Annals of Clinical Case Reports

Research Article
Published: 31 Jul, 2023

The Predictive Role of Blood Routine Test-Based Biomarkers in Patients with Osteoporosis

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Abstract

Aim: Osteoporosis (OP) is a bone metabolism disease involving immune dysfunction and chronic inflammation. Blood Routine Test (BRT) is easily available and contains abundant information on immune and inflammation. Thus, it is attractive to predict diagnosis of OP based on the biomarkers from BRT.

Methods: It was a retrospective study. Bone Mineral Density (BMD) at lumbar spines and Total Hip (TH) were measured using Dual-Energy X-ray Absorptiometry (DEXA). BRT parameters were recorded. Then, Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Lymphocyte-to-Monocyte Ratio (LMR) and Systemic Immune-Inflammation Index (SII) were calculated, respectively. Correlation analysis was performed using Spearman correlation test. Significant variables in the correlation test ($p<0.05$) were tested by a multinomial logistic regressions analysis to identify independent factors predicting OP. Finally, areas under the Receiver Operating Characteristic (ROC) curves were taken to determine the diagnostic value of BRT indexes.

Results: A total of 1,366 participants were enrolled. Subjects with OP were more female, and had lower Body Mass Index (BMI) and older age. Spearman correlation test showed that gender, BMI, hemoglobin, Red Blood Cell (RBC), lymphocyte, NLR, PLR, LMR and SII were significantly related with BMD both at L1-L4 and TH. Multinomial logistic regressions analysis further demonstrated that, after adjustment for gender, age and BMI, hemoglobin, RBC and lymphocyte were independent risk factors for OP. Finally, Areas Under the Curves (AUC) of lymphocyte was higher than those of hemoglobin and RBC.

Conclusion: Lymphocyte, hemoglobin and RBC count might act as predictors for OP diagnosis, which deserves further investigation and application.

Keywords: Osteoporosis; Lymphocyte; Hemoglobin; Red blood cell; Neutrophil-to-lymphocyte ratio; Systemic immune-inflammation index

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Received Date: *29 Jun 2023*
Accepted Date: *18 Jul 2023*
Published Date: *31 Jul 2023*

Citation:
Chen L, Wu Q, Lv X-L, Tong Q, Xu F, Wang GF. The Predictive Role of Blood Routine Test-Based Biomarkers in Patients with Osteoporosis. Ann Clin Case Rep. 2023; 8: 2445.
ISSN: 2474-1655.

Introduction

Due to rapid ageing in China, patients with Osteoporosis (OP), an age-related disease, will increase sharply from 83.9 million in 1997 to 212 million by 2050 [1]. Globally, a recent meta-analysis showed that the prevalence of OP in women was 23.1 (95% Confidence Interval (CI) 19.8-26.9), while the OP prevalence among men was 11.7 (95% CI 9.6-14.1) [2]. The most serious consequence of OP was Osteoporotic Fracture (OF). It was estimated that more than 2 million OF occurred annually in the U.S. and that the annual cost of caring for OF exceeded the annual costs of caring for breast cancer, myocardial infarction, or stroke in women aged 55 years and older [3,4]. On the other hand, it is well known that OP is a chronic disease. Once patients are diagnosed with OP, they will be at an increased risk for OF in the rest of their lives. Even when patients' Bone Mineral Density (BMD) improves after effective treatment, they will still be at increased risk for fracture and their risk for fracture will eventually return to baseline if they stop treatment, similarly to what occurs in patients with hypertension or diabetes [5]. Therefore, it is important to early diagnose for OP. Up to date, the golden diagnostic method for OP is based on the Dual-Energy X-ray Absorptiometry (DEXA). DEXA scanning, however, requires specialized equipment and trained staff. In addition, the cost-effectiveness of DEXA test for a whole population at risk has not been demonstrated [6]. Consequently, most countries do not recommend DEXA for population-based screening, with many guidelines recommending DEXA scanning for women aged above 65 years [3,7]. Thus, it's

necessary to develop convenient and inexpensive methods for OP screening and diagnose.

OP is the loss of bone mass due to an imbalance in bone remodeling where Osteoclast (OC)-mediated bone resorption exceeds Osteoblast (OB)-mediated bone formation. Since Takayanagi et al. first reported that IFN-γ could inhibit RANKL signaling during OC differentiation, growing evidence suggested, over the past decades, that OP was closely related with immune dysfunction and systematic inflammation activation [8,9]. For example, previous investigation demonstrated that Th17 cells were key drivers of bone absorption and that T-cell produced IFN-γ, TNF-a, IL-17A and IL-10 played critical role on bone destruction and bone formation [10-12]. So, it is reasonable to speculate that serum biomarkers of immune and inflammation might act as diagnostic predictor of OP.

Recently, a lot of studies demonstrated that immune and systematic inflammation biomarkers originated from Blood Routine Tests (BRT) parameters, including Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Lymphocyte-to-Monocyte Ratio (LMR) and Systemic Immune-Inflammation index (SII), were associated with inflammatory diseases, such as chronic obstructive pulmonary disease, pulmonary hypertension, ulcerative colitis, ANCA-associated vasculitis, malignancy, and son on [13-19]. Interestingly, such immune and inflammation biomarkers had been emerged as new predictors for OP. However, previous clinical investigations provided inconsistent or even contradictory results. For example, several researches showed NLR was inversely related with BMD [20-22]. In addition, in an article published by Eroglu et al. PLR was demonstrated to be an important marker in the diagnosis of OP in postmenopausal women [23]. In another paper published in Du et al. significant inverse association was observed between SII and BMD in postmenopausal women. After adjusting for covariates, SII levels remained significantly associated with BMD [24]. Also, Gao et al. found MLR and PLR levels were remarkably higher in OP patients than in osteopenia patients and that MLR had a higher diagnostic value for OP [25]. However, Al Salmani et al. conducted a retrospective cross-sectional study among 450 postmenopausal to assess the potential of NLR, MLR and PLR as markers of BMD loss and found that none of them could be useful indicators of bone loss [26]. Moreover, few researches have confirmed the predictive role of different blood cell count in OP patients. So, more study should be done to further clarify the predictive role of immune and inflammation biomarkers originated from BRT for OP.

Here, we performed a retrospective study to evaluate whether BRT-based biomarkers, including different blood cell count, NLR, PLR, MLR, and SII, might predict diagnosis of OP.

Methods

Study participants

This work was conducted with a respective design and the participants attending the health promotion center of Zhejiang Hospital for evaluation of bone health were analyzed from July 2019 to June 2022. It was approved by the Medical Ethics Committee of Zhejiang Hospital (2022-17K).

The criteria for the research inclusion were: (i) completing blood routine examination; (ii) taking DEXA measurement. The exclusion criteria in the present study mainly included metallic prosthesis/fixation at hip or lumbar spines, renal insufficiency, malignancy, connective tissue or musculoskeletal diseases, significant liver, thyroid, parathyroid gland, adrenal gland or pituitary diseases, inability to ambulate, taking bone active drugs (e.g., bisphosphonates, PTH, denosumab), hormone replacement therapy or glucocorticoids. BMD of lumbar vertebrae 1 to 4.

Clinical examinations

BMD was measured by DEXA (GE Lunar-iDXA, GE Medical Systems, Madison, WI, USA) at the lumbar spine (L1-L4) and Total Hip (TH). According to the OP diagnosis criteria [27], the participants with a T-score ≤ -2.5 were divided into the OP patients, the others were divided into the non-Osteoporosis (non-OP) group. BRT parameters, including hemoglobin, Red Blood Cell (RBC) count, platelet count, White Blood Cell (WBC) count and leukocyte subpopulation, were recorded. Then, NLR, PLR, and LMR were calculated. In addition, SII was defined as platelet counts × neutrophil counts/lymphocyte counts [28]. Serum C Reactive Protein (CRP) concentration was determined by AU Chemistry Systems (Beckman Coulter AU5800, Beckman Coulter Ireland Inc.).

Statistical analysis

Chi-square analysis and the Mann-Whitney U test were performed to compare categorical variables and continuous variables, respectively. Correlation analysis was performed using Spearman correlation test. Then, significant variables in the correlation test ($p<0.05$) were tested by a multinomial logistic regressions analysis with stepwise subset selection to identify independent factors predicting OP. Finally, an area under the Receiver Operating Characteristic (ROC) curves was taken to confirm the diagnostic value of BRT indexes. All statistical analyses were completed using the SPSS 21.0 software package. $P<0.05$ was considered statistically significant.

Results

Clinical characteristics of participants between OP group and non-OP control

We retrospectively recruited a total of 1,366 participants with a mean age of 66.23 ± 12.80, including 517 males (37.85%) and 849 females (62.15%). Among them, 357 patients were diagnosed as OP, with the OP prevalence of 26.13% (357/1366). As expected, women were more prone to suffering from OP than men. The average age of the OP patients was significantly older than that of non-OP controls (72.16 ± 11.34 *vs.* 64.13 ± 12.63, $p<0.001$). In contrast, OP patients had lower BMI than non-OP controls (22.52 ± 3.51 *vs.* 24.76 ± 10.39, $p<0.001$).

As for BRT parameters, except for WBC, neutrophil, eosinophil and basophil, other biomarkers, including hemoglobin, RBC, monocyte, lymphocyte, platelet, NLR, PLR, LMR and SII in OP group, were significantly different from non-OP group. In addition, CRP was obviously higher in OP group comparing to controls (15.47 ± 33.95 *vs.* 9.88 ± 25.24, $p=0.001$). Main clinical data and BRT results of the subjects were summarized in Table 1.

Correlation analysis between clinical parameters and BMD in different sites

First, Spearmon correlation analysis was employed to find the relationship between clinical parameters and lumbar vertebra and hip BMD, respectively. As shown in Table 2, most biomarkers, except for neutrophil, eosinophil, basophil platelet and LMR, were closely related to BMD L1-L4. On the other hand, except for WBC, neutrophil, monocyte, eosinophil, basophil, and platelet, other

Table 1: Comparison of clinical parameters between OP group and non-OP group.

Clinical data	Non-OP group (n=1009)	OP group (n=357)	*p* value
Gender (male:female)	435:574	82:275	<0.001
Age (year)	64.13 ± 12.63	72.16 ± 11.34	<0.001
BMI (kg/m^2)	24.76 ± 10.39	22.52 ± 3.51	<0.001
Lab Hemoglobin(g/L)	129.08 ± 16.89	120.06 ± 17.59	<0.001
data RBC (10^{12}/L)	4.58 ± 0.6	3.8 ± 0.46	<0.001
WBC (10^9/L)	6.73 ± 9.13	6.17 ± 2.67	0.218
Neutrophil (10^9/L)	4.2 ± 3.1	4.27 ± 2.57	0.394
Monocyte (10^9/L)	0.46 ± 0.59	0.47 ± 0.69	0.034
Lymphocyte (10^9/L)	1.58 ± 1.11	1.36 ± 0.53	<0.001
Eosinophil (10^9/L)	0.16 ± 0.01	0.16 ± 0.01	0.781
Basophil (10^9/L)	0.05 ± 0.04	0.06 ± 0.07	0.21
Platelet (10^9/L)	205.86 ± 65.92	198.77 ± 63.63	0.033
CRP (mg/L)	9.88 ± 25.24	15.47 ± 33.95	0.001
NLR	3.39 ± 4.06	4.0 ± 4.0	<0.001
PLR	155.15 ± 116.67	169.49 ± 88.46	<0.001
LMR	4.46 ± 9.31	3.9 ± 1.96	0.019
SII	703.42 ± 917.77	775.05 ± 767.21	0.001
BMD L1-L4 (g/cm^2)	1.11 ± 0.2	0.93 ± 0.15	0.001
Data TH (g/cm^2)	0.85 ± 0.18	0.72 ± 0.14	0.001

BMI: Body Mass Index; RBC: Red Blood Cell; WBC: White Blood Cell; CRP: C Reactive Protein; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; LMR: Lymphocyte-to-Monocyte Ratio; SII: Systemic Immune-Inflammation Index; L1-L4: Lumbar Vertebrae 1 to 4; TH: Total Hip

parameters had significant relationship with BMD TH.

Identifying independent risk factors for OP

Then, we used a multinomial logistic regressions analysis with stepwise subset selection to further identify potential factors for OP. In our model, after adjustment for gender, age, and BMI, only hemoglobin, RBC, lymphocyte and CRP were identified as independent risk factors for OP (Table 3).

Diagnostic value of BRT indexes for OP

Finally, in order to explore the diagnostic role of different indexes for OP, ROC curves were adopted. And, CRP, a well accepted inflammatory indicator, was used as control [29,30]. As presented in figure and Table 4, the Area Under the Curve (AUC) of lymphocyte was 0.409 (95% CI 0.375-0.444), which was higher than hemoglobin and RBC. While, CRP yielded a highest AUC value than other BRT-derived parameters, with AUC of 0.561 (95% CI 0.526-0.597).

Discussion

The main results in the current study included: (a) none of NLR, PLR, MLR, and SII was independent risk factors for OP, which was consistent with previously work by Al Salman et al. [26]. And, (b) hemoglobin, RBC, lymphocyte could predict the diagnosis for OP. Given that BRT is easily available, economical and contains abundant parameters, it should be useful in OP diagnosis and management.

The exact mechanism of how hemoglobin and RBC influence BMD remained unclear and need further clarification. Using a conditional logistic regression model among 69,760 OP patients, Kim et al. estimated the association of hemoglobin level with OP and found that 15% of the OP group and 14.17% of the comparison

Table 2: Correlation analysis between clinical data and BMD in different sites.

	BMD L1-L4		BMD TH	
	r	*p* value	r	*p* value
Gender	-0.323	<0.001	-0.302	<0.001
Age (year)	-0.169	<0.001	-0.388	<0.001
BMI (kg/m^2)	0.361	<0.001	0.378	<0.001
Hemoglobin(g/L)	0.258	<0.001	0.335	<0.001
RBC (10^{12}/L)	0.367	<0.001	0.391	<0.001
WBC (10^9/L)	0.087	0.002	0.016	0.566
Neutrophil (10^9/L)	0.021	0.441	-0.04	0.146
Monocyte (10^9/L)	0.128	<0.001	0.012	0.654
Lymphocyte (10^9/L)	0.156	<0.001	0.169	<0.001
Eosinophil (10^9/L)	-0.049	0.077	-0.024	0.374
Basophil (10^9/L)	0.018	0.517	0.001	0.978
Platelet (10^9/L)	0.024	0.389	0.035	0.195
CRP (mg/L)	-0.005	0.02	-0.097	<0.001
NLR	-0.081	0.003	-0.13	<0.001
PLR	-0.126	<0.001	-0.126	<0.001
LMR	0.007	0.797	0.113	<0.001
SII	-0.076	0.006	-0.109	<0.001

BMI: Body Mass Index; RBC: Red Blood Cell; WBC: White Blood Cell; CRP: C Reactive Protein; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; LMR: Lymphocyte-to-Monocyte Ratio; SII: Systemic Immune-Inflammation Index; L1-L4: Lumbar Vertebrae 1 to 4; TH: Total Hip

Table 3: Multivariate logistic analysis of risk factors for OP.

Parameters	Regression coefficient	Adjusted OR (95% CI)	*p* value
Hemoglobin(g/L)	-0.013	0.987 (0.979-0.996)	0.003
Lymphocyte (10^9/L)	-0.302	0.739 (0.577-0.947)	0.017
RBC (10^{12}/L)	-2.269	0.103 (0.075-0.143)	<0.001
CRP (mg/L)	0.005	1.005 (1.000-1.009)	0.038

RBC: Red Blood Cell; CRP: C Reactive Protein

Table 4: Comparison of diagnostic value of different markers in OP.

	AUC	*p* value	95% CI	
			Lower	Upper
Hemoglobin (g/L)	0.346	<0.001	0.315	0.377
Lymphocyte	0.409	<0.001	0.375	0.444
RBC (10^{12}/L)	0.151	<0.001	0.131	0.171
CRP (mg/L)	0.561	0.001	0.526	0.597

RBC: Red Blood Cell; CRP: C Reactive Protein; AUC: Area Under Curve

group had anemia. The hemoglobin level was associated with 0.98-fold lower odds for OP (95% CI 0.97-0.99, p<0.001) [31], similar to our results with 0.987--fold lower odds (95% CI 0.979-0.996, p<=0.003). However, in a relatively small sample size investigation with 673 postmenopausal women cases, hemoglobin and RBC levels of postmenopausal women in the OP group were both higher than those in the non-OP group [32].

The regulatory roles of lymphocytes in OP were well established *in vitro* [33,34]. However, in vivo studies yielded inconsistent results. Peng et al. found total T lymphocytes and CD8+ T lymphocytes in the OP group were significantly lower than those in the non-OP group [35], partly supporting our research results. Instead, through the analysis of 210 white women with hip fracture, Di Monaco et

al. observed a positive correlation between lymphocyte count and BMD measured at both total proximal femur (r=0.21; p<0.05) and intertrochanteric area (r=0.21; p<0.05) [36].

The current study had relatively large sample size, to date. Moreover, it covered participants of different ages and different gender, and had BMD data at different sites. However, there were some limitations. First, it was a retrospective, observational association study, which tended to leave uncertainty. Second, it lacked clinical outcome, including fracture and survival time, etc. Finally, the participants were heterogeneous, with diversities of medication and different morbidity, which might confound the results.

Conclusion

Our study showed that, after adjustment for gender, age, and BMI, hemoglobin, RBC, and lymphocyte count were independent risk factors for OP, implying that BRT might be useful and convenient diagnostic predictor for OP. However, more prospective randomized controlled study should be done to further confirm it.

Acknowledgement

This study was founded by a grant from Science Technology Bureau of Huzhou City, Zhejiang Province (2021GY68).

References

1. Lin X, Xiong D, Peng YQ, Sheng ZF, Wu XY, Wu XP, et al. Epidemiology and management of osteoporosis in the People's Republic of China: Current perspectives. Clin Interv Aging. 2015;10:1017-33.
2. Salari N, Ghasemi H, Mohammadi L, Behzadi MH, Rabieenia E, Shohaimi S, et al. The global prevalence of osteoporosis in the world: A comprehensive systematic review and meta-analysis. J Orthop Surg Res. 2021;16(1):609.
3. Singer A, Exuzides A, Spangler L, O'Malley C, Colby C, Johnston K, et al. Burden of illness for osteoporotic fractures compared with other serious diseases among postmenopausal women in the United States. Mayo Clin Proc. 2015;90:53-62.
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22:465-75.
5. Brown JP. Long term treatment of postmenopausal osteoporosis. Endocrinol Metab (Seoul). 2021;36(3):544-52.
6. US Preventive Services Task Force; Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, et al. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:2521-31.
7. Chinese Medical Association, Chinese Medical Journals Publishing House, Chinese Society of General Practice, Editorial Board of Chinese Journal of General Practitioners of Chinese Medical Association, Expert Group of Guidelines for Primary Care of Endocrine System Disease. Guideline for primary care of primary osteoporosis: practice version (2019). Chin J Gen Pract. 2020;19(4):304-15.
8. Takayanagi H, Ogasawara K, Hida S, Chiba T, Murata S, Sato K, et al. T-cell-mediated regulation of osteoclastogenesis by signaling cross-talk between RANKL and IFN-gamma. Nature. 2000;408(6812):600-5.
9. Wu D, Cline-Smith A, Shashkova E, Perla A, Katyal A, Aurora R. T-cell mediated inflammation in postmenopausal osteoporosis. Front Immunol. 2021;12:687551.
10. Sato K, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J Exp Med. 2006;203(12):2673-82.
11. Komatsu N, Okamoto K, Sawa S, Nakashima T, Oh-hora M, Kodama T, et al. Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis. Nat Med. 2014;20(1):62-8.
12. Zhao R, Wang X, Feng F. Upregulated cellular expression of IL-17 by CD4+ T-cells in osteoporotic postmenopausal women. Ann Nutr Metab. 2016;68(2):113-8.
13. Günay E, Ulaşlı SS, Akar O, Akar O, Ahsen A, Günay S, et al. Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: A retrospective study. Inflammation. 2014;37(2):374-80.
14. Yao CY, Liu XL, Tang Z. Prognostic role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio for hospital mortality in patients with AECOPD. Int J Chron Obstruct Pulmon Dis. 2017;12:2285-90.
15. Zuo H, Xie X, Peng J, Wang L, Zhu R. Predictive value of novel inflammation-based biomarkers for pulmonary hypertension in the acute exacerbation of chronic obstructive pulmonary disease. Anal Cell Pathol (Amst). 2019;2019:5189165.
16. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer: A meta-analysis. J Cancer. 2018;9(18):3295-302.
17. Akpinar MY, Ozin YO, Kaplan M, Ates I, Kalkan IH, Kilic ZMY, et al. Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio predict mucosal disease severity in ulcerative colitis. J Medical Bio. 2018;37(2):155-62.
18. Kim Y, Choi H, Jung SM, Song JJ, Park YB, Lee SW. Systemic immune-inflammation index could estimate the cross-sectional high activity and the poor outcomes in immunosuppressive drug-naïve patients with antineutrophil cytoplasmic antibody-associated vasculitis. Nephrology. 2018;24(7):711-7.
19. Mao W, Wu J, Zhang Z, Xu Z, Xu B, Chen M. Neutrophil-lymphocyte ratio acts as a novel diagnostic biomarker for kidney stone prevalence and number of stones passed. Transl Androl Urol. 2021;10(1):77-86.
20. Huang C, Li S. Association of blood neutrophil lymphocyte ratio in the patients with postmenopausal osteoporosis. Pak J Med Sci. 2016;32(3):762-5.
21. Öztürk ZA, Yesil Y, Kuyumcu ME, Bilici M, Öztürk N, Yeşil NK, et al. Inverse relationship between Neutrophil Lymphocyte Ratio (NLR) and Bone Mineral Density (BMD) in elderly people. Arch Gerontol Geriatr. 2013;57:81-5.
22. Yu XY, Li XS, Li Y, Liu T, Wang RT. Neutrophil-lymphocyte ratio is associated with arterial stiffness in postmenopausal women with osteoporosis. Arch Gerontol Geriatr. 2015;61(1):76-80.
23. Eroglu S, Karatas G. Platelet/lymphocyte ratio is an independent predictor for osteoporosis. Saudi Med J. 2019;40(4):360-6.
24. Du YN, Chen YJ, Zhang HY, Wang X, Zhang ZF. Inverse association between systemic immune-inflammation index and bone mineral density in postmenopausal women. Gynecol Endocrinol. 2021;37(7):650-4.
25. Gao K, Zhu W, Liu W, Ma D, Li H, Yu W, et al. The predictive role of monocyte-to-lymphocyte ratio in osteoporosis patient. Medicine (Baltimore). 2019;98(34):e16793.
26. Al Salmani A, Al Shidhani, A, Al-Alawi NM, Al Sulaimi AA, Al-Hashemi MA. Inflammatory markers as a predictor of postmenopausal osteoporosis: A cross-sectional study from the Sultan Qaboos University Hospital. Sultan Qaboos Univ Med J. 2022;22(4):508-14.
27. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. Endocr Pract. 2020;26(Suppl 1):1-46.
28. Hong X, Cui B, Wang M, Yang Z, Wang L, Xu Q. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte

ratio, is useful for predicting prognosis in small cell lung cancer. Tohoku J Exp Med. 2015;236(4):297-304.

29. de Pablo P, Cooper MS, Buckley CD. Association between bone mineral density and C-reactive protein in a large population-based sample. Arthritis Rheum. 2012;64(8):2624-31.

30. Ding C, Parameswaran V, Udayan R. Circulating levels of inflammatory markers predict change in bone mineral density and resorption in older adults: A longitudinal study. J Clin Endocrinol Metab. 2008;93(5):1952-8.

31. Kim SY, Yoo DM, Min C, Choi HG. Association between osteoporosis and low hemoglobin levels: A nested case-control study using a national health screening cohort. Int J Environ Res Public Health. 2021;18(16):8598.

32. Li L, Ge JR, Chen J, Ye YJ, Xu PC, Li JY. Association of bone mineral density with peripheral blood cell counts and hemoglobin in Chinese postmenopausal women: A retrospective study. Medicine (Baltimore). 2020;99(28):e20906.

33. Fischer V, Haffner-Luntzer M. Interaction between bone and immune cells: Implications for postmenopausal osteoporosis. Semin Cell Dev Biol. 2022;123:14-21.

34. Zhang W, Dang K, Huai Y, Qian A. Osteoimmunology: The regulatory roles of T lymphocytes in osteoporosis. Front Endocrinol (Lausanne). 2020;11:465.

35. Peng C, Guo Z, Zhao Y, Li R, Wang L, Gong W. Effect of lymphocyte subsets on bone density in senile osteoporosis: A retrospective study. J Immunol Res. 2022;2022:3337622.

36. Di Monaco M, Vallero F, Di Monaco R, Mautino F, Cavanna A. Total lymphocyte count and femoral bone mineral density in postmenopausal women. J Bone Miner Metab. 2004;22(1):58-63.