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Association between leukocyte-based inflammatory indices and bone mineral density in hemodialysis patients

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ABSTRACT

Aims: Osteoporosis and osteopenia are common among hemodialysis (HD) patients, yet current methods for risk stratification remain limited. This study aimed to investigate the relationship between leukocyte-based inflammatory indices and osteoporosis and osteopenia in HD patients and to assess their diagnostic performance in differentiating these conditions.

Methods: A retrospective analysis was conducted on 168 HD patients classified into normal bone mineral density (BMD) (n=43), osteopenia (n=70), and osteoporosis (n=55) based on T-scores by dual-energy X-ray absorptiometry measurements. The leukocyte-based inflammatory indices were calculated as follows: Platelet to lymphocyte ratio (PLR)=platelet count/ lymphocyte count ratio; neutrophil o lymphocyte ratio (NLR)=neutrophil count/ lymphocyte count ratio; systemic immune inflammation index (SII)=platelet count×neutrophil count / lymphocyte count ratio, and systemic inflammation response index (SIRI)=neutrophil count×monocyte count/ lymphocyte count ratio.

Results: Osteopenia and osteoporosis were identified in 41.7% and 32.7% of patients, respectively. Patients with osteoporosis exhibited higher neutrophil and monocyte counts and lower lymphocyte counts ($p<0.001$). All inflammatory indices were higher in osteoporosis group compared to other group. Also, these indices were higher in osteopenia group compared to normal BMD group. SIRI showed the strongest discriminative power for differentiating osteopenia from normal BMD (AUC=0.84; sensitivity=81.4%; specificity=79.2%, $p<0.001$) and osteoporosis from osteopenia (AUC=0.86; sensitivity=82.5%; specificity=78.6%; $p<0.001$).

Conclusion: Leukocyte-based inflammatory indices, particularly SIRI, are significantly associated with reduced BMD in HD patients and may serve as accessible biomarkers for identifying those at heightened risk of osteopenia and osteoporosis.

Keywords: Bone mineral density, hemodialysis, osteoporosis, systemic inflammation

INTRODUCTION

Chronic kidney disease (CKD) is a global health concern that affects millions of people and is associated with various complications, including mineral and bone disorders (CKD-MBD).[1] Among patients with end-stage renal disease (ESRD) receiving hemodialysis (HD), disturbances in bone mineral density (BMD) are particularly common, leading to an increased risk of osteoporosis and fractures.[2] The underlying pathophysiology of these skeletal complications is multifactorial and includes altered calcium-phosphorus metabolism, vitamin D deficiency, abnormalities of parathyroid hormone (PTH), and chronic inflammation.[3]

The connection between bone health and inflammation is well-demonstrated in the process of bone fracture healing, which represents a classic acute inflammatory response driven by the innate immune system.[4,5] At the fracture site, both bone-forming cells and immune cells are actively recruited, leading to a complex interplay between hematopoietic stem cell-derived lineages (monocytes, macrophages, osteoclasts) and mesenchymal stem cell-derived lineages (pre-osteoblasts, osteoblasts). This dynamic interaction highlights the crucial role of inflammation in bone remodeling and regeneration.[6,7] In patients suffering from chronic inflammation, such as CKD, persistent cytokine activation further disrupts bone homeostasis.[8,9] Pro-inflammatory cytokines stimulate osteoclast differentiation and activity, leading to increased bone resorption, while simultaneously inhibiting osteoblast function and bone formation. This imbalance accelerates bone loss and contributes to the development of osteoporosis.[10]

Recent studies have proposed leukocyte-based inflammatory indices, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune inflammation index (SIRI), as potential markers for systemic inflammation in various disease states, including CKD and osteoporosis.[11-13]

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However, the diagnostic performance of these leukocyte-based inflammatory indices, including SIRI, in distinguishing patients with osteopenia or osteoporosis has not been comprehensively investigated. This study aimed to investigate the relationship between leukocyte-based inflammatory indices and osteoporosis and osteopenia in HD patients and to assess their diagnostic performance in differentiating these conditions.

METHODS

Ethics

This retrospective study was carried out at the Başkent University Practice and Research Hospital Orthopedic Clinic between January 2018 and January 2023, adhering to the ethical principles outlined in the Declaration of Helsinki. Approval was obtained from the Başkent University Hospital Medicine and Health Sciences Ethics Committee (Date: 22/10/2024, Decision No: KA24/346). Given the retrospective nature of the study, the Local Ethics Committee waived the requirement for informed consent.

Study Population

During the study period, 216 HD patients who were followed up in the orthopedic clinic for bone health were retrospectively assessed for study eligibility. The inclusion criteria included that patients must be over 18 years old, have received HD for at least six months, and have bone densitometry measurements available. The exclusion criteria were patients with active infection, recent surgery, known inflammatory diseases unrelated to CKD, cardiac conditions such as atrial fibrillation, aortic stenosis, or myocardial infarction, uncontrolled hypertension (>180/100 mmHg), a history of acute respiratory failure or thromboembolism, a history of autoimmune disease or malignancy, and those receiving corticosteroids or other immunosuppressive treatments. After applying the exclusion criteria, 168 patients were included in the final analysis.

Study Protocol

Demographic, and clinical data were collected from electronic patient records. Hypertension was defined by a blood pressure measurement exceeding 140/90 mmHg or the administration of antihypertensive medications, whereas diabetes mellitus was identified based on a fasting plasma glucose level of ≥126 mg/dl or the use of antidiabetic agents. Biochemical parameters were obtained from patient records of venous blood samples collected during outpatient evaluations at the time of hospital admission. All analyses were conducted in a single laboratory using standardized methodologies, as summarized below.

Biochemical Analysis

Data on laboratory parameters were retrospectively retrieved from venous blood samples obtained at the time of hospital admission. Hematological parameters were evaluated through laser and impedance-based methods with the CellDyn Ruby hematology analyzer (Abbott Diagnostics, Abbott Park, Illinois, USA) device. The assessment of biochemical parameters was performed using commercial kits and an Architect C8000 and i2000 autoanalyzers (Abbott Diagnostics, Abbott Park, Illinois, USA). The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C).[14] Inflammation indices were calculated as follows: PLR=platelet count/lymphocyte count; NLR=neutrophil count/lymphocyte count; SII=platelet count×neutrophil count/lymphocyte count, and SIRI=neutrophil count×monocyte count/lymphocyte count.

BMD Examination

BMD measurements had been previously performed using a Hologic QDR 4500 Densitometer Machine (Hologic Inc., Bedford, MA, USA) by trained technicians, following the manufacturer's standardized protocol for imaging and analysis. The BMD assessments were conducted at two key skeletal sites: the lumbar spine (anteroposterior projection at L1–L4) and the femoral neck (FN). The World Health Organization classification system was used to categorize patients into the normal (-1≤ T-score), osteopenia (-2.5< T-score <-1), and osteoporosis (T-score ≤-2.5) groups.[15]

Statistical Analysis

All data were analyzed with STATA/MP v.16 software (StataCorp LLC, Texas, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean±standard deviation values, while non-normally distributed variables are given as median (25^{th}-75^{th} quartiles) values. ANOVA test (post-hoc: Bonferroni test) or Kruskall-Wallis H test (post-hoc: Dunn's test) were used for comparisons between more than two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher-exact tests. Multivariable logistic regression analysis with the backward Wald method was performed to identify any possible independent predictors of osteoporosis and osteopenia. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance, and the results of area under the curve (AUC), standard error (SE), and sensitivity and specificity are reported. The optimal threshold value of the inflammation indices was determined by the Youden index method. Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULTS

The mean age of HD patients was 57.0±10.2 years (range: 36–70), with the majority being male. Hypertension was present in 63.7% of patients, diabetes mellitus in 25.6%, and coronary artery disease in 14.9%. The median HD duration was 3.5 years. Normal BMD was detected in 25.6% of patients, while 41.7% had osteopenia and 32.7% had osteoporosis. There were no significant differences in demographic characteristics among the normal BMD, osteopenia, and osteoporosis groups (Table 1).

Table 2 presents the comparison of laboratory parameters among HD patients with normal BMD, osteopenia, and osteoporosis. Systemic inflammatory indices were higher in the osteoporosis group compared to other groups. Also, these indices were higher in the osteopenia group compared to normal BMD group (SIRI→ normal: 0.4±0.2 vs. osteopenia: 0.8±0.2 vs. osteoporosis: 1.2±0.4, $p<0.001$; SII→ normal: 401.6±104.5 vs. osteopenia: 473.2±115.2 vs. osteoporosis:

Table 1. Demographic and clinical characteristics of hemodialysis patients

Variables	Normal	Osteopenia	Osteoporosis	p-value
	n=43	n=70	n=55	
Age, years	56.7±10.8	57.1±9.2	57.0±10.4	0.854
Gender, n (%)				
Female	19 (44.2)	28 (40.0)	17 (30.9)	0.352
Male	24 (55.8)	42 (60.0)	38 (69.1)	
BMI, kg/m^2	26.4±3.9	25.7±4.4	24.8±4.5	0.257
Smoking, n (%)	16 (37.2)	27 (38.6)	20 (36.4)	0.981
Hypertension, n (%)	25 (58.1)	44 (62.9)	38 (69.1)	0.536
Diabetes mellitus, n (%)	10 (23.3)	17 (24.3)	16 (29.1)	0.785
CAD, n (%)	7 (16.3)	7 (10.0)	11 (20.0)	0.288
HD duration, years	3.0 (1.0-5.0)	3.5 (1.0-5.5)	4.0 (1.0-6.5)	0.757
L1-L4 total T score	0.3 [(-0.2)-(1.2)]	-1.3 [(-1.5)-(-0.9)]	-2.9 [(-3.1)-(-2.7)]	<0.001*
Femur neck T score	0.4 [(-0.5)-(1.3)]	-1.3 [(-1.6)-(-0.8)]	-2.8 [(-3.0)-(-2.5)]	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Differences between groups are highlighted in bold characters. Abbreviations: BMI: Body-mass index, CAD: Coronary artery diseases, HD: hemodialysis

Table 2. Comparison of laboratory findings in hemodialysis patients with normal bone density, osteopenia, and osteoporosis

Variables	Normal	Osteopenia	Osteoporosis	p-value
	n = 43	n = 70	n = 55	
Leukocytes, ×10^9/L	7.3±1.7	7.0±1.4	6.7±1.9	0.197
Neutrophils, ×10^9/L	3.6±0.6	3.7±0.7	4.0±0.7	<0.001*
Lymphocytes, ×10^9/L	2.6±0.6	2.3±0.5	2.0±0.6	<0.001*
Platelets, ×10^9/L	256.4±60.0	259.2±65.3	269.8±55.7	0.485
Monocytes, ×10^9/L	0.4±0.2	0.5±0.2	0.6±0.2	<0.001*
NLR	1.5±0.4	1.7±0.5	2.0±0.6	<0.001*
PLR	108.7±35.1	126.0±34.7	148.6±41.0	<0.001*
SIRI	0.4±0.2	0.8±0.2	1.2±0.4	<0.001*
SII	401.6±104.5	473.2±115.2	536.8±145.6	<0.001*
Hemoglobin, g/dl	10.8±1.3	10.7±1.3	10.7±1.0	0.948
Total-C, mg/dl	158.5±44.9	155.5±41.1	148.7±48.9	0.529
LDL-C, mg/dl	101.4±32.9	102.1±34.4	97.1±35.1	0.703
HDL-C, mg/dl	37.3±11.1	36.3±9.6	36.7±12.0	0.901
Triglycerides, mg/dl	172.0 (132.0-216.5)	152.0 (92.8-204.8)	158.0 (119.0-228.0)	0.443
Total protein, g/dl	65.1±9.2	66.5±9.8	67.6±7.9	0.962
Urea, mg/dl	153.0 (116.0-198.5)	150.5 (127.2-186.8)	157.0 (134.0-191.0)	0.728
Creatinine, mg/dl	8.8±2.8	9.0±3.0	9.1±2.7	0.176
Uric acid, mg/dl	6.4±1.4	6.8±1.4	6.5±1.1	0.145
Calcium, mg/dl	8.6±0.9	8.4±0.8	8.4±0.6	0.261
Phosphorus, mg/dl	4.5±1.4	4.4±1.5	4.3±1.6	0.261
Albumin, g/dl	3.5±0.6	3.6±0.3	3.7±0.4	0.226
CRP, mg/dl	6.1 (3.1-11.4)	8.6 (4.3-13.1)	11.3 (6.1-16.2)	0.042*
Vitamin D, µg/L	23.0 (17.8-33.0)	19.0 (15.4-25.0)	16.5 (12.4-24.1)	0.087
PTH, ng/L	107.1 (28.5-331.6)	238.5 (62.1-530.5)	401.1 (266.2-661.2)	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Differences between groups are highlighted in bold characters. Abbreviations: BMI: Body-mass index, CRP: C-reactive protein, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PTH: Parathyroid hormone, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, Total-C: Total cholesterol

536.8±145.6, p<0.001). The median CRP level was found to be higher in the osteoporosis group than in the other groups, while no statistically significant difference was observed between the osteopenia and normal groups (normal: 6.1 vs. osteopenia: 8.6 vs. osteoporosis: 11.3, p=0.042). The median PTH levels showed variation among all groups, with the osteoporosis group exhibiting the highest median value (normal: 107.1 vs. osteopenia: 238.5 vs. osteoporosis: 401.1, p<0.001) (Table 2).

The effects of leukocyte-based inflammation indices on osteoporosis and osteopenia are displayed in Table 3. In Model I regression analysis, the effects of age, sex, BMI, comorbid conditions, and HD duration were adjusted. In Model II regression analysis, in addition to the parameters in model I, the effects of CRP and PTH levels were also adjusted. In both adjusted regression models, leukocyte-based inflammation indices continued to have a significant impact on osteopenia and osteoporosis.

Table 4 summarizes the diagnostic performance of select laboratory parameters for differentiating patients with osteopenia from those with normal BMD and those with osteoporosis from osteopenic patients. Among these parameters, the SIRI emerged as the most robust indicator in both comparisons. For distinguishing osteopenia from normal BMD, SIRI had a threshold value of >0.57, with 81.4% sensitivity and 79.2% specificity (AUC±SE=0.84±0.04, 95% CI=0.77-0.91, p<0.001). For differentiating osteoporosis

Table 3. Impact of leukocyte-based inflammatory indices on osteopenia and osteoporosis in hemodialysis patients based on crude and adjusted models

Variables	Osteopenia			Osteoporosis		
	OR	95% CI	p-value	OR	95% CI	p-value
SIRI						
Crude	2.52	1.78-3.54	<0.001*	1.95	1.53-2.49	<0.001*
Adjusted model I	2.57	1.80-3.65	<0.001*	2.52	1.80-3.53	<0.001*
Adjusted model I	2.62	1.83-3.77	<0.001*	2.62	1.82-3.75	<0.001*
SII						
Crude	1.05	1.01-1.07	0.001*	1.03	1.01-1.05	<0.001*
Adjusted model I	1.05	1.01-1.08	0.008*	1.04	1.01-1.07	0.004*
Adjusted model I	1.05	1.03-1.08	0.007*	1.04	1.01-1.06	0.007*
NLR						
Crude	3.50	1.11-8.08	0.001*	3.09	1.48-6.45	0.003*
Adjusted model I	3.93	1.27-12.16	0.018*	3.24	1.47-7.56	0.005*
Adjusted model I	3.75	1.21-11.61	0.022*	3.36	1.08-10.48	0.007*
PLR						
Crude	1.02	1.01-1.03	0.001*	1.02	1.01-1.03	0.001*
Adjusted model I	1.02	1.01-1.03	0.008*	1.03	1.01-1.04	0.008*
Adjusted model I	1.03	1.01-1.04	0.007*	1.03	1.01-1.05	0.013*

Abbreviations: CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, OR: Odds ratio

Table 4. Diagnostic performance of laboratory parameters associated with osteopenia and osteoporosis

Variables		AUC±SE	95% CI	Sens. (%)	Spec. (%)	Threshold	p-value
Osteopenia *vs.* control	Neutrophils	0.53±0.06	0.42-0.64	22.9	90.7	>3.5	0.617
	Lymphocytes	0.63±0.06	0.53-0.736	71.2	67.8	<2.4	0.020*
	Monocytes	0.68±0.04	0.60-0.75	70.5	68.4	<0.5	<0.001*
	SIRI	0.84±0.04	0.77-0.91	81.4	79.2	>0.57	<0.001*
	SII	0.72±0.06	0.61-0.82	70.1	69.2	>438.4	0.001*
	NLR	0.68±0.05	0.59-0.78	65.4	67.3	>1.53	0.001*
	PLR	0.66±0.05	0.57-0.77	62.4	63.6	>118.4	0.001*
	CRP	0.50±0.06	0.39-0.61	67.1	45.8	>6.5	0.488
	PTH	0.62±0.06	0.52-0.73	70.4	71.3	>188.4	0.027*
Osteoporosis *vs.* osteopenia	Neutrophils	0.68±0.05	0.57-0.7	68.9	67.4	>3.7	0.909
	Lymphocytes	0.65±0.05	0.56-0.75	70.4	69.8	<2.1	0.002*
	Monocytes	0.70±0.04	0.62-0.79	64.5	78.2	>0.6	0.001*
	SIRI	0.86±0.03	0.78-0.94	82.5	78.6	>1.0	<0.001*
	SII	0.71±0.05	0.62-0.79	70.2	58.6	457.8	<0.001*
	NLR	0.68±0.05	0.58-0.75	58.2	75.7	>1.9	0.001*
	PLR	0.67±0.05	0.57-0.75	50.1	84.3	>140.9	<0.001*
	CRP	0.66±0.05	0.56-0.76	70.4	45.7	>9.0	0.045*
	PTH	0.69±0.05	0.59-0.579	76.9	51.4	>254.3	0.032*

*p<0.05 indicates statistical significance. Abbreviations: AUC: Area under the curve, CI: Confidence interval, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PTH: Parathyroid hormone: Sens: Sensitivity, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, Spec: Specificity

from osteopenia, the threshold value was >1.0, with 82.5% sensitivity and 78.6% specificity (AUC±SE=0.86±0.03, 95% CI=0.78-0.94, p<0.001) (**Figure**).

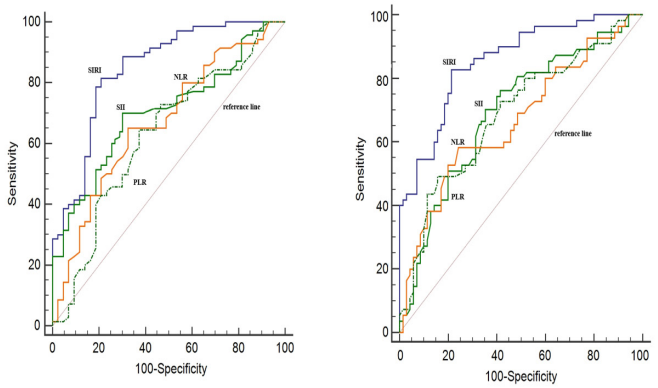

Figure. Diagnostic performance of leukocyte-based inflammatory indices in differentiating osteopenia (*vs.* normal bone mineral density) and osteoporosis (*vs.* osteopenia)

DISCUSSION

Osteoporosis and osteopenia are highly prevalent in HD patients, with some studies reporting rates exceeding 16–41% for osteoporosis and 32-52% for osteopenia.[2,16-19] The frequencies rates observed in this study were in agreement with findings from the existing literature. The mechanisms underlying osteoporosis and osteopenia in dialysis patients are multifactorial, falling under the umbrella of CKD-MBD. As kidney function declines, disturbances in mineral homeostasis and bone turnover develop early and worsen progressively.[20,21] Secondary hyperparathyroidism serves as a central mechanism, driven by diminished renal phosphate excretion and impaired synthesis of active vitamin D (calcitriol), culminating in hyperphosphatemia, hypocalcemia, and vitamin D deficiency. These changes trigger excess PTH secretion, which in turn stimulates osteoclast activity and bone resorption.[22,23] In agreement with these findings, HD patients, especially those with osteoporosis, were found to have lower vitamin D levels and higher PTH levels.

HD patients typically exhibit a chronic pro-inflammatory state, which is common in ESRD.[24] The bone and immune systems are tightly interconnected (osteoimmune regulation), meaning immune cell activity can directly influence bone remodeling.[25] In dialysis patients, who often have a sustained inflammatory burden, there is strong biologic plausibility that inflammation contributes to accelerated bone loss.[26] Immune cells and their cytokines can alter osteoclast and osteoblast function, affecting BMD.[27] Iron overload-induced osteoporotic mice exhibited a significant increase in leukocyte counts and their subtypes. Similarly, the same study reported comparable findings in osteoporotic patients relative to healthy controls.[28]

A growing body of evidence links higher leukocyte counts or imbalanced differentials to lower BMD.[28-30] Nonetheless, leukocyte subtypes may not serve as consistent predictors of BMD and clinical assessments of microarchitecture. A population-based prospective study found that in postmenopausal women enrolled between 2009 and 2012, only neutrophils demonstrated an inverse association with BMD. In contrast, among those enrolled between 2014 and April 2017, both leukocytes and monocytes exhibited inverse relationships with BMD.[31] This is in agreement with the low diagnostic performance of leukocyte subtypes reported in the present study. Therefore, inflammation indices generated from leukocyte subtypes may demonstrate improved diagnostic performance. A meta-analysis found that NLR and PLR were higher in the osteoporosis group, regardless of gender. Additionally, in a subgroup analysis focusing on postmenopausal women, NLR was found to be associated with osteoporosis independently of age and comorbidities.[32] A study conducted on patients with ESRD found that NLR levels were not associated with BMD.[33] In a study involving HD patients, NLR and PLR levels were reported to show no significant difference between those with normal BMD and those with osteoporosis or osteopenia.[12] Discrepancies among studies may stem from differences in patient selection criteria, demographic characteristics, HD duration, and the distribution of comorbid conditions. In this study, although higher NLR and PLR levels were observed in HD patients with osteoporosis or osteopenia compared to those with normal BMD, their sensitivity in distinguishing these conditions was found to be low. In light of these findings, leukocyte-derived ratios such as NLR and PLR may have limited utility in assessing bone health in HD patients. Given the complex interplay between inflammation and bone metabolism, broader inflammatory indices, such as the SII and the SIRI, may offer a more comprehensive assessment of inflammatory burden and its impact on BMD.

A study analyzing 2.302 CKD patients from the NHANES cohort identified an inverse association between SII and BMD. Notably, higher SII levels remained predictive of lower pelvic BMD even after adjustments for age, sex, and race.[11] In the present study, all leukocyte-based inflammatory indices remained significant after adjusting for age and sex. Notably, SIRI demonstrated superior diagnostic performance, exhibiting higher sensitivity and specificity than other leukocyte-derived inflammatory markers in distinguishing osteopenia from normal BMD and osteoporosis from osteopenia in dialysis patients. This may be attributed to SIRI's incorporation of monocytes, a key cell type involved in chronic inflammation and osteoclast precursor supply.[34] On the other hand, this is the first study to evaluate the association between SIRI and bone loss in HD patients. Therefore, further research is needed to validate the diagnostic performance of SIRI in assessing bone loss in HD patients. However, in certain selected cohorts, the diagnostic performance of SIRI in predicting bone loss aligns with the current findings. An elderly hypertensive patient study demonstrated that SIRI was significantly associated with lower BMD, higher osteoporosis prevalence, and even higher fracture incidence during follow-up.[35] Similarly, a study in postmenopausal women reported a strong negative association between SII and BMD across quartiles, with those in the highest SII and SIRI quartile exhibiting significantly lower femoral neck BMD compared to those in the lowest quartile. Notably, after controlling for confounding factors, SII and SIRI remained a significant predictor of BMD in postmenopausal women but not in premenopausal women, highlighting its potential role in age-related bone loss.[36]

Limitations

This study has some important limitations. The primary limitation of this study is its single-center, retrospective design, which may restrict its generalizability to HD patients and hinder causal interpretations regarding the impact of elevated inflammation on bone loss. Second, a single measurement of leukocyte counts and BMD may not fully account for temporal fluctuations in inflammation or bone metabolism. Third, additional confounding variables, including nutritional status, dialysis adequacy, and specific treatments like vitamin D analogs, phosphate binders, or steroids, were not analyzed in this study. Lastly, assessments such as cytokine profiling and flow cytometry were not feasible due to the study's design. Longitudinal studies with large cohorts that incorporate these limitations are required.

CONCLUSION

This study highlights the significant role of systemic inflammation in the deterioration of BMD among HD patients. Elevated inflammatory indices were associated with both osteopenia and osteoporosis, suggesting that chronic inflammation may contribute to bone metabolism dysregulation in this population. Among leukocyte-based inflammation indices, SIRI has the potential to serve as a novel and accessible screening tool for identifying individuals at increased risk of osteoporosis and osteopenia. These findings emphasize the need to incorporate inflammatory markers into osteoporosis risk assessment strategies in this cohort.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval was obtained from the Başkent University Hospital Medicine and Health Sciences Ethics Committee (Date: 22/10/2024, Decision No: KA24/346).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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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.

REFERENCES

1. Waziri B, Duarte R, Naicker S. Chronic kidney disease-mineral and bone disorder (CKD-MBD): current perspectives. *Int J Nephrol Renovasc Dis*. 2019;12:263-276. doi:10.2147/IJNRD.S191156
2. Huang GS, Chu TS, Lou MF, Hwang SL, Yang RS. Factors associated with low bone mass in the hemodialysis patients--a cross-sectional correlation study. *BMC Musculoskelet Disord*. 2009;10(1):60. doi:10.1186/1471-2474-10-60
3. Hu L, Napoletano A, Provenzano M, et al. Mineral bone disorders in kidney disease patients: the ever-current topic. *Int J Mol Sci*. 2022;23(20):12223. doi:10.3390/ijms232012223
4. Nich C, Takakubo Y, Pajarinen J, et al. Macrophages-key cells in the response to wear debris from joint replacements. *J Biomed Mater Res A*. 2013;101(10):3033-3045. doi:10.1002/jbm.a.34599
5. Charles JF, Nakamura MC. Bone and the innate immune system. *Curr Osteoporos Rep*. 2014;12(1):1-8. doi:10.1007/s11914-014-0195-2
6. Loi F, Cordova LA, Pajarinen J, Lin TH, Yao Z, Goodman SB. Inflammation, fracture and bone repair. *Bone*. 2016;86:119-30. doi:10.1016/j.bone.2016.02.020
7. Mazzaferro S, Cianciolo G, De Pascalis A, et al. Bone, inflammation and the bone marrow niche in chronic kidney disease: what do we know? *Nephrol Dial Transplant*. 2018;33(12):2092-2100. doi:10.1093/ndt/gfy115
8. Qian Q. Inflammation: a key contributor to the genesis and progression of chronic kidney disease. *Contrib Nephrol*. 2017;191:72-83. doi:10.1159/000479257
9. Zhou P, Zheng T, Zhao B. Cytokine-mediated immunomodulation of osteoclastogenesis. *Bone*. 2022;164:116540. doi:10.1016/j.bone.2022.116540
10. D'Amelio P, Sassi F. Osteoimmunology: from mice to humans. *Bonekey Rep*. 2016;5:802. doi:10.1038/bonekey.2016.29
11. Jiang Y, Bao X. Systemic immune-inflammatory indicators and bone mineral density in chronic kidney disease patients: a cross-sectional research from NHANES 2011 to 2018. *PLoS One*. 2024;19(4):e0302073. doi:10.1371/journal.pone.0302073
12. Şen Uzeli Ü, Doğan M. The relationship between neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), hemoglobin albumin lymphocyte and platelet (HALP) score and bone mineral density in hemodialysis Patients. *J Orthop Res Rehab*. 2024;2(1):5-8. doi:10.51271/JORR-0023
13. Chen S, Sun X, Jin J, Zhou G, Li Z. Association between inflammatory markers and bone mineral density: a cross-sectional study from NHANES 2007-2010. *J Orthop Surg Res*. 2023;18(1):305. doi:10.1186/s13018-023-03795-5
14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry*. 1972;18(6):499-502. doi:10.1093/clinchem/18.6.499
15. Siris ES, Adler R, Bilezikian J, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. *Osteoporos Int*. 2014;25(5):1439-1443. doi:10.1007/s00198-014-2655-z
16. Slouma M, Sahli H, Bahlous A, et al. Mineral bone disorder and osteoporosis in hemodialysis patients. *Adv Rheumatol*. 2020;60(1):15. doi:10.1186/s42358-020-0118-0
17. Polymeris A, Doumouchtsis K, Grapsa E. Bone mineral density and bone metabolism in hemodialysis patients. Correlation with PTH, 25OHD3 and leptin. *Nefrologia*. 2012;32(1):73-78. doi:10.3265/Nefrologia.pre2011.Jul.10916
18. Tamimi R, Bdair A, Shratih A, et al. Bone mineral density and related clinical and laboratory factors in peritoneal dialysis patients: implications for bone health management. *PLoS One*. 2024;19(5):e0301814. doi:10.1371/journal.pone.0301814
19. Binici DN, Gunes N. Risk factors leading to reduced bone mineral density in hemodialysis patients with metabolic syndrome. *Ren Fail*. 2010;32(4):469-474. doi:10.3109/08860221003675260
20. Sprague SM, Martin KJ, Coyne DW. Phosphate balance and CKD-mineral bone disease. *Kidney Int Rep*. 2021;6(8):2049-2058. doi:10.1016/j.ekir.2021.05.012
21. Hsu CY, Chen LR, Chen KH. Osteoporosis in patients with chronic kidney diseases: a systemic review. *Int J Mol Sci*. 2020;21(18):6846. doi:10.3390/ijms21186846
22. Feng X, McDonald JM. Disorders of bone remodeling. *Annu Rev Pathol*. 2011;6(1):121-145. doi:10.1146/annurev-pathol-011110-130203
23. Aguilar A, Gifre L, Urena-Torres P, et al. Pathophysiology of bone disease in chronic kidney disease: from basics to renal osteodystrophy and osteoporosis. *Front Physiol*. 2023;14:1177829. doi:10.3389/fphys.2023.1177829
24. Cobo G, Lindholm B, Stenvinkel P. Chronic inflammation in end-stage renal disease and dialysis. *Nephrol Dial Transplant*. 2018;33(suppl_3):iii35-iii40. doi:10.1093/ndt/gfy175

25. Lorenzo J, Horowitz M, Choi Y. Osteoimmunology: interactions of the bone and immune system. *Endocr Rev*. 2008;29(4):403-440. doi:10.1210/er.2007-0038
26. Mazzaferro S, De Martini N, Rotondi S, et al. Bone, inflammation and chronic kidney disease. *Clinica Chimica Acta*. 2020;506:236-240. doi:10.1016/j.cca.2020.03.040
27. Hong J, Luo F, Du X, Xian F, Li X. The immune cells in modulating osteoclast formation and bone metabolism. *Int Immunopharmacol*. 2024;133:112151. doi:10.1016/j.intimp.2024.112151
28. Li Y, Hao W, Guan J, et al. Relationship between indices of circulating blood cells and bone homeostasis in osteoporosis. *Front Endocrinol (Lausanne)*. 2022;13:965290. doi:10.3389/fendo.2022.965290
29. Valderrabano RJ, Lui LY, Lee J, et al. Bone density loss is associated with blood cell counts. *J Bone Miner Res*. 2017;32(2):212-220. doi:10.1002/jbmr.3000
30. Su YJ, Chen CT, Tsai NW, et al. The role of monocyte percentage in osteoporosis in male rheumatic diseases. *Am J Mens Health*. 2017;11(6):1772-1780. doi:10.1177/1557988317721642
31. Schyrr F, Marques-Vidal P, Hans D, Lamy O, Naveiras O. Differential blood counts do not consistently predict clinical measurements of bone mineral density and microarchitecture at homeostasis. *JBMR Plus*. 2022;6(9):e10669. doi:10.1002/jbm4.10669
32. Liu YC, Yang TI, Huang SW, Kuo YJ, Chen YP. Associations of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with osteoporosis: a meta-analysis. *Diagnostics (Basel)*. 2022;12(12):2968. doi:10.3390/diagnostics12122968
33. Ban TH, Choi BS, Yoon SA, et al. Clinical significance of neutrophil-to-lymphocyte ratio on the risk of abdominal aortic calcification and decreased bone mineral density in patients with end-stage kidney disease. *PLoS One*. 2023;18(10):e0286612. doi:10.1371/journal.pone.0286612
34. Xue J, Xu L, Zhu H, et al. CD14(+)CD16(-) monocytes are the main precursors of osteoclasts in rheumatoid arthritis via expressing Tyro3TK. *Arthritis Res Ther*. 2020;22(1):221. doi:10.1186/s13075-020-02308-7
35. Ma H, Cai X, Hu J, et al. Association of systemic inflammatory response index with bone mineral density, osteoporosis, and future fracture risk in elderly hypertensive patients. *Postgrad Med*. 2024;136(4):406-416. doi:10.1080/00325481.2024.2354158
36. Chen Y, Yu J, Shi L, et al. Systemic inflammation markers associated with bone mineral density in perimenopausal and postmenopausal women. *J Inflamm Res*. 2023;16:297-309. doi:10.2147/JIR.S385220