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Pan-immune inflammatory value a new diagnostic biomarker in postmenopausal osteoporosis

Pınar Özge Başaran, Duygu Tutan

Department of Physical Medicine and Rehabilitation, Hitit University Erol Olçok Education and Research Hospital, Çorum, Turkiye

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ABSTRACT

Aims: Postmenopausal osteoporosis (PMOP) is one of the most common bone diseases. We aimed to investigate the relationship between pan-immune inflammatory value and decreased bone mineral density in postmenopausal women.

Methods: This prospective cross-sectional study was composed of 186 postmenopausal women. Osteoporosis was diagnosed with dual-energy X-ray absorptiometry (DEXA) results according to World Health Organization (WHO) recommendations and patients were separated into 3 groups; 1. control group with a T-score >-1; 2. group osteopenia with a T-score between -1.0 and -2.5; 3. group osteoporosis with a T-score ≤-2.5. After the physical examinations of all patients, venous blood samples were collected and the pan-immune inflammation value (PIV) was calculated. The parameters were evaluated statistically with the PIV value between the groups.

Results: Groups are similar in terms of age, menopausal age, education, and occupation. PIV was significantly higher in postmenopausal women with osteoporosis than women with osteopenia and the control group ($p<0.001$, $p<0.001$). PIV was significantly higher in postmenopausal women with osteopenia than the control group ($p<0.001$). Distinguishing between osteoporosis and osteopenia, PIV≥306.20 was 72.6% sensitivity, 69.4% specificity, and 71.7% negative predictive value. Distinguishing between osteopenia and control, PIV≥152.02 was 85.5% sensitivity, 56.5% specificity, 66.3% positive predictive value, and 79.5% negative predictive value.

Conclusion: In our study, we found that the PIV was statistically higher in PMOP, it was also statistically higher in postmenopausal women with osteopenia compared to healthy controls. We believe that PIV can be a cheap, easy, and reliable evaluation parameter for determining the risk of osteoporosis and osteopenia in women with PMOP.

Keywords: Pan-immune-inflammatory value, postmenopausal osteoporosis, osteopenia

INTRODUCTION

Osteoporosis is a skeletal system disease, characterized by low bone mineral mass and impaired microarchitecture of bone tissue.[1] Osteoporosis is one of the most common chronic diseases in humans.[2] The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) less than 2.5 standard deviations lower than that of normal young adults.[3] Decreased bone mass results in decreased bone strength and increased risk of fractures. Osteoporosis is also the most common bone disease worldwide, affecting one in three women and one in five men over the age of 50[4] and with increasing aging, both the prevalence of osteoporosis and the prevalence of osteoporosis-related fragility fractures increase. Osteoporosis has become an important public health problem as the elderly population increases. Postmenopausal osteoporosis (PMOP) is characterized by mainly trabecular bone loss due to endogenous estrogen deficiency after menopause. It is estimated that at least 40% of postmenopausal women will develop a fracture at some point in their lives.[5] Therefore, the evaluation of osteoporosis in patients is important not only for the treatment of osteoporosis but also for preventing complications related to osteoporosis, reducing the risk of fractures, and decreasing mortality.[6]

Previous studies have shown a relationship between bone loss, the immune system, and systemic inflammation. In postmenopausal women, estrogen loss leads to T cell activation and the release of proinflammatory cytokines such as interleukin (IL) 17-A and tumor necrosing factor (TNF).[7,8] IL 17-A increases bone destruction.[9] However, TNF-alpha also stimulates osteoclastogenesis directly through osteoclasts.[10] As a result of all this, PMOP develops.

Bone mineral density measurements support and confirm the diagnosis of osteoporosis, assessment of

Corresponding Author: Pınar Özge Başaran, pinarozge@yahoo.com

fracture risk, and evaluation of the patient's treatment plan are among the methods used during the diagnosis and post-treatment follow-up.[11] Dual-energy X-ray absorptiometry (DEXA) is the most common measurement for the diagnosis of PMOP. However, DEXA is not available everywhere. Also, there is no definitive biomarker for which a patient should be referred for a DEXA scan. For this reason, some inexpensive and rapid blood parameters that can assess the risk of osteoporosis in outpatient clinic conditions are being studied. Neutrophil and lymphocyte ratio (NLR),[12] monocyte lymphocyte ratio (MLR),[13] platelet lymphocyte ratio (PLR),[14] systemic immune-inflammation index (SII)[15] have been studied at osteoporosis.

Pan-immune inflammatory value (PIV) is a new diagnostic biomarker. PIV is calculated from a complete blood count that includes neutrophils, platelets, monocytes, and lymphocytes. Each of these immune cells plays a role in inflammation. PIV has been previously studied in inflammatory diseases such as colorectal cancer, melanoma, rheumatoid arthritis, and vasculitis.[16-19]

In this study, we aimed to investigate the relationship between PIV and decreased bone mineral density in postmenopausal women.

METHODS

This prospective cross-sectional study was composed of 186 postmenopausal women over 45. Participants who applied to physical medicine and rehabilitation outpatient clinics between October 2023 and February 2024, and who had been in natural menopause for the last 1 year were included. Participants with endocrinologic or rheumatic diseases such as diabetes mellitus, rheumatism, thyroid diseases, parathyroid diseases, or hepatorenal insufficiency, malignancy, presence of acute and chronic infection, use of medication associated with osteoporosis such as corticosteroids, calcium medications or chemotherapy drugs, use of hematopoietic drugs that affect blood parameters, surgical menopause or those with a metal prosthesis that will obstacle DEXA examination were excluded. The study was carried out according to the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients. Hitit University Clinical Researches Ethics Committee approved the study (Date: 26.12.2023, Decision No: 2023-170).

Patients were asked about their education, occupation, age at menopause, chronic diseases, medications, and smoking status. After the physical examinations of all patients, venous blood samples were collected and the complete blood cell parameters; monocyte counts (10^9/L), neutrophil counts (10^9/L), lymphocyte counts (10^9/L), and platelet counts (10^9/L) were noted. Pan-immune inflammation value (PIV) was calculated with the formula: (neutrophil count×platelet count×monocyte count)/lymphocyte count.[16]

Before DEXA measurement, the height of the patients was measured with a tape measure in centimeters and weight was measured with a scale in kilograms, and body mass index (BMI) kg/m^2 was calculated. Bone mineral density was measured at three sites: femoral neck, total femur, and total lumbal (lumbal 1-4 vertebrae) using the Horizon bone densitometry system (MAN-04871). In the light of WHO osteoporosis diagnostic criteria, patients were categorized into 3 groups; control, osteopenia, and osteoporosis, according to DEXA results.[3] 1. Group control group with a T-score >-1; 2. group osteopenia with a T-score between -1,0 and -2.5; 3. group osteoporosis with a T-score ≤-2.5.

In the light of the previous study, the effect size for the ANOVA test (followed by the t-test) was found to be approximately 0.243, and in the a priori power analysis performed with a statistical significance of 0.05 and a statistical power of 0.80, the total sample size of the 3 groups was found to be 168 people, consisting of 3 groups of 56 participants in each group, so that significance could be achieved in the pair group analysis between the groups.[20]

Statistical Analysis

This study was designed prospectively. All statistical analyses were conducted using IBM SPSS Statistics for Windows software (version 26; IBM Corp., Armonk, N.Y., USA). The normal distribution of data was assessed using the Shapiro-Wilks test. Correlations between variables were evaluated using Pearson and Spearman correlation coefficients, depending on the data distribution. Comparison of numerical measurements between independent groups according to research groups, such as age, height, weight, menopausal age, neutrophil, monocyte, lymphocyte counts, femur neck T score, femur total T score, lumbar total T score, and PIV, was assessed using the Mann-Whitney U test and Kruskal-Wallis Test for post-hoc tests, in accordance with the distribution of the data. An ANOVA test was done for the assessment of the difference between means of platelet counts between groups. Categorical variables such as educational status, current occupation, and smoking history were evaluated for ratio comparisons between research groups using the Chi-square test. Receiver Operating Characteristic (ROC) curves were utilized to demonstrate the discriminative ability of statistically significant variables. Cut-off values for these markers were determined using the area under the curve and the Youden index. Sensitivity, specificity, positive

predictive value (PPV), negative predictive value (NPV), and accuracy values were calculated based on these cut-off values. Odds ratio values were computed for these cut-off points. A significance level of p<0.05 was considered statistically significant.

RESULTS

Of the total 186 female patients in the entire group, the median age was found to be 62.5 (46-83) years. Patients were categorized into three groups: control (n=62), osteopenic (n=62), and osteoporotic (n=62). When assessed in terms of mean ages, the median age in the control group was 61 years; in the osteopenic group, it was 63.5 years; and in the osteoporotic group, it was 63 years; however, no statistically significant difference was observed (p=0.056). There was no difference in terms of height, menopausal age, education, and occupation between groups (p=0.280, p=0.297, p=0.845, and p=0.052, respectively). The median weight of osteoporotic patients was lower than control and osteopenic patients (p<0.001 for control vs osteoporotic and p=0.007 for osteopenic vs osteoporotic) (Table 1). While evaluating the smoking history of the groups, osteoporotic patients were found to have a higher ratio of smokers at 38.71%, indicating a statistically significant difference compared to other groups (p<0.001 against control participants, p<0.001 against osteopenic patients (Table 1).

The comparisons between hematological laboratory values between groups and radiological indices of osteoporosis are extensively detailed in Table 1, including post-hoc test results. When examining the PIV of patients in the groups, the median PIV for the control group was 143.91, while the median PIV for the osteopenic patients was 245.49, and the median PIV for the osteoporotic patients was higher with 441.90, indicating a statistically significant difference between all groups (p<0.001 for Kruskal-Wallis and all post-hoc tests) (Table 1, Figure 1 and Figure 2).

To assess the optimal cut-off point of PIV for distinguishing between control and osteopenia groups, the area under the curve and the Youden index were employed in ROC analysis. For the diagnosis of osteopenia, the most suitable PIV cut-off value was determined to be ≥152.02 with 85.5% sensitivity, 56.5% specificity, 66.3% positive predictive value, 79.5% negative predictive value, and 70.96% test accuracy (OR 7.634, 95% CI 3.208-18.163, p<0.001). A PIV of or exceeding 152.02 increased the likelihood of osteopenia by 6.634 times (Table 2, Figure 3).

Table 1. Descriptive variables of all participants. comparisons between groups and results of post-hoc comparisons

Variables		All participants (n=186)	Control (n=62)	Osteopenic (n=62)	Osteoporotic (n=62)	Statistical significance	Control vs osteopenic	Control vs osteoporotic	Osteopenic vs osteoporotic
Age		62.5 (46-83)	61 (46-78)	63.5 (48-80)	63 (46-83)	0.056			
Height		152 (51-170)	153 (144-165)	152 (90-168)	151.5 (51-170)	0.280			
Weight		71 (7-147)	76.5 (53-113)	73.5 (7-146)	68.5 (38-147)	<0.001	0.356	<0.001	0.007
Menopausal age		47 (29-162)	47 (35-56)	48 (36-55)	45.5 (29-162)	0.297			
Education	Primary shool	165 (88.71%)	54 (87.1%)	57 (91.94%)	54 (87.1%)	0.845			
	High school	14 (7.53%)	5 (8.06%)	3 (4.84%)	6 (9.68%)				
	University	7 (3.76%)	3 (4.84%)	2 (3.23%)	2 (3.23%)				
Occupation	Housewife	168 (90.32%)	53 (85.48%)	60 (96.77%)	55 (88.71%)	0.052			
	Working	8 (4.3%)	2 (3.23%)	1 (1.61%)	5 (8.06%)				
	Retired	10 (5.38%)	7 (11.29%)	1 (1.61%)	2 (3.23%)				
Smoking History	Non-smoker	151 (81.18%)	56 (90.32%)	57 (91.94%)	38 (61.29%)	<0.001	0.752	<0.001	<0.001
	Smoker	35 (18.82%)	6 (9.68%)	5 (8.06%)	24 (38.71%)				
Neutrophil count		3.98 (1.36-8.43)	3.16 (1.36-6.47)	3.75 (2.12-8.43)	4.92 (3.1-7.42)	<0.001	0.009	<0.001	<0.001
Monocyte count		0.49 (0.21-1.57)	0.51 (0.31-1.57)	0.49 (0.21-1.16)	0.49 (0.26-1.2)	0.657			
Lymphocyte count		2.29 (1.09-5.54)	2.7 (1.51-5.54)	2.13 (1.1-3.92)	2.05 (1.09-4.06)	<0.001	<0.001	<0.001	0.292
Platelet count		271.49±52.33	240.77±38.56	262.79±52.8	310.9±37.63	<0.001	0.016	<0.001	<0.001
Femur neck T score		-1.1 (-3-2.3)	0 (-1.5-2.3)	-1.35 (-2.3-1.9)	-1.7 (-3-1.9)	<0.001	<0.001	<0.001	0.025
Femur total T score		-0.7 (-2.8-5)	0.55 (-1.2-2.8)	-1 (-2.3-5)	-1.4 (-2.8-1.6)	<0.001	<0.001	<0.001	0.056
Lumbar total T score		-1.8 (-4.2-2.6)	-0.35 (-3-2.4)	-1.9 (-2.6--0.7)	-3 (-4.2-2.6)	<0.001	<0.001	<0.001	<0.001
PIV		248.65 (35.04-2238.82)	143.91 (35.04-485.10)	245.49 (70.18-749.58)	441.90 (147.11-2238.82)	<0.001	<0.001	<0.001	<0.001

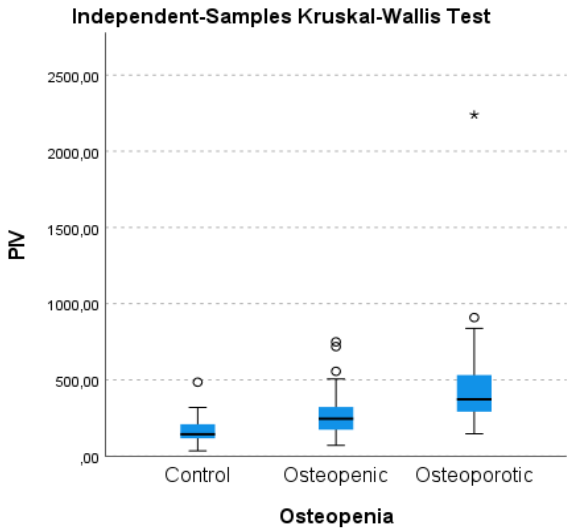

Figure 1. Boxplot diagrams of pan-immune inflammation values between groups

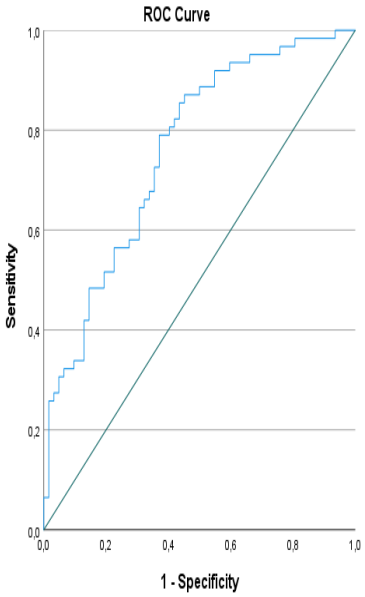

Figure 3. Receiver Operating Curve of PIV for the distinction between control and osteopenic groups

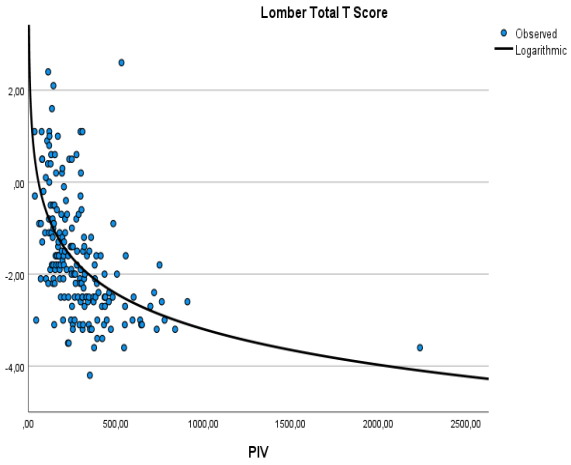

Figure 2. Logarithmic curve estimation of PIV and Lomber Total T Score

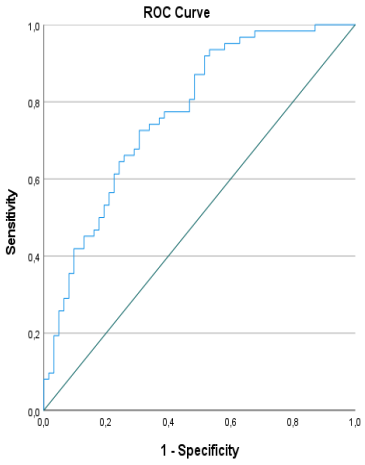

Figure 4. Receiver Operating Curve of PIV for the distinction between osteopenic and osteoporotic groups

Similarly, another ROC analysis was done for the assessment between osteopenic and osteoporotic groups. For the diagnosis of osteoporosis, the optimal PIV cut-off point was found to be ≥306.20 with 72.6% sensitivity, 69.4% specificity, 70.3% positive predictive value, 71.7% negative predictive value, and 70.96% test accuracy (OR 5.991, 95% CI 2.756-13.022, p<0.001). A PIV of or exceeding 306.20 increased the likelihood of osteoporosis by 4.991 times (Table 2, Figure 4).

DISCUSSION

To our knowledge, this is the first study investigating the relationship between PIV and BMD in women with PMOP. We found that high PIV levels were associated with low BMD and PIV was found to be significant both in differentiating healthy patients and those with osteoporosis, and in differentiating osteoporosis and osteopenia.

Table 2. Cut-off points and diagnostic values of variables for distinction between non-appendicitis patients and appendicitis patients

Variables	Cut-Off	Diagnostic values					ROC curve			Odds ratio		
		Sensitivity	Specificity	PPV	NPV	Accuracy	Area (SE)	95%CI	p	Odds ratio	95%CI	p
Control vs osteopenic	≥152.02	85.5%	56.5%	66.3%	79.5%	70.96%	0.758 (0.043)	0.675-0.842	<0.001	7.634	3.208-18.163	<0.001
Osteoporotic vs osteopenic	≥306.20	72.6%	69.4%	70.3%	71.7%	70.96%	0.770 (0.042)	0.688-0.852	<0.001	5.991	2.756-13.022	<0.001

PMOP is a common chronic disease. At least 40% of postmenopausal women are predicted to develop a fracture at some point in their lives.[5] As a result of fracture development due to PMOP, chronic pain, deformity, reduced independence due to physical limitation, psychosocial difficulties, deterioration in quality of life, disability, and even fracture-related deaths can be observed.[21] With the increase in the elderly population, both osteoporosis and related fractures are increasing day by day and are becoming a serious public health problem.[22] Therefore it is important to understand osteoporosis and blood parameters associated with osteoporosis.

In previous studies, it was found that some blood parameters were associated with bone hemostasis. In a study on mice, T and B lymphocytes have been shown to be effective in bone homeostasis. osteoprotogenin, which regulates bone resorption, was shown to be driven by B cells.[23] T cells have also been shown to be activated in PMOP due to decreased estrogen levels and to produce inflammatory cytokines involved in bone destruction such as receptor activator of nuclear factor kappa-B ligand (RANKL) and TNF alfa.[24] In the presence of inflammation, neutrophils have been shown to destroy bone tissue by releasing chemokines that summon T17 cells.[25] Circulating platelet levels also increase inflammation and osteoclastogenesis is triggered.[26] Monocytes in the blood turn into osteoclasts in case of estrogen deficiency and inflammation and increase bone destruction.[27] In our study, we aimed to find out whether there is a relationship between BMD and complete blood count parameters, which are frequently evaluated in outpatient clinics. There are several studies investigating complete blood count parameters in PMOP. Kale demonstrated that MLR and PLR were significantly higher in PMOP.[28] Another study conducted on Chinese women found a strong relationship between NLR and BMD.[12] Du et al.[29] evaluated a relationship between high SII levels and low BMD.When the research in the literature is evaluated, it is thought that there is a relationship between immune system cells and PMOP. We wanted to use PIV, a more comprehensive assessment tool that includes all these immune cells; neutrophils platelets monocytes, and lymphocytes. In our study, an inverse relationship was found between PIV and BMD values. PIV was even significant in differentiating osteoporosis and osteopenia. PIV was statistically higher in PMOP, and also higher in women with osteopenia than healthy individuals. According to Fang et al.[15] SII was not only found to be associated with BMD but also found to be effective in determining the risk of fractures in PMOP. However, we did not investigate the relationship between fracture risk and PIV in our study. It will be useful to conduct studies in which this relationship is investigated in the future.

If we can distinguish patients with osteopenia in the postmenopausal period, we can start their treatment early and reduce the risk of complications. In our study, PIV was also found effective in making this distinction. In differentiating healthy individuals from patients with osteopenia PIV was a 66.3% positive predictive value and in osteopenic and osteoporotic groups PIV was a 70.3% positive predictive value.

Smoking is an independent risk factor for osteoporosis. According to Weng et al.[30] in their review, it was also discussed that there is a negative relationship between smoking and BMD values of the femoral and lumbar vertebrae. Trevisan et al.[31] In patients with PMOP, they found a greater decrease in femoral BMD in smokers than in non-smokers at the end of 2 years. In our study, BMD values were also found to be lower in smokers both in the femur and lumbar vertebrae, but we could not determine the rate of change over the years because we did not follow the patients.

Currently, new potential therapeutic agents such as denosumab, IL-1 receptor antagonist, and TNF-α antibody are being developed for the treatment of osteoporosis secondary to inflammation. This shows the importance of understanding the relationship between the immune system and osteoporosis both in diagnosis and treatment. Since our study is a cross-sectional study, we evaluated the patients once. It would be useful to follow up on patients with PMOP and investigate the change in PIV values after treatment.

Limitations

Since we planned a cross-sectional study, we evaluated the patients once. We did not evaluate other parameters that may be associated with osteoporosis. We did not measure other blood values that may be associated with bone turnover.

Studies in larger groups of patients, taking into account other parameters that may be associated with osteoporosis, are needed.

CONCLUSION

Osteoporosis is a significant global public health problem with rising prevalence due to increasing morbidity, fracture-related mortality risk, and high treatment costs. Although DEXA is the most commonly used diagnostic method, it is not available in all areas. Therefore, the determination of new biomarkers that are easily accessible and cost-effective has gained prominence. In our study, we found that the PIV was statistically higher in PMOP, it was also statistically higher in

postmenopausal women with osteopenia compared to healthy controls. We believe that PIV can be a cheap, easy, and reliable evaluation parameter for determining the risk of osteoporosis and osteopenia in women with PMOP.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by Hitit University Clinical Researches Ethics Committee (Date: 26.12.2023, Decision No: 2023-170).

Informed Consent

In this study, each patient provided informed consent prior to participation.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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