

# Systemic Inflammation Markers Associated with Bone Mineral Density in perimenopausal and Postmenopausal Women

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**Objective:** The aim of this research was to determine whether systemic inflammatory indicators, including aggregate index of systemic inflammation (AIS), neutrophils lymphocyte to platelet ratio (NLPR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI), are related to bone mineral density (BMD) in perimenopausal and postmenopausal women.

**Methods:** One hundred and eighty-one perimenopausal and 390 postmenopausal women were enrolled in this cross-sectional study. Continuous variables by analysis of variance and Kruskal Wallis test for comparing the clinical characteristics. Linear regression analysis was conducted to investigate the associations between inflammatory indicators with BMD. The comparison between the subgroups was performed using the nonparametric test and the *T*-test.

**Results:** AIS, NLPR, SII, and SIRI quartile values were inversely associated with BMD in menopausal women ( $P = 0.021$ ;  $P = 0.047$ ;  $P < 0.001$ ;  $P < 0.001$ , respectively). After adjusting for confounding factors, four inflammatory indicators remained significantly associated with BMD (all  $P$  for trend  $< 0.001$ ). Analysis according to menopausal status demonstrated that AIS, SII, and SIRI were significantly correlated with mean femoral neck BMD in postmenopausal women ( $P$  for trend = 0.015, 0.004, and 0.001), but not significantly associated with BMD in perimenopausal women ( $P$  for trend = 0.248, 0.054, and 0.352) after adjustment for covariates.

**Conclusion:** The quartile values of AIS, SII, and SIRI were inversely associated with BMD in postmenopausal women, following adjustment for individual variables, hormone profiles and glucolipid metabolism profiles. AIS, SII, and SIRI have potential to be important tools for screening and prevention of bone loss in menopausal women in future clinical practice.

**Keywords:** menopause, female, femur neck, cross-sectional studies, regression analysis, inflammation

## Introduction

Postmenopausal osteoporosis (PMOP) is a primary disease characterized by increased bone turnover and decreased bone mass with concomitant skeletal fragility, leading to an increased risk of fractures.<sup>1</sup> Among women in China  $\geq 40$  years, the prevalence of osteoporosis was 20.6% (95% confidence interval, 19.3%–22.0%) in 2021; however, despite the high prevalence of PMOP, only 1.4% of women with osteoporosis received treatment to prevent fractures.<sup>2</sup> The prevalence of PMOP is increasing with the aging of the global population, causing a heavy economic and medical burdens.<sup>3</sup> Accordingly, it is important to explore prevail biomarkers that can be applied for the early identification of bone loss in menopausal women.

Hip fracture is a very serious health problem for an individual, that often leads to a decline in mobility and may reduce life expectancy.<sup>4</sup> Bone loss is closely related to inflammation and the immune system, and the skeletal system is exquisitely sensitive to persistent inflammatory burden.<sup>5</sup> Various chronic inflammatory diseases are accompanied by osteoporosis, including osteoarthritis, gout, psoriasis, and rheumatoid arthritis, which can contribute to disability and increased mortality.<sup>6–8</sup> Previous studies have indicated that the rapid decrease in estrogen during menopause increases inflammatory responses, which enhance bone resorption and bone remodeling.<sup>9–11</sup> Further, the sudden decline of estrogen in older women has a direct negative effect on bone, while postmenopausal women also show gradual development of a chronic low-grade inflammatory state, and the indirect effect of this altered immune status may also contribute to sustained bone destruction.<sup>12</sup>

There have been extensively studies of blood indexes in patients with osteoporosis, including C reactive protein (CRP) levels, platelet to lymphocyte ratio (PLR), monocyte lymphocyte ratio (MLR) and neutrophil to lymphocyte ratio (NLR).<sup>13,14</sup> The systemic immune-inflammation index (SII) is a new inflammation marker that is strongly predictive of tumor prognosis and immune response state.<sup>15,16</sup> Clear associations between SII and inflammatory conditions have been observed.<sup>17,18</sup> In our previous study, we found that quartile SII levels were negatively correlated with femoral neck bone mineral density (BMD) in postmenopausal women.<sup>19</sup> The systemic inflammation response index (SIRI) is reported to be an effective predictor of survival of patients with breast cancer or aneurysmal subarachnoid hemorrhage.<sup>20,21</sup> While very few studies have evaluated its relationship with PMOP. Neutrophil to lymphocyte\*platelet ratio (NLPR) was reported as a promising predictor of acute kidney injury.<sup>22,23</sup> Further, Zinellu et al found that the aggregate index of systemic inflammation (AISI) can predict idiopathic pulmonary fibrosis mortality and guide patient management.<sup>24</sup>

Data regarding SIRI, NLPR, SII, and AISI in patients with osteoporosis are limited. Here, we aimed to investigate the relationship between these combined systemic indicators of inflammation and BMD and evaluate whether they have potential as markers for early identification of decreased BMD in perimenopausal and postmenopausal women.

## Methods

### Study Population

This cross-sectional survey was included 571 women, 181 subjects undergoing menopausal transition and 390 subjects with postmenopausal status, determined according to the 2011 Stages of Reproductive Aging Workshop +10 recommendations.<sup>25</sup> Menopausal transition is marked by irregular menstrual cycles, while postmenopausal women had experienced natural menopause (no menstrual bleeding for 1 year), accompanied by menopause symptoms. Patients (aged from 40 to 65 years old) were admitted to the clinic of Hangzhou Women's Hospital from October 2016 to November 2021. The exclusion criteria were as follows: missing more than three laboratory results; taking medication that could affect bone density and bone metabolism; diseases history that could affect bone metabolism, such as hematological diseases, immune diseases, or malignant tumor. The research was approved by the institutional ethics committee of the Hangzhou Women's Hospital (docket#2021-03-004). All subjects submitted a medical informed consent document and were informed the research purposes. Our manuscript complies with the Declaration of Helsinki.

### Biochemical Measurements and Instruments

Venous blood samples (2–3 mL) were collected after overnight fasting for  $\geq 8$  h. A Mindray CAL 8000 cell analysis line was used to measure white blood cells (WBC), including neutrophils (N), platelets (PLT), monocytes (M), and lymphocytes (L). Four inflammatory indexes were also calculated to comprehensively reflect individual inflammation status, as follows: AISI =  $N \times PLT \times M/L$ ; NLPR =  $N/(L \times PLT)$ ; SII =  $N \times PLT/L$ ; and SIRI =  $N \times M/L$ . Estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (T), thyroid-stimulating hormone (TSH) and fasting insulin levels were measured using a chemiluminescence methods (Beckman Coulter UniCel Dxl-800). For perimenopausal women, hormone assessments were performed in days 1–5 of the menstrual cycle. Fasting glucose, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), C-reactive protein (CRP), and homocysteine (HCY) levels were measured using a Beckman Coulter AU5821 chemistry analyzer. Biochemical parameters were evaluated using commercially available kits and standard automated laboratory methods,

according to relevant protocols. The formula for calculation of homeostatic model assessment index of insulin resistance (HOMA-IR) was as follows:  $[\text{fasting insulin (pmol/L)} \times \text{fasting glucose (mmol/L)}] / (22.5 \times 6.965)$ . A specialist nurse measured patient weight and height, and body mass index (BMI) was calculated as weight/height squared. Femoral neck BMD was measured by dual-energy X-ray absorptiometry (DPX Bravo, Ge Medical Systems China Ltd.). All BMD scans were performed by the same technician and the subjects were not carrying removable metal objects.

## Statistical Analysis

BM-SPSS 22.0 statistics (IBM Inc., Armonk, NY, USA) was used for statistical analyses. Data are expressed as mean  $\pm$  standard deviation. We analyzed continuous variables by analysis of variance (Conforming to homogeneity of variance) and Kruskal-Wallis test (heterogeneity of variance) for comparing the clinical characteristics across quartiles of AISI, NLPR, SII, and SIRI (Q1–Q4, AISI groups; Q5–Q8, NLPR groups; Q9–Q12, SII groups; Q13–Q16, SIRI groups). Multiple comparisons were made between the four groups with statistical significance. The multiple comparison method of parametric test was LSD, and the nonparametric was Nemenyi test, see [STables 1–5](#). Associations between combined inflammatory indices and BMD were assessed using linear regression models. Four models were established to evaluate the possibility of confounding; Model 1 included adjustments for BMI and age; Model 2 was based on model 1, but included further adjustments for FSH, LH, E2, T, and TSH; Model 3 included the adjustments of model 2 plus HCY, CRP, HDL, LDL, and triglycerides; Model 4 included the adjustments in model 3 plus fasting glucose and fasting insulin. Linear trends of inflammatory index quartiles were evaluated by modeling the median values of all quartiles as continuous variables. Subgroup analysis was conducted based on menopause status, and comparisons between the two groups were performed using a nonparametric test (uneven square difference between the two groups) and the *T*-test. Tests were two-sided and  $P < 0.05$  indicated statistical significance.

## Results

### Characteristics of Study Participants

Based on relevant data from the 571 participants, we calculated the inflammatory markers, AISI, NLPR, SII, and SIRI, and divided the results for each index into four groups based on quartile values.

Women with AISI values in the highest quartile had significantly higher serum levels of WBC, CRP, triglycerides, fasting glucose, fasting insulin, and HOMA-IR than those in the lower quartiles. In addition, women with AISI levels in higher quartiles had significantly lower BMD (groups Q1–Q4,  $P = 0.021$ , one-way ANOVA) ([Table 1](#)). Hence, our findings indicated that the higher AISI was significantly associated with lower BMD; however, there were no significant associations of BMD with age, BMI, or serum levels of FSH, LH, total T, TSH, HDL, LDL, or HCY. Regarding NLPR, BMI and LDL differed significantly among groups Q5–Q8, as did femoral neck BMD ( $P = 0.047$ ) ([Table 2](#)); there was no significant difference in other variables. There were significant differences in serum WBC, CRP, fasting glucose, fasting insulin, and HOMA-IR levels among groups Q9–Q12 of SII. Further, there was significant difference in femoral neck BMD among groups Q9–Q12 ( $P < 0.001$ ); as shown in [Table 3](#), lower BMD was associated with higher SII (0.887, 0.862, 0.853, and 0.832 g/cm<sup>2</sup>, respectively). There were no significant differences in age, BMI, FSH, LH, E2, total T, TSH, triglycerides, HDL, LDL, or HCY among the four SII groups.

There were significant differences in serum WBC, triglycerides, fasting glucose, and HOMA-IR among SIRI groups Q13–Q16. Further, higher quartile SIRI levels were significantly associated with lower BMD in groups Q13–Q16 (0.870, 0.859, 0.875, 0.827,  $P = 0.001$ , [Table 4](#)).

Overall, although several other variables differed among patients with inflammatory index values across the four quartiles, associations between quartiles and femoral neck BMD were consistently significant, with a trend toward association of higher values for the four inflammatory indexes with lower BMD.

**Table 1** Participant Characteristics Classified According to Quartile Values of AISI

Variable	Overall n=571	Q1 (19.950–68.174) n=143 Mean (SD)	Q2 (68.174–96.055) n=142 Mean (SD)	Q3 (96.055–134.682) n=143 Mean (SD)	Q4 (134.682–1410.847) n=143 Mean (SD)	P
Age (year)	51.24 (4.49)	51.24 (4.47)	51.43 (4.49)	50.84 (4.54)	51.45 (4.50)	0.641
BMI (kg/m <sup>2</sup> )	22.12 (2.62)	22.11 (2.93)	22.08 (2.30)	22.23 (2.57)	22.04 (2.68)	0.936
FSH (IU/L)	72.21 (30.90)	73.20 (29.21)	75.12 (30.24)	71.97 (32.93)	68.58 (31.04)	0.336
LH (IU/L)	34.18 (15.15)	34.21 (13.84)	36.09 (15.17)	33.49 (16.26)	32.95 (15.19)	0.323
E2 (pmol/L) <sup>a</sup>	132.20 (148.02)	121.85 (117.43)	119.12 (122.53)	156.90 (209.80)	130.83 (119.76)	0.011*
Total T (nmol/L)	1.16 (0.65)	1.19 (0.63)	1.14 (0.66)	1.12 (0.57)	1.19 (0.74)	0.748
TSH (IU/L)	2.16 (1.42)	2.11 (1.38)	2.22 (1.47)	2.21 (1.55)	2.11 (1.28)	0.866
WBC (10 <sup>9</sup> /L) <sup>a</sup>	5.28 (1.28)	4.39 (0.80)	4.79 (0.85)	5.53 (1.00)	6.38 (1.39)	< 0.001*
CRP (mg/L) <sup>a</sup>	1.47 (2.08)	1.78 (2.07)	1.32 (2.76)	1.65 (1.77)	1.78 (2.07)	0.024*
Triglycerides (mmol/L) <sup>a</sup>	1.28 (0.72)	1.10 (0.60)	1.31 (0.75)	1.34 (0.67)	1.37 (0.83)	0.007*
HDL (mmol/L)	1.55 (0.37)	1.59 (0.31)	1.55 (0.47)	1.53 (0.31)	1.55 (0.37)	0.636
LDL (mmol/L)	3.01 (0.70)	2.90 (0.79)	3.01 (0.70)	3.06 (0.66)	3.06 (0.63)	0.172
HCY (mmol/L)	11.80 (14.73)	12.16 (14.06)	10.45 (2.33)	12.43 (18.73)	12.17 (17.75)	0.665
Fasting glucose (mmol/L)	5.19 (0.64)	5.09 (0.46)	5.17 (0.55)	5.17 (0.53)	5.33 (0.90)	0.074
Fasting insulin (pmol/L) <sup>a</sup>	37.29 (20.14)	31.92 (16.45)	34.68 (14.92)	41.52 (22.78)	41.00 (23.46)	< 0.001*
HOMA-IR <sup>a</sup>	1.27 (0.86)	1.05 (0.58)	1.17 (0.61)	1.39 (0.86)	1.45 (1.18)	< 0.001*
The femoral neck BMD (g/cm <sup>2</sup> ) <sup>a</sup>	0.858 (0.108)	0.875 (0.115)	0.863 (0.110)	0.860 (0.104)	0.836 (0.101)	0.021*

**Notes:** \*Statistically significant difference. <sup>a</sup>Multiple comparisons had the statistically significant.

**Abbreviations:** AISI, aggregate index of systemic inflammation; BMD, bone mineral density; CRP, C reactive protein; WBC, white blood cell; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HCY, homocysteine; BMI, body mass index; HOMA-IR, homeostatic model assessment index of insulin resistance.

**Table 2** Participant Characteristics Classified According to Quartile Values of NLPR

Variable	Overall n=571	Q5 (0.002–0.006) n=143 Mean (SD)	Q6 (0.006–0.008) n=143 Mean (SD)	Q7 (0.008–0.011) n=143 Mean (SD)	Q8 (0.011–0.035) n=142 Mean (SD)	P
Age (year)	51.24 (4.49)	51.37 (4.20)	50.58 (4.23)	51.73 (4.70)	51.28 (4.78)	0.177
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	22.12 (2.62)	22.68 (2.64)	22.20 (2.81)	21.99 (2.48)	21.60 (2.46)	0.005*
FSH (IU/L)	72.21 (30.90)	69.59 (27.98)	73.49 (30.35)	74.98 (33.43)	70.78 (31.61)	0.436
LH (IU/L)	34.18 (15.15)	32.53 (13.30)	34.62 (14.33)	35.78 (16.48)	33.79 (16.23)	0.321
E2 (pmol/L)	132.20 (148.02)	120.72 (98.96)	120.25 (102.45)	141.63 (189.61)	146.29 (177.11)	0.793
Total T (nmol/L)	1.16 (0.65)	1.16 (0.62)	1.12 (0.55)	1.22 (0.67)	1.14 (0.76)	0.549
TSH (IU/L)	2.16 (1.42)	2.01 (1.27)	2.10 (1.22)	2.20 (1.68)	2.34 (1.46)	0.250
WBC (10 <sup>9</sup> /L)	5.28 (1.28)	5.20 (1.06)	5.19 (1.20)	5.25 (1.35)	5.469 (1.47)	0.541
CRP (mg/L)	1.47 (2.08)	1.50 (2.81)	1.46 (1.55)	1.49 (1.95)	1.42 (1.82)	0.989
Triglycerides (mmol/L)	1.28 (0.72)	1.29 (0.74)	1.31 (0.68)	1.30 (0.84)	1.23 (0.62)	0.821
HDL (mmol/L)	1.55 (0.37)	1.56 (0.35)	1.56 (0.42)	1.56 (0.35)	1.55 (0.35)	0.999
LDL (mmol/L) <sup>a</sup>	3.01 (0.70)	3.11 (0.71)	3.07 (0.77)	2.97 (0.61)	2.88 (0.68)	0.022*
HCY (mmol/L)	11.80 (14.73)	12.11 (18.50)	11.82 (13.82)	12.24 (17.77)	11.04 (4.66)	0.903
Fasting glucose (mmol/L)	5.19 (0.64)	5.17 (0.47)	5.17 (0.62)	5.19 (0.72)	5.24 (0.71)	0.759
Fasting insulin (pmol/L)	37.29 (20.14)	37.27 (18.49)	36.33 (21.56)	39.03 (22.90)	36.52 (17.16)	0.662
HOMA-IR	1.27 (0.86)	1.25 (0.68)	1.22 (0.82)	1.35 (1.13)	1.25 (0.72)	0.579
The femoral neck BMD (g/cm <sup>2</sup> ) <sup>a</sup>	0.858 (0.108)	0.866 (0.100)	0.871 (0.115)	0.860 (0.109)	0.837 (0.109)	0.047*

**Notes:** \*Statistically significant difference. <sup>a</sup>Multiple comparisons had the statistically significant.

**Abbreviations:** NLPR, neutrophils lymphocyte to platelet ratio; BMD, bone mineral density; CRP, C reactive protein; WBC, white blood cell; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HCY, homocysteine; BMI, body mass index; HOMA-IR, homeostatic model assessment index of insulin resistance.

**Table 3** Participant Characteristics Classified According to Quartile Values of SII

Variable	Overall n=571	Q9 (107.811–269.500) n=143 Mean (SD)	Q10 (269.500–356.148) n=143 Mean (SD)	Q11 (356.148–472.000) n=143 Mean (SD)	Q12 (472.000–2709.000) n=142 Mean (SD)	P
Age (year)	51.24 (4.49)	51.30 (4.43)	51.21 (4.70)	51.55 (4.40)	50.90 (4.46)	0.675
BMI (kg/m <sup>2</sup> )	22.12 (2.62)	22.21 (3.07)	22.01 (2.16)	22.24 (2.48)	22.01 (2.72)	0.814
FSH (IU/L)	72.21 (30.90)	73.11 (29.54)	75.69 (29.19)	71.60 (31.83)	68.42 (32.77)	0.249
LH (IU/L)	34.18 (15.15)	33.80 (13.45)	36.54 (15.72)	33.36 (15.08)	33.02 (16.11)	0.185
E2 (pmol/L)	132.20 (148.02)	119.22 (106.69)	129.11 (166.37)	1443.79 (180.45)	136.70 (126.90)	0.539
Total T (nmol/L)	1.16 (0.65)	1.13 (0.57)	1.16 (0.62)	1.16 (0.65)	1.18 (0.76)	0.945
TSH (IU/L)	2.16 (1.43)	2.23 (1.35)	2.00 (1.36)	2.31 (1.62)	2.10 (1.32)	0.258
WBC (10 <sup>9</sup> /L) <sup>a</sup>	5.28 (1.28)	4.55 (0.99)	5.17 (1.01)	5.32 (1.18)	6.06 (1.44)	<0.001*
CRP (mg/L) <sup>a</sup>	1.47 (2.08)	1.10 (1.46)	1.56 (2.92)	1.41 (1.41)	1.81 (2.12)	0.001*
Triglycerides (mmol/L)	1.28 (0.72)	1.15 (0.64)	1.33 (0.82)	1.35 (0.61)	1.29 (0.78)	0.069
HDL (mmol/L)	1.55 (0.37)	1.56 (0.33)	1.57 (0.45)	1.53 (0.32)	1.57 (0.36)	0.739
LDL (mmol/L)	3.01 (0.70)	2.92 (0.73)	2.99 (0.71)	3.08 (0.69)	3.04 (0.66)	0.242
HCY (mmol/L)	11.80 (14.73)	12.19 (14.00)	10.59 (3.14)	10.62 (2.23)	13.83 (25.65)	0.705
Fasting glucose (mmol/L) <sup>a</sup>	5.19 (0.64)	5.06 (0.44)	5.15 (0.51)	5.24 (0.67)	5.31 (0.83)	0.004*
Fasting insulin (pmol/L) <sup>a</sup>	37.29 (20.14)	33.35 (16.99)	34.45 (15.26)	40.07 (22.36)	41.31 (23.73)	0.003*
HOMA-IR <sup>a</sup>	1.27 (0.86)	1.09 (0.60)	1.15 (0.59)	1.36 (0.85)	1.46 (1.19)	0.001*
The femoral neck BMD (g/cm <sup>2</sup> ) <sup>a</sup>	0.858 (0.108)	0.887 (0.117)	0.862 (0.109)	0.853 (0.101)	0.832 (0.100)	<0.001*

**Notes:** \*Statistically significant difference. <sup>a</sup>Multiple comparisons had the statistically significant.

**Abbreviations:** SII, systemic immune-inflammation index; BMD, bone mineral density; CRP, C reactive protein; WBC, white blood cell; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HCY, homocysteine; BMI, body mass index; HOMA-IR, homeostatic model assessment index of insulin resistance.

**Table 4** Participant Characteristics Classified According to Quartile Values of SIRI

Variable	Overall n=571	Q13(0.105–0.347) n=144 Mean (SD)	Q14(0.347–0.452) n=145 Mean (SD)	Q15(0.452–0.620) n=147 Mean (SD)	Q16(0.620–4.687) n=135 Mean (SD)	P
Age (year)	51.24 (4.49)	50.89 (4.20)	51.18 (4.46)	51.46 (4.73)	51.43 (4.59)	0.686
BMI (kg/m <sup>2</sup> )	22.12 (2.62)	22.20 (2.56)	22.07 (2.74)	22.29 (2.39)	21.89 (2.81)	0.598
FSH (IU/L)	72.21 (30.90)	72.41 (27.73)	73.58 (32.34)	72.72 (30.52)	69.98 (33.07)	0.794
LH (IU/L)	34.18 (15.15)	33.48 (12.78)	34.96 (15.92)	35.08 (15.87)	33.12 (15.86)	0.797
E2 (pmol/L)	132.20 (148.02)	112.47 (90.01)	122.69 (117.97)	158.91 (207.26)	134.37 (146.59)	0.252
Total T (nmol/L)	1.16 (0.65)	1.25 (0.66)	1.08 (0.63)	1.15 (0.56)	1.17 (0.74)	0.201
TSH (IU/L)	2.16 (1.42)	1.99 (1.32)	2.29 (1.57)	2.25 (1.46)	2.11 (1.30)	0.265
WBC (10 <sup>9</sup> /L) <sup>a</sup>	5.28 (1.28)	4.48 (0.87)	4.98 (0.89)	5.39 (1.05)	6.31 (1.51)	< 0.001*
CRP (mg/L)	1.47 (2.08)	1.31 (2.69)	1.25 (1.56)	1.62 (1.81)	1.69 (2.08)	0.194
Triglycerides (mmol/L) <sup>a</sup>	1.28 (0.72)	1.12 (0.61)	1.32 (0.71)	1.32 (0.69)	1.36 (0.84)	0.022*
HDL (mmol/L)	1.55 (0.37)	1.60 (0.34)	1.54 (0.43)	1.55 (0.34)	1.54 (0.35)	0.441
LDL (mmol/L)	3.01 (0.70)	2.99 (0.82)	3.07 (0.68)	2.96 (0.66)	3.01 (0.62)	0.551
HCY (mmol/L)	11.80 (14.73)	10.65 (2.88)	13.16 (22.72)	11.14 (4.20)	12.29 (18.35)	0.467
Fasting glucose (mmol/L)	5.19 (0.64)	5.15 (0.50)	5.18 (0.59)	5.12 (0.41)	5.33 (0.93)	0.499
Fasting insulin (pmol/L) <sup>a</sup>	37.29 (20.14)	31.68 (13.50)	37.03 (21.53)	41.31 (20.94)	39.16 (22.37)	< 0.001*
HOMA-IR <sup>a</sup>	1.27 (0.86)	1.06 (0.52)	1.26 (0.86)	1.37 (0.74)	1.39 (1.17)	0.001*
The femoral neck BMD (g/cm <sup>2</sup> ) <sup>a</sup>	0.858 (0.108)	0.870 (0.103)	0.859 (0.116)	0.875 (0.108)	0.827 (0.100)	< 0.001*

**Notes:** \*Statistically significant difference. <sup>a</sup>Multiple comparisons had the statistically significant.

**Abbreviations:** SIRI, systemic inflammation response index; BMD, bone mineral density; CRP, C reactive protein; WBC, white blood cell; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HCY, homocysteine; BMI, body mass index; HOMA-IR, homeostatic model assessment index of insulin resistance.

## Model for Prediction of Femoral Neck BMD Based on Inflammatory Markers

To assess the potential for confounding, we established a series of models using multivariate linear regression analysis (Table 5). In the unadjusted model, mean femoral neck BMD decreased with increasing AISI levels. After adjustment for

**Table 5** Association of Systemic Inflammatory Blood Indexes and the Femoral Neck BMD Among Perimenopausal and Postmenopausal Women

	Quartile Median Value	Mean BMD (SD) (g/cm <sup>2</sup> ) <sup>a</sup>	Model 1 <sup>b</sup>			Model 2 <sup>c</sup>			Model 3 <sup>d</sup>			Model 4 <sup>e</sup>		
			β(SE)	f	P	β(SE)	f	P	β(SE)	f	P	β(SE)	f	P
<b>AISI</b>														
Q1	53.677	0.875 (0.115)	0.038	(0.012)	0.003*	0.039	(0.012)	0.002*	0.039	(0.013)	0.002*	0.037	(0.013)	0.004*
Q2	81.431	0.863 (0.110)	0.027	(0.012)	0.034*	0.026	(0.012)	0.035*	0.026	(0.013)	0.040*	0.025	(0.013)	0.049*
Q3	112.174	0.860 (0.104)	0.020	(0.012)	0.103	0.025	(0.013)	0.050*	0.024	(0.013)	0.056	0.022	(0.013)	0.081
Q4	173.54	0.836 (0.101)	0(Referent)			0(Referent)			0(Referent)			0(Referent)		
P for trend		0.021*	< 0.001*			<0.001*			<0.001*			<0.001*		
<b>NLPR</b>														
Q5	0.005	0.866 (0.100)	0.022	(0.013)	0.085	0.021	(0.013)	0.092	0.023	(0.013)	0.072	0.021	(0.013)	0.097
Q6	0.007	0.871 (0.115)	0.027	(0.013)	0.032*	0.027	(0.013)	0.036*	0.028	(0.013)	0.028*	0.026	(0.013)	0.037*
Q7	0.009	0.860 (0.109)	0.022	(0.013)	0.082	0.022	(0.013)	0.086	0.023	(0.013)	0.067	0.022	(0.013)	0.079
Q8	0.013	0.837 (0.109)	0(Referent)			0(Referent)			0(Referent)			0(Referent)		
P for trend		0.047*	< 0.001*			< 0.001*			< 0.001*			< 0.001*		
<b>SII</b>														
Q9	226.571	0.887 (0.117)	0.055	(0.012)	<0.001*	0.056	(0.012)	<0.001*	0.056	(0.012)	<0.001*	0.054	(0.013)	< 0.001*
Q10	312.378	0.862 (0.109)	0.031	(0.012)	0.012*	0.031	(0.012)	0.012*	0.031	(0.012)	0.013*	0.030	(0.013)	0.016*
Q11	397.879	0.853 (0.101)	0.022	(0.012)	0.079	0.024	(0.012)	0.050*	0.024	(0.012)	0.058	0.023	(0.012)	0.065
Q12	554.510	0.832 (0.100)	0(Referent)			0(Referent)			0(Referent)			0(Referent)		
P for trend		< 0.001*	< 0.001*			< 0.001*			< 0.001*			< 0.001*		
<b>SIRI</b>														
Q13	0.279	0.870 (0.103)	0.040	(0.013)	0.002*	0.039	(0.013)	0.002*	0.039	(0.013)	0.002*	0.037	(0.013)	0.004*
Q14	0.394	0.859 (0.116)	0.030	(0.013)	0.017*	0.030	(0.013)	0.018*	0.030	(0.013)	0.018*	0.028	(0.013)	0.024*
Q15	0.526	0.875 (0.108)	0.046	(0.013)	<0.001*	0.048	(0.013)	<0.001*	0.047	(0.013)	<0.001*	0.045	(0.013)	< 0.001*
Q16	0.780	0.827 (0.100)	0(Referent)			0(Referent)			0(Referent)			0(Referent)		
P for trend		< 0.001*	< 0.001*			< 0.001*			< 0.001*			< 0.001*		

**Notes:** <sup>a</sup>Non-adjusted and <sup>b</sup>adjusted for age (years), BMI. <sup>c</sup>Further adjusted for FSH, LH, E2, T, TSH. <sup>d</sup>Further adjusted for HCY, CRP, HDL, LDL, TG. <sup>e</sup>Further adjusted for fasting glucose (mmol/L), fasting insulin (pmol/L). Q1–Q4, AISI groups. Q5–Q8, NLPR groups. Q9–Q12, SII groups. Q13–Q16, SIRI groups. \*Statistically significant difference.

**Abbreviations:** AISI, aggregate index of systemic inflammation; NLPR, neutrophils lymphocyte to platelet ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; BMD, bone mineral density.



age and BMI (model 1), a significant inverse association remained between AISI levels and BMD across the quartiles ( $P$  for trend  $< 0.001$ ). Additional adjustment for FSH, LH, E2, T, and TSH (model 2) only modestly attenuated the results and the association remained significant ( $P$  for trend  $< 0.001$ ). Further adjustment for HCY, CRP, HDL, LDL (model 3), and fasting glucose and fasting insulin (model 4) had a minimal impact on the findings, with higher AISI level remaining significantly associated with lower BMD. In model 4, the regression coefficients for quartiles 1–3 of AISI versus quartile 4 were 0.037, 0.025, and 0.022, respectively ( $P$  for trend  $< 0.001$ ).

NLPR levels were linearly related to mean BMD. Unadjusted mean BMD values across groups Q5–Q8 were 0.866, 0.871, 0.860, and 0.837 g/cm<sup>2</sup>, respectively ( $P = 0.047$ ). After adjustment for age and BMI (model 1) the association was significant ( $P$  for trend  $< 0.001$ ). Further, following adjustment for individual variables, hormone profiles, and glucolipid metabolism profiles, higher NLPR level remained significantly associated with lower BMD ( $P$  for trend  $< 0.001$ ).

Mean BMD values in SII groups Q9–Q12 were 0.887, 0.862, 0.853, and 0.832 g/cm<sup>2</sup>, respectively ( $P < 0.001$ ). Application of the adjustments in models 1–4 modestly attenuated the association, but higher SII levels remained significantly associated with lower BMD (all  $P$  for trend  $< 0.001$ ). The model 4 regression coefficients for Q9–Q11 versus Q12 were 0.054, 0.030, and 0.023, respectively.

We also detected a negative association between SIRI levels and BMD in perimenopausal and postmenopausal women. Model 1–4 adjustments had minimal effects on the results ( $P$  for trend = 0.001,  $< 0.001$ ,  $< 0.001$ , and  $< 0.001$ , respectively). The model 4 regression coefficients for Q13–Q15 versus Q16 were 0.037, 0.028 and 0.045, respectively.

## Subgroup Analysis Based on Menopausal Status

To facilitate comparisons according to menopausal status, we stratified the data into perimenopausal and postmenopausal groups (Table 6; Figures 1–4). Mean BMD levels were marginally lower in postmenopausal women than those in perimenopausal women (0.852 vs 0.871 g/cm<sup>2</sup>). Among postmenopausal women, higher AISI levels were related to lower mean BMD, with regression coefficients larger than those generated by analysis of the entire study group ( $P$  for trend = 0.015). In contrast, among perimenopausal women, AISI levels were not significantly linearly associated with BMD ( $P$  for trend = 0.248). The association between NLPR levels and mean BMD also varied according to menopausal status, with no significant association in either perimenopausal ( $P$  for trend = 0.276) or postmenopausal ( $P$  for trend = 0.190) women. Among postmenopausal women, those with the highest SII and SIRI levels had a lower mean BMD than those with the lowest levels ( $P$  for trend = 0.004 and = 0.001, respectively); however, in perimenopausal women, associations with SII and SIRI were not significant ( $P$  for trend = 0.054,  $P$  for trend = 0.352). In addition, comparisons of inflammatory indices between the premenopausal and the postmenopausal groups showed that AISI differed significantly ( $P = 0.021$ ), while there were no significant differences in the other inflammatory indexes.

## Discussion

Here, we analyzed data obtained during 2016 to 2021, with the aim of assisting in the management of PMOP, to prevent fractures, depending on some easily accessible, simple inflammation indices; specifically, we investigated associations between systemic inflammatory indicators (AISI, NLPR, SII, and SIRI) and BMD in menopausal women. Associations between altered neutrophil, lymphocyte, monocyte, and bone homeostasis factors with osteoporosis have been reported previously.<sup>26,27</sup> Therefore, we hypothesized that predictive tools, such as AISI, NLPR, SII, and SIRI, based on measurements of neutrophils, lymphocytes, monocytes, and platelets, might represent superior, easy-to-use indices, which better reflect inflammatory status in the context of specific disease states.

To our knowledge, the inverse association between AISI and BMD in menopausal women detected in this study has not been observed previously. As summarized in Tables 1 and 5, menopausal women with the highest AISI levels had higher WBC, fasting glucose, and HOMA-IR levels than those with lower AISI levels. Further, AISI was negatively correlated with BMD, even after adjustment for age, BMI, metabolic profile, individual variables, hormone profile, and glucolipid metabolic profile. AISI is reported to be valuable for predicting length of stay in patients undergoing elective open thoracic surgery, as well as prognosis of patients with COVID-19 and idiopathic pulmonary fibrosis.<sup>28–30</sup> Few previous studies have assessed the relationship between AISI and BMD during the menopausal period, when participants are likely in a state of chronic inflammation.

**Table 6** Association of Systemic Inflammation Blood Indexes and the Femoral Neck BMD by Menopausal Status Group

	Quartile Median Value	Menopausal Status Group <sup>a</sup>							
		Perimenopause				Postmenopause			
		Number of Women (n=181)	Mean BMD (SD) (g/cm <sup>2</sup> ) <sup>b</sup>	β(SE) <sup>c</sup>	P	Number of Women (n=390)	Mean BMD (SD) (g/cm <sup>2</sup> ) <sup>b</sup>	β(SE) <sup>c</sup>	P
<b>AISI<sup>d</sup></b>		Total	0.871 (0.108)			Total	0.852 (0.108)		
Q1	53.677	32	0.869 (0.123)	0.021 (0.025)	0.41	111	0.877 (0.114)	0.044 (0.015)	0.004*
Q2	81.431	48	0.895 (0.113)	0.029 (0.022)	0.194	94	0.847 (0.105)	0.015 (0.015)	0.322
Q3	112.174	53	0.871 (0.096)	0.014 (0.022)	0.511	90	0.853 (0.108)	0.020 (0.016)	0.191
Q4	173.54	48	0.850 (0.104)	0(Reference)		95	0.829 (0.099)	0(Reference)	
P for trend		0.248				0.015*			
<b>NLPR<sup>e</sup></b>		Total	0.871 (0.108)			Total	0.852 (0.108)		
Q5	0.005	50	0.880 (0.097)	0.024 (0.022)	0.285	93	0.858 (0.098)	0.019 (0.016)	0.231
Q6	0.007	49	0.890 (0.122)	0.041 (0.022)	0.068	94	0.861 (0.111)	0.022 (0.015)	0.153
Q7	0.009	39	0.861 (0.095)	0.014 (0.023)	0.543	104	0.859 (0.114)	0.026 (0.015)	0.078
Q8	0.013	43	0.849 (0.114)	0(Reference)		99	0.832 (0.106)	0(Reference)	
P for trend		0.276				0.190			
<b>SII<sup>f</sup></b>		Total	0.871 (0.108)			Total	0.852 (0.108)		
Q9	226.571	37	0.904 (0.117)	0.060 (0.024)	0.013*	106	0.881 (0.117)	0.052 (0.015)	0.001*
Q10	312.378	47	0.872 (0.102)	0.026 (0.022)	0.248	96	0.857 (0.112)	0.031 (0.016)	0.046*
Q11	397.879	49	0.877 (0.105)	0.031 (0.022)	0.167	94	0.840 (0.097)	0.016 (0.015)	0.295
Q12	554.510	48	0.839 (0.105)	0(Reference)		94	0.828 (0.097)	0(Reference)	
P for trend		0.054				0.004*			
<b>SIRI<sup>g</sup></b>		Total	0.871 (0.108)			Total	0.852 (0.108)		
Q13	0.279	38	0.888 (0.116)	0.034 (0.023)	0.15	106	0.864 (0.098)	0.041 (0.016)	0.009*
Q14	0.394	51	0.871 (0.110)	0.014 (0.022)	0.511	94	0.852 (0.119)	0.034 (0.016)	0.032*
Q15	0.526	44	0.880 (0.107)	0.023 (0.023)	0.306	103	0.873 (0.109)	0.053 (0.015)	0.001*
Q16	0.780	48	0.849 (0.101)	0(Reference)		87	0.814 (0.098)	0(Reference)	
P for trend		0.352				0.001*			

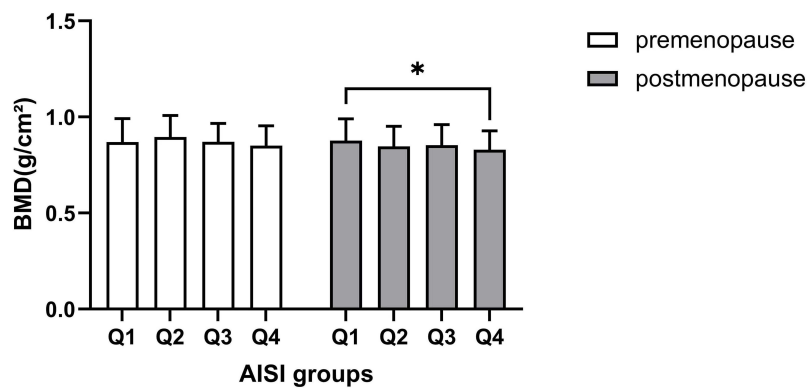
**Notes:** <sup>a</sup>Menopausal status. <sup>b</sup>Unadjusted mean BMD (SD) (not transformed). <sup>c</sup>Mean BMD values were transformed (negative reciprocal transformation) to improve normality. Results were adjusted for age (years), BMI, FSH, LH, E2, T, TSH, HCY, CRP, HDL, LDL, TG, fasting glucose, and fasting insulin. <sup>d</sup>Interaction with menopausal status: *P* = 0.021\*. <sup>e</sup>Interaction with menopausal status: *P* = 0.215. <sup>f</sup>Interaction with menopausal status: *P* = 0.163. <sup>g</sup>Interaction with menopausal status: *P* = 0.164. \*Statistically significant difference.

**Abbreviations:** AISI, aggregate index of systemic inflammation; NLPR, neutrophils lymphocyte to platelet ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; BMD, bone mineral density.

Some studies have indicated that NLR, MLR, and PLR values are higher in patients with osteoporosis than in those with osteopenia or healthy controls, suggesting their potential as inflammation indicators in osteoporosis.<sup>31,32</sup> There are few reports of analysis of NLPR, which is a relatively novel indicator with predictive value in patients with COVID-19,<sup>30</sup> and the relationship between NLPR and osteoporosis has not previously been reported. We observed that there was significant association between femoral neck BMD and NLPR, even following comprehensive adjustment (Models 1–4). Nevertheless, analysis of data divided into perimenopausal and postmenopausal groups generated a *P* for trend > 0.05 for NLPR, suggesting that correlation of this index with BMD was weaker than those of the other three inflammatory indexes.

Menopausal women with the highest SII had lower femoral neck BMD. After adjustment for age, BMI, metabolic profile, individual variables, hormone profile, and glucolipid metabolic profile, *P* for trend remained < 0.001 in postmenopausal women. Yang et al previously proposed that higher systemic immune inflammatory index is associated with an increased risk of hemorrhagic conversion in patients with anterior circulation acute ischemic stroke due to aorta

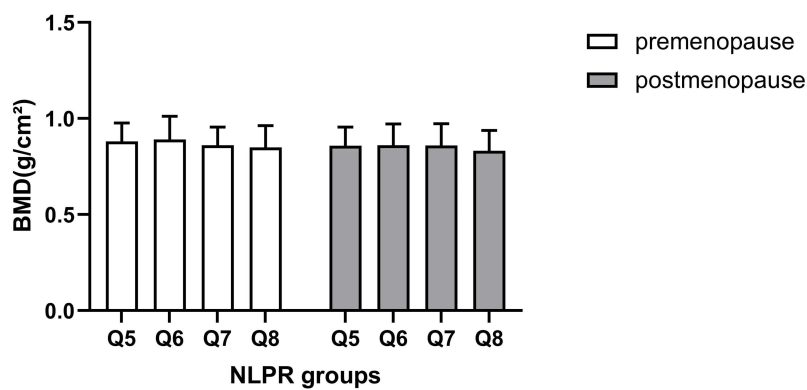




**Figure 1** Femoral neck BMD across quartiles of AISI in perimenopausal and postmenopausal women.

**Note:** \*Statistically significant difference.

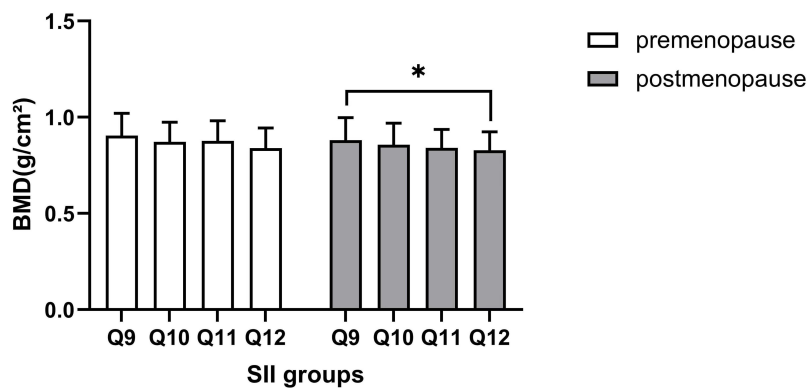
**Abbreviations:** AISI, aggregate index of systemic inflammation; BMD, bone mineral density.



**Figure 2** Femoral neck BMD across quartiles of NLPR in perimenopausal and postmenopausal women.

**Note:** \*Statistically significant difference.

**Abbreviations:** NLPR, neutrophils lymphocyte to platelet ratio; BMD, bone mineral density.

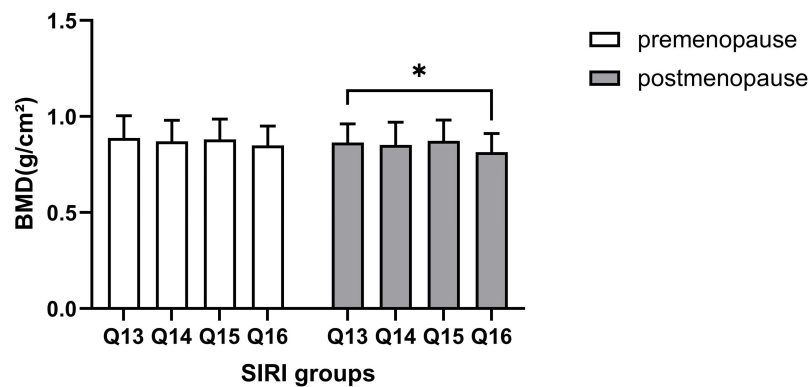


**Figure 3** Femoral neck BMD across quartiles of SII in perimenopausal and postmenopausal women.

**Note:** \*Statistically significant difference.

**Abbreviations:** SII, systemic immune-inflammation index; BMD, bone mineral density.

atherosclerosis.<sup>33</sup> Further, high SII is a novel factor for predicting overall survival in patients with pancreatic ductal adenocarcinoma, superior to PLR and NLR.<sup>34</sup> Moreover, a previous study indicated that quartile SII levels were negatively correlated with femoral neck BMD in postmenopausal women, consistent with our findings.<sup>19</sup>



**Figure 4** Femoral neck BMD across quartiles of SIRI in perimenopausal and postmenopausal women.

**Note:** \*Statistically significant difference.

**Abbreviations:** SIRI, systemic inflammation response index; BMD, bone mineral density.

T cells, B cells, and cytokines play key roles in regulating bone resorption.<sup>35,36</sup> B cells appear to be important in regulating osteoclast formation through the NF- $\kappa$ B ligand (RANKL)/osteoprotegerin signaling system. Activation of B cells by estrogen deficiency and pro-inflammatory conditions promotes bone resorption by secreting enhanced levels of granulocyte colony stimulating factor and RANKL during PMOP.<sup>37,38</sup> T lymphocytes can regulate inflammatory factors, thereby influencing bone cells and immune system hematopoietic function.<sup>39,40</sup> Neutrophils can affect bone homeostasis under estrogen deficiency, but their excessive activation increases osteoclast formation and promotes osteoblast apoptosis by releasing reactive oxygen species and stimulating RANKL signal transduction.<sup>41,42</sup>

High levels of SIRI and SII can predict adverse clinical outcomes in patients with aneurysmal subarachnoid hemorrhage.<sup>21</sup> In addition, SIRI can be used to predict overall survival of patients with advanced soft tissue sarcoma and the efficacy of follow-up drugs.<sup>43</sup> We found that fasting insulin and HOMA-IR are significantly related with AISI, SII and SIRI. There is few research about these systemic inflammation markers with insulin metabolism. Gasmi A et al describes the relationship between chronic low-grade inflammation and insulin.<sup>44</sup> The relationship between SIRI and BMD in menopausal women is poorly investigated. We found that menopausal women with the highest SIRI values had higher levels of WBC, triglycerides, fasting insulin, and HOMA-IR than those with lower SIRI levels. Further, SIRI was negatively correlated with BMD (Tables 4 and 5).

The limitations of this study include its cross-sectional design, which made it impossible to evaluate causal effects. Further, the computational complexity of the related indicators mean that they may be difficult to implement in clinical practice. Further, there is no clear consensus on standard threshold values for AISI, NLPR, SII, and SIRI, unlike other biomarkers. In addition, our research did not include some factors that may influence BMD, such as markers of bone turnover, ethnicity, and smoking status, among others. Moreover, we did not stratify subjects based on bone loss or osteoporosis compared with healthy groups for further follow-up. The number of perimenopausal women in this study was also relatively small, relative to that of postmenopausal women. Further multi-center studies with larger sample numbers are warranted to validate and confirm our results.

We found that, of the four indicators tested, all except NLPR were negatively correlated with mean femoral neck BMD in postmenopausal women (Table 6). Notably, the difference between quartiles was reflected in mean femoral neck BMD value in postmenopausal women, while in premenopausal women the difference was not significant, suggesting that inflammatory markers are more likely to be useful as predictors of BMD in postmenopausal women.

## Conclusion

Our results suggested that elevated levels of systemic inflammatory markers, determined using the AISI, SII, and SIRI indexes, are associated with lower femoral neck BMD in menopausal women. Further, AISI, SII, and SIRI can be used as independent predictors of BMD in postmenopausal women, and their utility is superior in postmenopausal women than in premenopausal women. In summary, AISI, SII, and SIRI are an economical, effective and independent predictor of bone loss in the older adult women.

## Abbreviations

AISI, aggregate index of systemic inflammation; ANOVA, analysis of variance; BMD, bone mineral density; BMI, body mass index; CRP, C reactive protein; E2, estradiol; FSH, follicle stimulating hormone; HCY, homocysteine; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment index of insulin resistance; L, lymphocytes; LDL, low-density lipoprotein; LH, luteinizing hormone; M, monocytes; MLR, monocyte lymphocyte ratio; N, neutrophils; NLR, neutrophil to lymphocyte ratio; NLPR, neutrophils lymphocyte to platelet ratio; PLT, platelets; PLR, platelet to lymphocyte ratio; PMOP, postmenopausal osteoporosis; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; T, testosterone; TSH, thyroid-stimulating hormone; WBC, white blood cell.

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## Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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