiver operating characteristic curve was used to determine the area under the curve (AUC). Multivariate logistic regression was performed to identify independent predictors of low BMD. ***Results:*** A total of 65 (14.4%), 164 (36.4%) and 221 (49.1%) women were allocated to the control, osteopenia and osteoporosis groups, respectively. No significant differences in PLR, MLR and NLR values were observed among the groups. BMD t-score values were reversely correlated with age (P = 0.007) and PLR (P = 0.004) and positively correlated with body mass index (BMI; P <0.001). The AUC was 0.59. The independent predictors of low BMD were age (>65 years) and BMI (<25 kg/m^2). ***Conclusion:*** None of the three inflammatory biomarkers studied were found to be useful prognostic indicators of bone loss. Further research is recommended to reject or support theories regarding the role of inflammatory status in the pathogenesis.

Keywords: Postmenopausal woman; Bone Mineral Density; Osteoporosis; Oman.

Advances in Knowledge

- *Platelet-to-lymphocyte ratio was found to be a poor indicator of bone loss in postmenopausal women. As such, evaluation of this marker would have minimal use from a prognostic or diagnostic perspective.*
- *Although neither neutrophil-to-lymphocyte ratio nor monocyte-to-lymphocyte ratio values were found to be correlated with lumbar spine bone mineral density (BMD) t-score values and BMD group allocation, these findings cannot be used to either support or reject current theories related to the role of inflammation in the pathogenesis of postmenopausal osteoporosis (PMOP).*

Application to Patient Care

- *Based on the findings, bone mineral densitometry remains the best prognostic indicator of PMOP.*

Osteoporosis is a chronic progressive metabolic bone disease, affecting approximately 10% of the global population.[1,2] The progressive systemic disease is characterised by low bone mass and microarchitectural impairment of the bone tissue.[3] The prevalence of osteoporosis is significantly higher among postmenopausal women and men over 70 years of age.[1,4] Primary osteoporosis is classified into types 1 and 2, also referred to as oestrogen-related postmenopausal osteoporosis (PMOP) and age-related senile osteoporosis, respectively.[5]

The pathogenesis of PMOP is mainly related to the sudden onset of hypoestrogenemia at menopause, which has both a direct and indirect effect on bone resorption. Indirectly, impaired T-cell function increases the recruitment and lifespan of osteoclasts by releasing pro-inflammatory cytokines such as interleukin (IL)1 beta, IL-6, IL-11, IL-15, IL1-7 and tumour necrosis factor alpha (TNF-α).[6] Prolonged exposure to these pro-inflammatory cytokines induces receptor activator of nuclear factor kappa B ligand (RANKL) and suppresses osteoprotegerin (OPG). Moreover, oestrogen deficiency also influences the release of high levels of RANKL by B and T lymphocytes.[7] Increased expression of RANK results in increased interaction between RANK and RANKL, thereby increasing osteoclast bone resorption activity and osteoclast precursor cell differentiation and inhibiting osteoclast apoptosis.[8] This overactive osteoclastic status results in the greater resorption of trabecular than cortical bone.[9]

Clinically, PMOP increases the risk of asymptomatic vertebral compression fractures as well as symptomatic fractures such as Colles fractures or those of the wrist or hip.[10] Mild compression fractures are usually painless with no obvious clinical symptoms. However, most patients diagnosed with osteoporosis

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present with osteoporotic fractures usually following trauma. As such, the disease accounts for a considerable medical and socioeconomic burden. In 2010, there were an estimated 2.7 million hip fractures worldwide, of which 50% were attributable to osteoporosis and, thus, preventable.[11] Risk factors for PMOP include age, genetic factors, calcium and vitamin D deficiency, use of corticosteroids and anticancer drugs, hormonal levels, physical inactivity and low peak bone mass.[1,5,12] However, previous studies have shown that the prevalence of osteoporosis among women aged over 50 years varies widely (10.3–34.8%).[13,14] In particular, Omani women may be at a higher risk of PMOP as a consequence of calcium and vitamin D deficiency and inactive lifestyles.[15,16]

According to the diagnostic criteria of the World Health Organization, osteopenia and osteoporosis should be considered in young adult females if their bone mineral density (BMD) is 1–2.5 or ≥2.5 standard deviations (SDs) below the mean, respectively.[3] Although various methods can be used to assess BMD, dual-energy X-ray absorptiometry (DEXA) is the gold standard, particularly to calculate bone mineral content of the lumbar spine, hip bone and femur neck.[12] The often delayed presentation and serious complications exhibited by osteoporotic patients underline the need for an early, rapid and simple predictive marker. Despite the predictive role of levels of certain inflammatory cytokines in the blood, such as RANKL and OPG, these markers are not often used due to the complex nature of such laboratory monitoring.[17] Previous research has confirmed that serum inflammatory markers can play a diagnostic role in various diseases, with researchers reporting an association between inflammatory response and potential loss of bone mass.[9]

However, few studies have assessed the predictive role of inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR). Moreover, the results of such studies have been conflicting. Ye *et al.* reported a correlation between increased bone loss and osteoporosis severity with low lymphocyte and high neutrophil and monocyte ratios among 487 patients at a hospital in China.[17] Yilmaz *et al.* found a significant negative correlation between NLR and lumbar spine BMD values, concluding that NLR might be a better predictor of PMOP than C-reactive protein (CRP) level.[18] In a cross-sectional study of 252 postmenopausal women in Turkey, Eroglu and Karatas reported that the osteoporotic group demonstrated a significantly higher PLR; however, no association was noted with NLR.[19] In contrast, a cross-sectional study of 407 postmenopausal women in Korea conducted by Lee *et al.* found that NLR was significantly higher in the PMOP group, but not PLR.[20] Two other studies conducted in China confirmed that BMD was negatively correlated with NLR among 233 postmenopausal women and 316 osteoporotic patients.[21,22]

As the onset of osteoporosis lacks obvious disease characteristics, it is difficult to diagnose it early; once a patient has visible changes in body shape or bone pain, the lesion has already entered an accelerated phase. At present, clinical diagnostic methods primarily include osteoporosis screening tools such as the FRAX® tool (University of Sheffield, Sheffield, UK), bone turnover markers and BMD detection technologies, with the latter being some of the most common methods. An objective and non-invasive diagnostic predictor at an earlier disease stage is needed. For instance, peripheral blood markers are newly proposed inflammatory factors with various advantages over other modalities, such as simplicity, cost-effectiveness and non-invasiveness. As such, this study aimed to clarify the association between inflammatory markers—specifically NLR, PLR and MLR values—and lumbar spine BMD t-score values in a cohort of postmenopausal Omani women. Assessment of these simple inflammatory serum markers may help in the early diagnosis of osteoporosis, thus precluding the development of serious complications such as asymptomatic compression fractures. Ideally, the results of this study can add to existing knowledge in the literature and may inform future systematic reviews and meta-analyses designed to conclude on the effectiveness of these markers.

Methods

This retrospective cross-sectional study was conducted among postmenopausal women who underwent DEXA scanning from January 2017 to December 2019 at the Sultan Qaboos University Hospital in Muscat, Oman. A non-probability convenience sampling strategy was used to recruit all women presenting to this hospital during the above-mentioned period who were either ≥50 years of age or <50 years of age if postmenopausal status was confirmed. However, women with a history of menopause of less than a year in duration were excluded, as were women with conditions or factors thought to affect immunoinflammatory response, including those with hepatic, renal, oncological, haematological or rheumatologic diseases. Similarly, women with a history of steroid use, trauma, hospitalisation over the preceding six months and blood transfusions over the last 12 months were also excluded.

Data were collected from the database of the electronic hospital information system. Information regarding the demographic characteristics of the participants was collected including age, weight and height. The body mass index (BMI) of each participant was calculated as follows:

$$BMI = \text{weight in kg}/(\text{height in m})^2$$
[Equation 1]

In addition, various laboratory results from the participants' most recent blood tests were collected, including their haemoglobin (Hb) level, mean cell volume, platelet count, neutrophil count, lymphocyte count and monocyte count. Inflammatory markers PLR, NLR and MLR were subsequently calculated using the following formulae:

$$PLR = \text{platelet count}/\text{lymphocyte count}$$
[Equation 2]

$$NLR = \text{neutrophil count}/\text{lymphocyte count}$$
[Equation 3]

$$MLR = \text{monocyte count}/\text{lymphocyte count}$$
[Equation 4]

Finally, BMD t-score values were obtained from DEXA imaging of the lumbar spine, femoral neck or hip bone. These values were then used to allocate the participants to control, osteopenia or osteoporosis group. For the purposes of the analysis, the participants in the osteopenia and osteoporosis groups were combined to draw comparisons between those with normal and low BMD values.

Data calculations and statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 25 (IBM Corp., Armonk, NY, USA). Age and BMI were expressed as means ± SDs, while all other continuous variables were expressed as means and ranges, including Hb levels and PLR, NLR and MLR values. The one-sample Kolmogorov–Smirnov test was conducted to determine the normality of continuous variables, with all variables found to be non-normally distributed. Non-parametric tests such as the Mann–Whitney U and Kruskal–Wallis tests were performed to determine the difference between two groups or more than two groups, respectively. Associations were determined between BMD group allocation and selected variables including age, BMI, Hb levels and PLR, NLR and MLR values.

Spearman's correlation test was applied to evaluate the significance of correlations between age; BMI; Hb level; PLR, NLR and MLR values and lumbar spine BMD t-score values. A receiver operating characteristic (ROC) curve analysis was employed to find the area under the curve (AUC) and determine the PLR cut-off value. The multivariate logistic regression analysis was performed to identify the strongest independent predictors of osteoporosis. A *P* value of <0.05 was considered statistically significant.

The Medical Research and Ethics Committee of the College of Medicine and Health Sciences, Sultan Qaboos University, approved this study.

Results

A total of 450 women were included in the study. The mean age was 63.69 ± 8.23 years, with the majority (56.7%) being 50–65 years old, followed by >65 years (40.2%) and <50 years (2.9%). The mean BMI was 29.24 ± 5.93 kg/m^2. Based on their BMD values, 65 (14.4%), 164 (36.4%) and 221 (49.1%) women were allocated to the control, osteopenia and osteoporosis groups, respectively. The mean ages of women in these groups were 59.80 ± 8.66, 62.71 ± 6.90 and 65.76 ± 8.29 years, respectively. Age was significantly higher in the osteoporosis group (*P* <0.001), while BMI was significantly higher in the control group (*P* <0.001) [Tables 1 and 2].

No significant differences in mean PLR, MLR and NLR values were observed between women with normal BMD values and those with low BMD values (*P* >0.05 each) [Table 1]. Furthermore, no significant differences were noted in mean PLR, MLR and NLR values between the control, osteopenia and

Table 1: Comparison of age, haemoglobin levels, body mass index and platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio values between subjects with normal and low bone mineral density values (N = 450)

Variable	Mean (range)		*P* value
	Normal BMD group (n = 65)	Low BMD group (n = 385)	
Mean age in years ± SD	59.80 ± 8.66	64.50 ± 7.88	<0.001
Mean BMI in kg/m^2 ± SD	32.66 ± 4.94	28.64 ± 5.89	<0.001
Hb level in g/dL	12.59 (11.0–14.7)	12.41 (10.3–15.3)	0.218
PLR	122.93 (59.68–245.00)	127.68 (39.74–256.92)	0.311
NLR	1.22 (0.36–2.93)	1.18 (0.20– 4.43)	0.263
MLR	0.194 (0.08–0.37)	0.212 (0.09–0.65)	0.182

BMD = bone mineral density; SD = standard deviation; BMI = body mass index; Hb = haemoglobin; PLR = platelet-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio.

Table 2: Comparison of age, haemoglobin levels, body mass index and platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio values between the control, osteopenia and osteoporosis groups

Variable	Mean (range)			*P* value
	Control group (n = 65)	Osteopenia group (n = 164)	Osteoporosis group (n = 221)	
Mean age in years ± SD	59.80 ± 8.66	62.71 ± 6.90	65.76 ± 8.29	< 0.001
Mean BMI in kg/m² ± SD	32.66 ± 4.94	30.38 ± 5.73	27.47 ± 5.72	< 0.001
Hb level in g/dL	12.59 (11.0–14.7)	12.47 (10.3–15.3)	12.37 (10.3–15.0)	0.313
PLR	122.93 (59.68–245.00)	122.36 (46.30–240.00)	131.47 (39.74–256.92)	0.186
NLR	1.22 (0.36–2.93)	1.17 (0.38–4.21)	1.19 (0.20–4.43)	0.534
MLR	0.194 (0.08–0.37)	0.204 (0.09–0.47)	0.218 (0.10–0.65)	0.268

SD = standard deviation; BMI = body mass index; Hb = haemoglobin; PLR = platelet-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio.

Table 3: Correlations between lumbar spine bone mineral density t-score values and age, body mass index, haemoglobin levels and platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio values

Variable		Age	BMI	Hb level	PLR	NLR	MLR
Lumbar spine BMD t-score values	Correlation coefficient	-0.150	0.345	0.032	-0.160	-0.003	-0.087
	P value	0.007	<0.001	0.571	0.004	0.963	0.119

BMI = body mass index; Hb = haemoglobin; PLR = platelet-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio; BMD = bone mineral density.

Table 4: Logistic regression analysis of age and body mass index as potential predictors of low bone mineral density

Risk factor	OR (95% CI)	*P* value
Age ≥65 years	1.942 (1.10–3.44)	0.023
BMI <25 kg/m²	8.419 (2.01–35.20)	0.004

OR = odds ratio; CI = confidence interval; BMI = body mass index.

osteoporosis groups (*P* >0.05 each) [Table 2]. Similarly, differences in Hb level among the groups were non-significant (*P* >0.05) [Tables 1 and 2].

According to the correlation analysis, lumbar spine BMD t-score values were inversely correlated with age (*P* = 0.007) and PLR values (*P* = 0.004) and positively correlated with BMI (*P* <0.001). However, no significant correlations were observed with Hb levels and NLR or MLR values (*P* >0.05) [Table 3].

The PLR cut-off value was estimated to be 117.11. An ROC curve analysis indicated that the AUC was 0.59, which was significant for PLR values only [Figure 1].

Age was positively correlated with all three inflammatory markers: NLR (*P* = 0.001), PLR (*P* = 0.031) and MLR (*P* <0.001). In addition, age was inversely correlated with BMI (*P* = 0.046) and Hb levels (*P* = 0.002). There was also a positive correlation between all three of the inflammatory markers studied (*P* <0.001).

Based on the logistic regression analysis, an age >65 years (*P* = 0.023) and a BMI <25 kg/m² (*P* = 0.004) were identified as independent predictors of low BMD [Table 4].

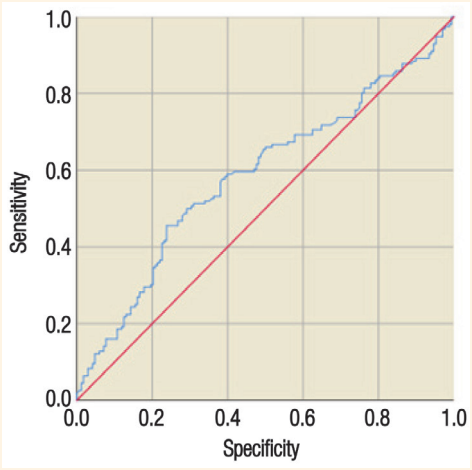

Figure 1: Receiver operating characteristic curve analysis for platelet-to-lymphocyte ratio.
Area under the curve = 0.59; platelet-to-lymphocyte ratio cut-off = ~117.11.

Discussion

Serum inflammatory markers are considered indicators of many chronic inflammatory diseases, with both PLR and NLR values reported as indicators of severity in ulcerative colitis and acute pancreatitis as well as various neoplastic conditions such as hepatocellular carcinoma and colorectal, breast and lung cancer.[6,23] Similarly, there is strong evidence to support the association between systemic inflammatory status and osteoporosis, with pro-inflammatory markers, hormones and growth factors all playing a role in the

pathogenesis of the disease.[6,24] Various epidemiological studies have shown an increased risk of osteoporosis in chronic inflammatory conditions, such as systemic lupus erythematosus, ankylosing spondylitis, Crohn's disease, rheumatoid arthritis and ulcerative colitis.[21,25] In addition, a previous study reported a negative correlation between low BMD and NLR, CRP and erythrocyte sedimentation rate in elderly people.[6]

While the role of inflammation in osteoporosis has been proven by many studies at the molecular level, there is still insufficient evidence to support the relationship between serum levels of these inflammatory markers and degree of bone loss. This may be because serum levels of inflammatory markers may not always reflect the processes happening at the tissue level. A prospective case-cohort study reported a correlation between certain serum inflammatory markers—specifically IL-6 and its soluble receptor (SR) and TNF SR1 and TNF SR2—and an increased risk of hip fractures.[26] Alternatively, other research has shown no correlation between IL-6 and osteoporosis.[6] The present cross-sectional study sought to assess the relationship between BMD and three serum inflammatory markers—NLR, PLR and MLR values—among a cohort of 450 postmenopausal Omani women. No significant differences with regard to NLR, PLR and MLR values were noted among the participants according to their allocation into normal and low BMD groups. Likewise, there were no significant differences in these markers when the participants were further subcategorised into control, osteopenia and osteoporosis groups. Moreover, a correlation analysis of lumbar spine BMD t-score values indicated no significant correlations with NLR and MLR values.

Overall, PLR was the only studied inflammatory marker found to be significantly correlated with BMD t-score values, with PLR values inversely correlated with lumbar spine BMD t-scores. These results confirm findings reported from a similar study performed in Turkey, wherein PLR was the only inflammatory marker found to be negatively correlated with lumbar spine BMD t-score values.[19] Accordingly, PLR can be considered an indicator of BMD in postmenopausal women and may even reflect the degree of osteoporosis when correlated with lumbar spine BMD t-score values. However, an ROC curve analysis revealed that PLR failed to predict osteoporosis in the present study and appeared to be a poor test for low BMD in a previous study conducted in Turkey.[19]

Based on the findings of the present study, neither NLR nor MLR values can be considered predictive markers of osteoporosis as they do not appear to directly indicate osteoporotic risk. These findings may be explained by the large number of factors affecting white blood cells, such as infection, cardiovascular diseases, ulcerative colitis, acute appendicitis, metabolic syndrome, malignancy, pharmacological agents and non-alcoholic fatty liver disease.[6,27,28] However, conflicting findings regarding the relationship between NLR and BMD values have been reported. Three cross-sectional studies demonstrated negative correlations in different populations in East Asia.[20,22,29] Additionally, one of those studies found a negative correlation between MLR and BMD values.[22] In contrast, neither the present study nor a previous one conducted in Turkey reported correlations between BMD and NLR or MLR values.[19] These differences could be attributed to varying ethnicity or genetic and environmental factors, particularly when comparing differences between East Asian and Middle Eastern populations. Regardless, further research is necessary to either support or reject current theories regarding the role of inflammatory status in the pathogenesis of osteoporosis.

In the current study, both age and BMI were significantly associated with group allocation based on BMD values, with the logistic regression analysis indicating that advanced age and low BMI were independent predictors of low BMD. In addition, age was negatively correlated with lumbar spine BMD t-score values. These findings were expected given that osteoporosis is a progressive age-related disease, with old age considered the greatest risk factor for the disease.[13] In contrast, BMI was positively correlated with both lumbar spine BMD t-score values and BMD group allocation, with women in the control group having a significantly greater BMI than those in the low BMD groups. This finding can be explained by the loss of muscle and adipocyte replacement due to lack of physical activity in the osteoporosis group, especially for those with osteoporotic fractures, as well as the minimal loss of bone weight due to the osteoporosis.[30] Nevertheless, high BMI cannot be considered a protective factor for osteoporosis, as obesity is associated with both physical inactivity and low bone quality.[31]

Daytime variation of haematological parameters can also affect PLR, NLR and MLR values, particularly with regard to neutrophil, monocyte and lymphocyte percentages. Conversely, red blood cells, platelets and other related parameters have been found to exhibit less frequent daytime variation.[32] Bektas *et al.* emphasised that chronic inflammatory status and the dysregulation of proinflammatory markers correlate with the natural ageing process in all species, resulting in the elevation of inflammatory markers such as CRP, IL-6, IL-8 and TNF-α.[33] The findings of the present study confirm this concept, as all three

of the inflammatory markers studied were found to be positively correlated with age. Such factors may have resulted in the non-significant capacity of these plasma inflammatory markers to indicate low BMD, considering the inability to separate two intertwined factors, namely age and low oestrogen levels.

The current study was subject to certain limitations. First, as a convenience sampling strategy was employed, no minimum sample size was calculated. As such, it was not possible to determine the representativeness of the cohort to the population being studied. Second, all patients with medical conditions known to interfere with NLR, MLR and PLR values could not be excluded due to insufficient patient medical information and the huge number of conditions known to affect these factors.[27] Third, all secondary causes of osteoporosis could not be excluded. Finally, as the study was conducted at a single centre using a cross-sectional design, longitudinal changes in NLR, MLR and PLR values could not be determined in the study population. As such, the role of these serum inflammatory markers in the pathogenesis of osteoporosis could not be assessed. Further longitudinal studies are recommended to determine changes in these serum inflammatory markers among women in the early postmenopausal period. Moreover, additional research is recommended to assess more specific markers of PMOP inflammation in this population, including cytokines such as interferon (IFN) α-2, IFN-γ, IL-12p70, IL-33 and monocyte chemoattractant protein 1.[24]

Conclusion

PLR was found to be a poor indicator of bone loss in postmenopausal women in this study. As such, evaluation of this marker would have minimal use from a prognostic or diagnostic perspective. Although neither NLR nor MLR values were found to be correlated with lumbar spine BMD t-score values and BMD group allocation, these findings cannot be used to either support or reject current theories related to the role of inflammation in the pathogenesis of PMOP. Further research is recommended and should focus on other specific serum inflammatory markers for osteoporosis.

AUTHORS' CONTRIBUTION

AASa was involved in question formulation, methodology designing, data cleaning and manuscript writing, submission and revision. AASh was involved in question formulation and methodology designing. NMA-A contributed to data analysis and manuscript writing. AAAS contributed towards data collection, data analysis and manuscript writing. MAA-H was involved in data collection and manuscript writing. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

No funding was received for this study.

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