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Blood cell count-derived inflammation indices as predictors of the osteoporotic risk of postmenopausal women

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Abstract. – OBJECTIVE: We investigated the associations between osteoporosis (OP) and systemic immune inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) in postmenopausal women.

PATIENTS AND METHODS: This retrospective study included 966 postmenopausal women. Logistic regression and receiver operating characteristic curve (ROC) analyses were applied to explore the relationships between SII, NLR, MLR, and PLR with the bone mineral density (BMD) and risk of OP.

RESULTS: Logistic regression analyses showed that SII, PLR, NLR, and MLR had independent negative associations with the OP risk. The ROC curve analysis showed that SII, NLR, and MLR predicted a low BMD, with NLR having the highest predictive value (area under the curve = 0.624). SII > 504.09, PLR > 131.87, NLR > 2.02, and MLR > 0.12 correlated with a particularly high OP risk.

CONCLUSIONS: High levels of SII, PLR, NLR, and MLR were associated with a high OP risk. In particular, NLR > 2.02 strongly predicted the risk of OP, thereby representing a valuable and convenient inflammatory marker of the OP risk.

Key Words:
Osteoporosis, Postmenopausal women, Systemic immune inflammation index, Neutrophil-to-lymphocyte ratio, Monocyte-to-lymphocyte ratio, Platelet-to-lymphocyte ratio.

Introduction

Osteoporosis (OP), characterized by a decline in bone mineral density (BMD) and degradation of the bone microstructure, is a common public health issue[1]. The prevalence rates of low BMD and OP are increasing with the rising global life expectancy, particularly due to the increasing number of postmenopausal women[2]. OP predisposes to femur and vertebral fractures, frequently affecting the activities of daily living of patients and placing a substantial burden on their family and society[3]. The identification of patients at risk for OP is essential for targeted preventive strategies[4], discharge planning, and prognostication[5]. Such patients are the most likely to benefit from preventive strategies. Several methods are available for predicting the OP risk, including markers of bone turnover and devices to detect the BMD. Traditional predictive tools lack specificity and use a standardized approach without accounting for individual differences. The delayed presentation and severity of fragility fractures in osteoporotic patients emphasize the need to develop an early, rapid, and simple predictive marker of OP.

Serum inflammatory markers are useful for the diagnosis of various diseases. The inflammatory response is associated with a loss of bone mass. Bone immunology has demonstrated that inflammation plays a critical role in the pathogenesis of OP and fragility fractures[6], potentially mediated by age-related oxidative stress and low activation of the immune system[7]. Chronic, low-grade inflammation is a risk factor for bone loss, OP, and fragility fractures[8]. Dysfunctional activated lymphocytes can initiate a cascade reaction of inflammatory cytokines and

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chemokines, leading to the aggregation of neutrophils and macrophages, thus disrupting the dynamic balance of bone formation[9]. Previous *in vitro* studies[10] have shown that inflammatory cytokines act on mesenchymal stem cells and osteoclast precursors to enhance osteoclast-mediated bone resorption, which is closely related to the pathogenesis of OP. These cytokines include interleukin-1, C-reactive protein (CRP), and tumor necrosis factor-α.

In recent years, the systemic immune inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have gained significant attention as novel inflammatory markers with potential diagnostic and prognostic applications in multiple inflammatory diseases, cardiovascular diseases, malignant tumors, depression, neurological diseases, sepsis, and joint diseases[11-21]. These markers have several advantages, including their low cost and convenience. Because these markers are based on the complete blood count, which is readily available and inexpensive, SII, NLR, MLR, and PLR are accurate and reliable indicators of the immune and inflammatory status[22,23]. However, previous studies in the literature have shown inconsistent results. A cross-sectional study[24] of older adults showed that high levels of NLR and PLR were closely associated with OP, suggesting their usefulness for OP screening. Zhang et al[25] demonstrated that high levels of SII and NLR can predict the potential risk of low BMD and OP in postmenopausal women. Lee et al[26] found a negative correlation between NLR and the lumbar spine BMD but did not observe any significant relationship between PLR and BMD. However, Zhang et al[27] showed a positive relationship between NLR and the lumbar BMD, but a negative relationship between PLR and the lumbar BMD. Few studies have investigated the relationships between SII, PLR, NLR, MLR, and bone metabolism. Furthermore, previous studies have focused on only one or two inflammatory indexes. The complex relationship between inflammatory markers and BMD requires further investigation in large-scale clinical studies.

Given the scarcity of evidence, we investigated the associations of four inflammation indexes and BMD in patients with OP, as well as explored their predictive value for OP. The aim of the present study was to establish the usefulness of simple and convenient predictive markers for OP.

Patients and Methods

Study Participants

This retrospective cohort study was conducted among postmenopausal women who underwent dual-energy X-ray absorptiometry (DEXA) scanning at the Third Hospital of Hebei Medical University, a general hospital with specialized orthopedics and endocrinology services. The study protocol was approved by the Research Ethics Committee of the Third Hospital of Hebei Medical University (No.: W2020-014-1). Electronic data were obtained from inpatient and outpatient medical records between January 1, 2021, and December 31, 2022. Routine blood tests were performed during hospitalization and outpatient physical examination to facilitate data collection. The study screened all postmenopausal participants who had complete data available (n = 1,366). Demographic data, including age, address, weight, height, and date of hospital visit, were collected from the electronic hospital information system.

Exclusion Criteria

We excluded women with a history of menopause < 1 year; factors or conditions that affect the immunoinflammatory response, including hepatic, renal, hematological, oncological, and rheumatologic diseases; history of steroid use, trauma, or blood transfusions over the last 12 months; and use of anti-osteoporotic treatment within six months before inclusion.

BMD by DEXA

DEXA (Medilink, Montpellier, France) was performed to examine the BMD at the lumbar spine (L2-L4), right femoral neck (FN), and total femur (TF) in the appropriate positions. DEXA was conducted by the same technician for all patients, and automated analysis was used. BMD (g/cm^2) was calculated from the bone mineral content and bone area. The densitometer was standardized using a standard phantom before each measurement. Individuals with BMD $\geq$ 2.5 standard deviations (SDs) below the mean were considered to have OP, whereas those with BMD $\geq$ 1.0 SD above the mean were considered to have normal BMD; the remaining cases were considered to have osteopenia.

Data Collection

We recorded the alcohol consumption (drinker or non-drinker), smoking status (current, former,

or never), and body mass index (BMI) (kg/m^2) of participants. The BMI was calculated as weight in kg/(height in m^2).

We obtained the most recent laboratory results of participants, including albumin (ALB, g/dL), blood urea nitrogen (BUN, mg/dL), creatinine (Cr, mg/dL), uric acid (UA, mg/dL), total cholesterol (TC, mg/dL), triglycerides (TG, mg/dL), total calcium (Ca, mg/dL), phosphorus (P, mg/dL), CRP, red blood cell count (million cells/μL), hemoglobin (Hb, g/dL), platelet count (PLT, 1,000 cells/μL), neutrophil count (NC, 1,000 cells/μL), lymphocyte count (LC, 1,000 cells/μL), monocyte count (MC, 1,000 cells/μL), and mean cell volume (fL). An automated hematology analyzer (Beckman Coulter LH-750, Brea, CA, USA) and an automatic biochemical analyzer (Beckman Coulter AU5800, Brea, CA, USA) were used for these analyses. The inflammatory markers SII, PLR, NLR, and MLR were calculated based on the complete blood count as follows:

SII = PLT × NC/LC
PLR = PLT/LC
NLR = NC/LC
MLR = MC/LC

Statistical Analysis

The data were preliminarily sorted using Excel 2010. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 26; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± SD or interquartile range (P25-P75), as appropriate, whereas categorical variables are expressed as absolute numbers and percentages (%). Normally distributed data were compared using the Least Significant Difference test and Analysis of Variance, whereas non-normally distributed data were compared using the Nemenyi and Kruskal-Wallis tests. Categorical variables were compared between groups using the Chi-square test. In addition, the associations between SII, PLR, NLR, MLR, and OP were assessed using multivariate logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the area under the curve (AUC) and the cut-off value for each indicator. p-value < 0.05 was considered statistically significant.

Table I. Baseline characteristics of participants.

Characteristic	n (%)/$\bar{x}$ ± s SD/M (IQR)
Age (year)	61 (56-65)
Time since menopause (years)	6 (4-10)
BMI (kg/m^2)	23.76 (21.04-26.14)
Alcohol consumption (%)	
No (< 1/month)	643 (66.6)
Yes (≥ 1/month)	323 (33.4)
Smoking status (%)	
Current	41 (4.2)
Former	105 (10.9)
Never	820 (84.9)
Family history of OP (%)	
No	861 (89.1)
Yes	105 (10.9)
Diabetes (%)	
No	865 (89.5)
Yes	101 (10.5)
Hypertension (%)	
No	858 (88.8)
Yes	108 (11.2)
LS-BMD (g/cm^2)	0.85 (0.68-0.97)
FN-BMD (g/cm^2)	0.75 (0.62-0.86)
TF-BMD (g/cm^2)	0.83 (0.7-0.94)
ALP (U/L)	112.5 (89.8-134.9)
BUN (mmol/L)	4.79 (3.76-5.76)
SCr (umol/L)	63 (53-71)
UA (umol/L)	281 (256-307)
TC (mmol/L)	4.77 (4.15-5.34)
TG (mmol/L)	1.54 (1.31-1.79)
HDL-C (mmol/L)	1.34 (1.09-1.56)
LDL-C (mmol/L)	2.86 (2.44-3.27)
CA (mmol/L)	2.28 (2.15-2.41)
P (mmol/L)	1.21 (1.1-1.34)
CRP (mg/L)	6.29 (2.73-13.39)
PLT (×10^9/L)	208 (150-264)
NC (×10^9/L)	4.05 (2.9-5.2)
LC (×10^9/L)	2.3 (1.7-2.7)
MC (×10^9/L)	0.4 (0.3-0.6)
PLR	93.33 (65-131.36)
SII	350.81 (227.86-539.69)
NLR	1.81 (1.29-2.44)
MLR	0.19 (0.11-0.29)

BMI, body mass index; BMD, bone mineral density; LS, lumbar spine; FN, neck of femur; TF, total femur; ALP, alkaline phosphatase; BUN, blood urea nitrogen; SCr, serum creatinine; UA, uric acid; OP, osteoporosis; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CA, calcium; P, phosphorus; CRP, C-reactive protein; PLT, platelet; NC, neutrophil count; LC, lymphocyte count; MC, monocyte count; PLR, platelet count/lymphocyte count; SII, platelet count × neutrophil count/lymphocyte count; NLR, neutrophil count/lymphocyte count; MLR, monocyte count/lymphocyte count.

Results

Baseline Characteristics

The median age of the 966 participants was 61 (range: 56-65) years. Table I presents the basic information of all participants. The median time since menopause was 6 (4-10) years. The median lumbar spine (LS)-BMD, FN-BMD, and TF-BMD values were 0.85, 0.75, and 0.83, respectively.

The participants were categorized into the control group (n = 273, -1.0 < T < 1.0), osteopenia group (n = 336, -2.5 < T ≤ -1.0), and OP group (n = 390, T ≤ -2.5) based on the BMD values. We compared the inflammatory indices among the three groups. The three groups exhibited significant differences in terms of the age, time since menopause, BMI, alcohol consumption, family history of OP, LS-BMD, FN-BMD, TF-BMD, alkaline phosphatase (ALP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), calcium (CA), CRP, PLT, LC, PLR, SII, NLR, and MLR ($p < 0.05$) (Table II). The OP group had a significantly higher age, time since menopause, BMI, and LS-BMD, FN-

Table II. Comparison of variables among the three groups.

	Control group (n = 173)	Osteopenia group (n = 336)	OP group (n = 457)	χ^2/F/H	p
Age (year)	58 (54-62)	59.5 (55.5-63)*	64 (59-68)*#	122.261	< 0.001
Time since menopause (years)	5 (4-7)	6 (3-8)	8 (5-12)*#	96.928	< 0.001
BMI (kg/m^2)	25.17 (23.74-26.62)	24.34 (22.19-26.31)*	22.56 (20.31-25.06)*#	64.366	< 0.001
Alcohol consumption (%)				18.254	< 0.001
No (< 1/month)	92 (53.2)	226 (67.3)	325 (71.1)		
Yes (≥ 1/month)	81 (46.8)	110 (32.7)*	132 (28.9)*		
Smoking status (%)				8.441	0.077
Current	12 (6.9)	9 (2.7)	20 (4.4)		
Former	19 (11.0)	29 (8.6)	57 (12.5)		
Never	142 (82.1)	298 (88.7)	380 (83.2)		
Family history of OP (%)				7.104	0.029
No	163 (94.2)	301 (89.6)	397 (86.9)*		
Yes	10 (5.8)	35 (10.4)	60 (13.1)		
Diabetes (%)				1.586	0.452
No	154 (89)	296 (88.1)	415 (90.8)		
Yes	19 (11)	40 (11.9)	42 (9.2)		
Hypertension (%)				5.210	0.074
No	159 (91.9)	304 (90.5)	395 (86.4)		
Yes	14 (8.1)	32 (9.5)	62 (13.6)		
LS-BMD (g/cm^2)	1.09 (1.01-1.17)	0.92 (0.85-0.97)*	0.67 (0.58-0.8)*#	611.745	< 0.001
FN-BMD (g/cm^2)	0.93 (0.88-0.98)	0.81 (0.72-0.87)*	0.65 (0.54-0.72)*#	474.73	< 0.001
TF-BMD (g/cm^2)	1.03 ± 0.10	0.86 ± 0.10*	0.71 ± 0.13*#	541.635	< 0.001
ALP (U/L)	88.6 (74.7-99.6)	114.8 (88.35-139.9)*	122.3 (102.2-141.1)*#	157.618	< 0.001
BUN (mmol/L)	4.78 ± 1.31	4.79 ± 1.51	4.74 ± 1.47	0.132	0.876
SCr (umol/L)	62.58 ± 11.25	63.23 ± 15.25	61.44 ± 14.25	1.610	0.200
UA (umol/L)	284.68 ± 35.15	279.38 ± 39.22	280.26 ± 37.8	1.192	0.304
TC (mmol/L)	5.25 ± 1.04	4.92 ± 0.99*	4.51 ± 0.71*#	48.805	< 0.001
TG (mmol/L)	1.72 ± 0.31	1.65 ± 0.28*	1.38 ± 0.33*#	107.1	< 0.001
HDL-C (mmol/L)	1.47 ± 0.31	1.40 ± 0.30*	1.22 ± 0.35*#	48.627	< 0.001
LDL-C (mmol/L)	2.70 ± 0.61	2.79 ± 0.59	2.94 ± 0.58*#	13.254	< 0.001
CA (mmol/L)	2.34 ± 0.18	2.29 ± 0.19*	2.24 ± 0.18*#	17.313	< 0.001
P (mmol/L)	1.20 ± 0.19	1.22 ± 0.17	1.22 ± 0.18	0.699	0.497
CRP (mg/L)	5.66 (2.49-10.62)	6.05 (2.57-15.62)	6.84 (2.91-14.15)*	6.117	0.047
PLT (×10^9/L)	221 (171-270)	204.5 (152-263)	205 (143-256)*	8.726	0.013
NC (×10^9/L)	3.4 (2.4-5)	4 (3-5.1)*	4.2 (3-5.3)*	13.546	0.001
LC (×10^9/L)	2.6 (2.2-3)	2.3 (1.8-2.7)*	2 (1.5-2.5)*#	77.887	< 0.001
MC (×10^9/L)	0.4 (0.2-0.6)	0.4 (0.2-0.6)	0.4 (0.3-0.6)	0.348	0.84
PLR	86.21 (65.15-111.07)	91.79 (65.09-125.99)	97.5 (65-151)*	10.522	0.005
SII	275.63 (193.15-444)	352.16 (239.21-514.33)*	381.33 (241.28-605.45)*	24.163	< 0.001
NLR	1.4 (0.93-1.92)	1.79 (1.3-2.32)*	2.05 (1.47-2.79)*#	68.900	< 0.001
MLR	0.17 (0.09-0.24)	0.18 (0.1-0.29)	0.2 (0.13-0.31)*#	22.133	< 0.001

*$p < 0.05$ *vs*. control group; #$p < 0.05$ *vs*. Osteopenia group. BMI, body mass index; BMD, bone mineral density; LS, lumbar spine; FN, neck of femur; TF, total femur; ALP, alkaline phosphatase; BUN, blood urea nitrogen; SCr, serum creatinine; UA, uric acid; OP, osteoporosis; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CA, calcium; P, phosphorus; CRP, C-reactive protein; PLT, platelet; NC, neutrophil count; LC, lymphocyte count; MC, monocyte count; PLR, platelet count/lymphocyte count; SII, platelet count × neutrophil count/lymphocyte count; NLR, neutrophil count/lymphocyte count; MLR, monocyte count/lymphocyte count.

BMD, TF-BMD, ALP, TC, TG, HDL-C, LDL-C, CA, LC, NLR, and MLR levels than those of the other groups. The OP group had a significantly higher SII, NLR, and MLR compared to the other groups ($p < 0.001$). Furthermore, the BMD was significantly lower at the lumbar spine, FN, and TF in the OP group than the other groups ($p < 0.001$) (Table II).

Associations Between SII, PLR, NLR, MLR, and Osteoporosis

The associations between low BMD and SII, PLR, NLR, and MLR are presented in Table III. In Model 1, in which no covariates were adjusted, SII, PLR, NLR, and MLR were negatively associated with OP. After adjusting for age, BMI, and alcohol consumption in Model 2, similar results were obtained: SII, PLR, NLR, and MLR were negatively associated with OP. Finally, adjusting for all covariates in Model 3 further confirmed the results from Models 1 and 2: SII, PLR, NLR, and MLR had an independent negative association with OP.

The ROC curve analysis showed that SII, PLR, NLR, and MLR have predictive values for a low BMD, with NLR having the highest predictive

Table III. Comparison of influencing factors between the OP and non-OP groups.

	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)
SII			
Q1	Reference	Reference	Reference
Q2	1.100 (0.767, 1.579)	1.037 (0.692, 1.556)	1.258 (0.774, 2.044)
	0.603	0.859	0.354
Q3	1.049 (0.727, 1.514)	1.005 (0.665, 1.517)	1.646 (0.960, 2.820)
	0.799	0.983	0.070
Q4	1.963 (1.358, 2.838)	2.165 (1.427, 3.284)	3.688 (2.043, 6.660)
	< 0.001	< 0.001	< 0.001
p for tend	< 0.001	< 0.001	< 0.001
PLR			
Q1	Reference	Reference	Reference
Q2	0.726 (0.506, 1.041)	0.872 (0.582, 1.307)	1.570 (0.916, 2.690)
	0.082	0.508	0.101
Q3	0.744 (0.519, 1.067)	0.933 (0.624, 1.395)	2.531 (1.366, 4.688)
	0.108	0.735	0.003
Q4	1.789 (1.245, 2.569)	2.113 (1.403, 3.183)	6.901 (3.364, 14.155)
	0.002	< 0.001	< 0.001
p for tend	< 0.001	< 0.001	< 0.001
NLR			
Q1	Reference	Reference	Reference
Q2	1.484 (1.027, 2.143)	1.371 (0.907, 2.073)	1.468 (0.903, 2.387)
	0.035	0.134	0.121
Q3	1.628 (1.128, 2.348)	1.466 (0.969, 2.218)	1.531 (0.938, 2.500)
	0.009	0.07	0.088
Q4	3.535 (2.429, 5.146)	4.229 (2.757, 6.487)	3.814 (2.326, 6.253)
	< 0.001	< 0.001	< 0.001
p for tend	< 0.001	< 0.001	< 0.001
MLR			
Q1	Reference	Reference	Reference
Q2	1.688 (1.168, 2.439)	1.736 (1.45, 2.633)	1.723 (1.056, 2.811)
	0.005	0.009	0.029
Q3	1.705 (1.190, 2.445)	1.646 (1.102, 2.458)	1.759 (1.093, 2.830)
	0.004	0.015	0.020
Q4	2.02 (1.410, 2.894)	1.987 (1.329, 2.972)	1.645 (1.025, 2.641)
	< 0.001	0.001	0.039
p for tend	< 0.001	0.001	0.046

Model 1: Confounding factors were not controlled; Model 2: Age, time since menopause, BMI, alcohol consumption, family history of OP, and diabetes were controlled; Model 3: Age, time since menopause, BMI, alcohol consumption, family history of OP, diabetes, TC, TG, HDL-C, CA, CRP, and PLT were controlled. BMI, body mass index; OP, osteoporosis; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; CA, calcium; C-reactive protein; PLT, platelet; PLR, platelet count/lymphocyte count; SII, platelet count × neutrophil count/lymphocyte count; NLR, neutrophil count/lymphocyte count; MLR, monocyte count/lymphocyte count.

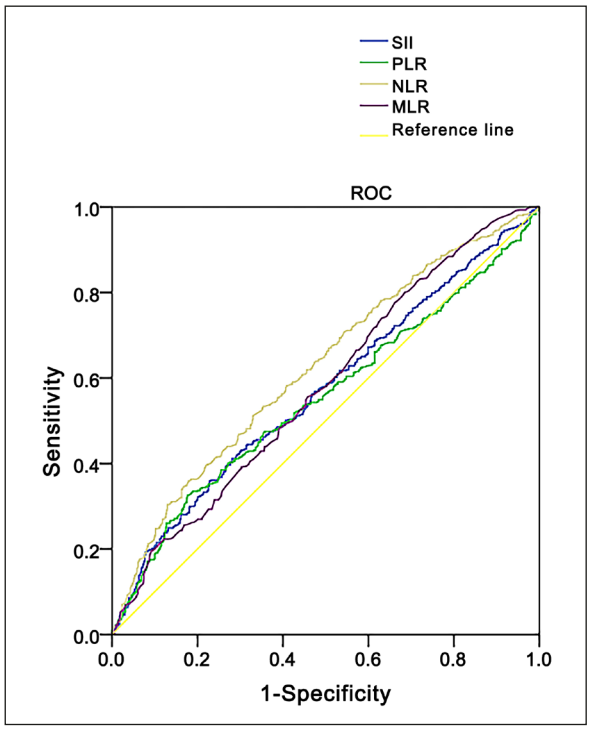

Figure 1. ROC curve for the associations of SII, PLR, NLR, and MLR with low BMD in postmenopausal women.

value (AUC = 0.624) (Figure 1 and Table IV). According to the principle of maximizing the Jordan index, the corresponding truncation values for SII, PLR, NLR, and MLR are 504.09, 131.87, 2.02, and 0.12, respectively. Therefore, SII > 504.09, PLR > 131.87, NLR > 2.02, and MLR > 0.12 were associated with an increased likelihood of OP.

Discussion

SII, NLR, MLR, and PLR are novel inflammatory markers that can comprehensively reflect the immune and inflammatory state of the body. However, few studies have investigated the associations between these inflammatory markers and OP. We investigated the relationships between SII, NLR, MLR, PLR, and BMD in postmenopausal women, as well as explored their predictive value for OP. Because NC, LC, MC, and PLT are measured routinely, the inflammatory markers evaluated in this study represent useful, simple, and economical parameters for clinical application.

Few studies have investigated the relationships between SII, PLR, NLR, MLR, and bone metabolism. However, previous studies investigated only one or two inflammatory indexes. Our study comprehensively evaluated the usefulness of SII, PLR, NLR, and MLR for predicting the risk of OP among postmenopausal women in a clinical setting. We found that SII, PLR, NLR, and MLR were negatively associated with the BMD, whereas increased levels of SII, PLR, NLR, and MLR were positively associated with an increased OP risk, even after adjusting for covariates. In line with this, compared to postmenopausal women in the lowest quartiles of SII, PLR, NLR, and MLR, those in the highest quartiles had higher OP risks at the lumbar spine (L2-L4), right FN, and TF.

To the best of our knowledge, this is the first study of the relationships of SII, PLR, NLR, and MLR with OP among postmenopausal women. Our results have highlighted the importance of immuno-inflammatory responses in the OP risk. A prospective cohort study of 238 postmenopausal women showed that women with postmenopausal osteoporosis had higher SII values than controls[22]. Another study[28] of 413 postmenopausal women showed negative associations between the SII and BMD of the femoral neck. Ye et al[29] found an association between increased bone loss and OP severity with a low LC ratio and high NC and MC ratios among 487 individuals from China. Yilmaz et al[30] reported a significant negative correlation between NLR and BMD values of the lumbar spine, concluding that NLR is a better predictor of postmenopausal OP than the

Table IV. Prediction value of SII, PLR, NLR, and MLR for OP.

	AUC	95% CI	*p*	Sensitivity (%)	Specificity (%)	Cutoff value
SII	0.569	0.533-0.605	< 0.001	35.9	77.2	504.09
PLR	0.552	0.516-0.589	0.005	32.6	82.3	131.87
NLR	0.624	0.589-0.659	< 0.001	51.2	67.0	2.02
MLR	0.578	0.543-0.614	< 0.001	80.1	31.4	0.12

AUC, area under the curve; OP, osteoporosis; PLR, platelet count/lymphocyte count; SII, platelet count × neutrophil count/lymphocyte count; NLR, neutrophil count/lymphocyte count; MLR, monocyte count/lymphocyte count.

CRP level. Eroglu and Karatas[31] demonstrated a significantly increased PLR, but not NLR, in the OP group of postmenopausal women. Two other studies[22,32] confirmed that the BMD was negatively correlated with NLR among OP individuals from China. In the present study, we investigated the association among individuals representative of the general population to obtain valid and representative results. Consistent with a previous study[25], we found a relationship between the SII and FN-BMD among postmenopausal women. Furthermore, we found that SII, PLR, NLR, and MLR were associated with decreased BMD at the lumbar spine and TF.

In the present study, logistic regression models showed that the SII, PLR, NLR, and MLR were associated with the risks for postmenopausal OP. Huang and Li[33] found that an increased NLR was associated with an increased risk of OP among Chinese postmenopausal women without diabetes. In the present study, although the ROC curves showed significant differences among SII, PLR, NLR, and MLR for detecting OP, NLR had a relatively high discriminatory power for OP (AUC = 0.624). The ROC curve analysis suggested that NLR > 2.02 had a high efficacy for discriminating between individuals with and without OP. Further studies are needed to explore the clinical usefulness of NLR as an early marker of OP.

Using the World Health Organization diagnostic criteria[34], osteopenia and OP were diagnosed in cases of BMD 1-2.5 and ≥ 2.5 SDs below the mean, respectively. Although blood levels of certain inflammatory cytokines have a good predictive value, such as osteoprotegerin and receptor activator of nuclear factor-κB ligand, these are not commonly used due to the complex requirements of laboratory monitoring[29].

Normal bone formation and function depend on homeostasis between osteogenesis and bone resorption[35]. Under physiological conditions, these two processes occur in an orderly manner, called bone remodeling[36]. Bone remodeling begins with the absorption of mineralized bone by osteoclasts, followed by osteoblast-mediated formation of bone matrix, which is subsequently mineralized[37]. However, the process of bone remodeling is affected by physiological alterations, including estrogen deficiency, drugs, aging, and disease states. Imbalance of bone remodeling results in bone loss and, ultimately, OP. Activation of the inflammatory microenvironment and a compromised immune system significantly affect the bone microarchitecture[38]. Dysfunctional lymphocytes can initiate cascades of inflammatory chemokines and cytokines that trigger the aggregation of inflammatory cells[39]. These changes lead to disruption of bone homeostasis, leading to osteoclast-induced bone resorption. Therefore, the immune-inflammation imbalance can cause osteopenia and reduce bone strength and density, ultimately leading to OP.

Although OP is traditionally considered an endocrine disease[40], multiple studies[7-10] have demonstrated interactive communication between the immune and skeletal systems in OP. Osteoclast and osteoblast activities are regulated by various soluble mediators secreted from immune cells, including chemokines, cytokines, and growth factors. Several studies[41] have shown that estrogen deficiency can lead to the activation of multiple immune cells that produce pro-inflammatory factors, which induce dysfunctional bone remodeling and decreased bone density in postmenopausal women. Besides, the post-menopause years might be the time when women can benefit more from physical exercise and a balanced diet in contrast to the negative effects of aging[42]. SII, PLR, NLR, and MLR are likely to be strongly influenced by estrogen levels. However, further studies are needed to determine the role of estrogen and inflammation in the development of postmenopausal OP. Sun et al[43] found that the use of standard doses of estrogen (0.625 mg) has been shown to be clinically superior to lower doses. However, in terms of safety, there is a need to be alert to the possible risks associated with the use of standard doses of estrogen and higher-quality clinical trials are needed to provide the basis for an optimal balance of benefit and risk. As SII, PLR, NLR, and MLR are indicators of the general level of inflammation in the human body, specific inflammatory indexes should be developed to allow more comprehensive studies.

The strengths of our study include the use of statistical models that adjusted for several important confounders, which increased the generalizability of our results. In addition, we analyzed the SII, PLR, NLR, and MLR as continuous variables to reduce the contingency in the statistical analysis and enhance the robustness of our results. Furthermore, our study's indexes differed from those used in previous studies in the literature. Our results provide new evidence on the associations of BMD with SII, PLR, NLR, and MLR among the general postmenopausal women.

Limitations

Certain limitations of this study should also be considered. First, we could not evaluate the temporal relationship of inflammatory indexes with OP because of the retrospective cross-sectional study design. Therefore, prospective studies are needed to determine the causal nature of these relationships. Second, our study only adjusted for some lifestyle and demographic variables, whereas many additional genetic and non-genetic factors are linked to the pathogenesis of OP. Third, we excluded women with infections, lymphoma, or autoimmune diseases, which may have influenced the SII, PLR, NLR, MLR, and BMD values and limited the generalizability of our results. Further studies are needed to verify our results by accounting for the multiple residual confounders.

Conclusions

The SII, PLR, NLR, and MLR had significant negative associations with the BMD of the lumbar spine (L2-L4), right FN, and TF in postmenopausal women. Elevated levels of SII, PLR, NLR, and MLR indicate an increased OP risk. In particular, NLR > 2.02 has a high efficacy for discriminating women with OP. Therefore, NLR may be a valuable and convenient inflammatory marker for the prediction of OP risk. Our study provides new evidence for the role of immuno-inflammatory responses in bone loss in women. Postmenopausal women with a high level of SII, PLR, NLR, and MLR should be informed regarding their potential risk of OP. However, given the inherent limitations of our study, further longitudinal population-based and experimental studies are needed to verify our findings.

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Authors' Contributions

ZXJ contributed to the study conceptualization, methodology, analysis, and drafting of the article; ZH, ZD, YDD, and QJ contributed to data acquisition, study validation, and reviewing the article; ZYR contributed to the study conceptualization, methodology, and reviewing the article; ZYZ contributed to the study conceptualization, methodology, project administration, and drafting and reviewing the article. All authors read and approved the version to be published and agreed to be accountable for all aspects of the work.

Conflict of Interest

All the authors declare that they have no conflict of interest.

Ethics Approval

All procedures performed in the study involving human participants were in accordance with the ethical standards of the National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved on March 16, 2020, by the Research Ethics Committee of the Third Hospital of Hebei Medical University (No. W2020-014-1).

Informed Consent

All patients signed the informed consent form.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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