Risk Factors and Outcome of Decreased Bone Mineral Density in Chronic Kidney Disease Stages 5-5D Patients

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Abstract

Background: Mineral and bone disorders in chronic kidney disease (CKD) involve disturbances in mineral metabolism and hormonal regulation that lead to bone loss, fractures, and increased mortality. While bone mineral density (BMD) testing does not directly assess bone turnover, the 2017 KDIGO guidelines recommend BMD testing in CKD stages G3a–G5D for those at risk of osteoporosis, given the growing evidence linking low BMD to adverse outcomes. However, data in advanced CKD remains limited.

Methods: This retrospective study evaluated BMD in 189 patients with CKD stages 5-5D who underwent total hip, femoral neck, or lumbar spine BMD testing between 2011 and 2022, with an average follow-up of 51.2 months.

Results: Multivariate analyses revealed that the presence of a lower T-score or osteoporosis at any skeletal site, as well as at each site separately, was associated with traditional risk factors, including older age, lower body mass index, and female sex. Biochemical markers, such as reduced serum calcium, elevated alkaline phosphatase, decreased total lymphocyte and platelet counts, as well as elevated mean corpuscular volume, were associated with reduced BMD. Patients with CKD stage 5D experienced greater BMD decline than those in stage 5. Osteoporosis at all skeletal sites predicted all-cause mortality.

Conclusion: Reduced BMD and osteoporosis in advanced CKD were linked to traditional risk factors, disordered mineral metabolism, systemic inflammation, and nutritional deficiencies, and were predictors of mortality.

Keywords: bone loss; survival; kidney failure; ESKD; dialysis; CKD-MBD; fracture

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ปัจจัยเสี่ยงและผลลัพธ์ของความหนาแน่นมวลกระดูกที่ลดลงในผู้ป่วยโรคไตเรื้อรังระยะ 5–5D

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บทคัดย่อ

บทนำ: ความผิดปกติของแร่ธาตุและกระดูกในโรคไตเรื้อรังเกิดจากความบกพร่องของการควบคุมสมดุลแร่ธาตุและฮอร์โมน ส่งผลให้เกิดการสูญเสียมวลกระดูก กระดูกหัก และอัตราการเสียชีวิตที่เพิ่มสูงขึ้น แม้ว่าการตรวจวัดความหนาแน่นมวลกระดูกจะไม่สามารถประเมินอัตราการสร้าง–สลายกระดูกได้โดยตรง แต่แนวทาง KDIGO ปี 2017 แนะนำให้ทำการตรวจมวลกระดูกในผู้ป่วยโรคไตเรื้อรังระยะ G3a–G5D ที่มีความเสี่ยงต่อโรคกระดูกพรุน เนื่องจากมีหลักฐานเพิ่มขึ้นอย่างต่อเนื่องที่เชื่อมโยงมวลกระดูกต่ำกับผลลัพธ์ที่ไม่พึงประสงค์ อย่างไรก็ตามข้อมูลในผู้ป่วยโรคไตเรื้อรังระยะสุดท้ายยังมีจำกัด

ระเบียบวิธีวิจัย: การศึกษาย้อนหลังนี้ประเมินมวลกระดูกในผู้ป่วยโรคไตเรื้อรังระยะ 5–5D จำนวน 189 ราย ที่ได้รับการตรวจมวลกระดูกบริเวณสะโพกทั้งหมด คอสะโพก หรือกระดูกสันหลังส่วนเอว ระหว่างปี ค.ศ. 2011 ถึง 2022 โดยมีระยะเวลาติดตามเฉลี่ย 51.2 เดือน

ผลการวิจัย: การวิเคราะห์แบบพหุตัวแปรพบว่า ค่า T-score ที่ต่ำ การมีภาวะกระดูกพรุนที่ตำแหน่งใดก็ตาม และเมื่อพิจารณาแต่ละตำแหน่งแยกกัน มีความสัมพันธ์กับปัจจัยเสี่ยงแบบดั้งเดิม ได้แก่ อายุที่มากขึ้น ดัชนีมวลกายต่ำ และเพศหญิง นอกจากนี้ยังมีความสัมพันธ์กับระดับแคลเซียมในเลือดที่ลดลง ระดับเอนไซม์อัลคาไลน์ฟอสฟาเตสที่เพิ่มสูง จำนวนลิมโฟไซต์และเกล็ดเลือดที่ลดลง รวมถึงค่าเฉลี่ยปริมาตรเม็ดเลือดแดงที่เพิ่มขึ้น ผู้ป่วยโรคไตเรื้อรังระยะ 5D มีการลดลงของมวลกระดูกมากกว่าผู้ป่วยโรคไตเรื้อรังระยะ 5 และภาวะกระดูกพรุนทุกตำแหน่งสามารถทำนายอัตราการเสียชีวิตจากทุกสาเหตุได้

สรุป: มวลกระดูกที่ลดลงและภาวะกระดูกพรุนในผู้ป่วยโรคไตเรื้อรังระยะสุดท้ายมีความเชื่อมโยงกับปัจจัยเสี่ยงแบบดั้งเดิม ความผิดปกติของเมแทบอลิซึมของแร่ธาตุ ภาวะอักเสบของร่างกาย และภาวะโภชนาการบกพร่อง และยังเป็นตัวทำนายการเสียชีวิตอีกด้วย

คำสำคัญ: กระดูกบาง; กระดูกหัก; กระดูกผุ; ฟอกเลือด; บำบัดทดแทนไต; ไตวาย; ฟอกไต

Introduction

Mineral and bone disorders in chronic kidney disease (CKD) encompass a spectrum of abnormalities in mineral metabolism and hormone regulation, ultimately leading to bone loss, fractures, extraosseous calcification, and increased mortality. In the early stages of CKD, elevated levels of sclerostin and DKK1 inhibit the Wnt signaling pathway, which is essential for bone formation. This inhibition suppresses bone formation, resulting in low bone turnover and adynamic bone disease[1,2]. In later stages, a decline in 1,25-dihydroxy vitamin D levels leads to an increase in parathyroid hormone (PTH), which

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stimulates bone turnover and contributes to high-turnover bone disease[3]. However, in dialysis patients, low bone turnover remains common due to CKD-related factors that contribute to PTH resistance and calcium load, such as the accumulation of uremic toxins, high doses of active vitamin D, calcium-based phosphate binders, and high dialysate calcium concentrations[3,4]. As a result, patients with CKD stage 5D may present with low, high, or mixed bone turnover histology.

To accurately identify bone turnover types and guide treatment, a bone biopsy with histomorphometry is required. However, due to its invasive nature, associated patient discomfort, and the need for specialized tissue processing and software, this procedure is not widely available and is infrequently used in routine clinical practice. Physicians often rely on bone turnover biomarkers such as PTH and alkaline phosphatase. Recently, non-kidney-retained bone turnover markers, including bone alkaline phosphatase, intact procollagen 1 N-terminal propeptide, and tartrate-resistant acid phosphatase 5b have been proposed as more accurate predictors of bone turnover[5,6].

The 2009 KDIGO guidelines did not recommend bone mineral density (BMD) testing for evaluating bone disorders in CKD, particularly in later stages, due to its inability to distinguish different types of bone turnover[7] However, growing evidence linking decreased BMD to adverse clinical outcomes led the 2017 KDIGO guidelines to suggest BMD testing in patients with CKD stages G3a-G5D who have evidence of CKD-MBD or osteoporosis risk factors, especially if the results would influence treatment decisions[8].

Despite these recommendations, data on BMD and clinical outcomes, particularly in advanced CKD, remain limited. The discrepancies in the ability of reduced BMD at each site to predict outcome also varied. A systematic review and meta-analysis published a decade ago, which included 13 studies (three conducted by the same group of authors) in CKD patients, found an association between decreased BMD at the femoral neck, lumbar spine, and radius and an increased risk of fractures[9] More recent studies in dialysis patients have suggested a relationship between decreased BMD at the femoral neck and the distal one-third of the radius and increased mortality[10,11]. The present study evaluated BMD at the femoral neck, total hip, and lumbar spine in patients with CKD stages 5 and 5D. It further examined the associations between osteopenia or osteoporosis, defined both at any site and at each skeletal site separately, with baseline biochemical factors, as well as evaluating their ability to predict all-cause mortality

Materials and Methods

Study design and setting

This is a retrospective cohort analysis of patients with CKD stages 5-5D who underwent BMD test by dural-x-ray absorptiometry at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. The study was approved by the Human Research Ethics Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (Approval number: MURA2022/260). The Ethics Committee granted a waiver of informed consent. The study adhered to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments.

Participants

Patients with CKD stage 5 and 5D who received care at Ramathibodi Hospital between 2011 and 2022 were identified through the electronic medical record system and cross-referenced with the Department of Nuclear Medicine's BMD database, yielding 644 patients. Medical records were reviewed, and those who underwent BMD testing before reaching CKD stage 5 or after kidney transplantation were excluded. A total of 189 patients were included. For patients with multiple BMD tests, the worst BMD result for each patient was used. This resulted in 189 patients who underwent BMD testing at any site, including 183 who had total hip or femoral neck assessments and 187 who had lumbar spine assessments. The study flowchart is shown in **Figure 1**.

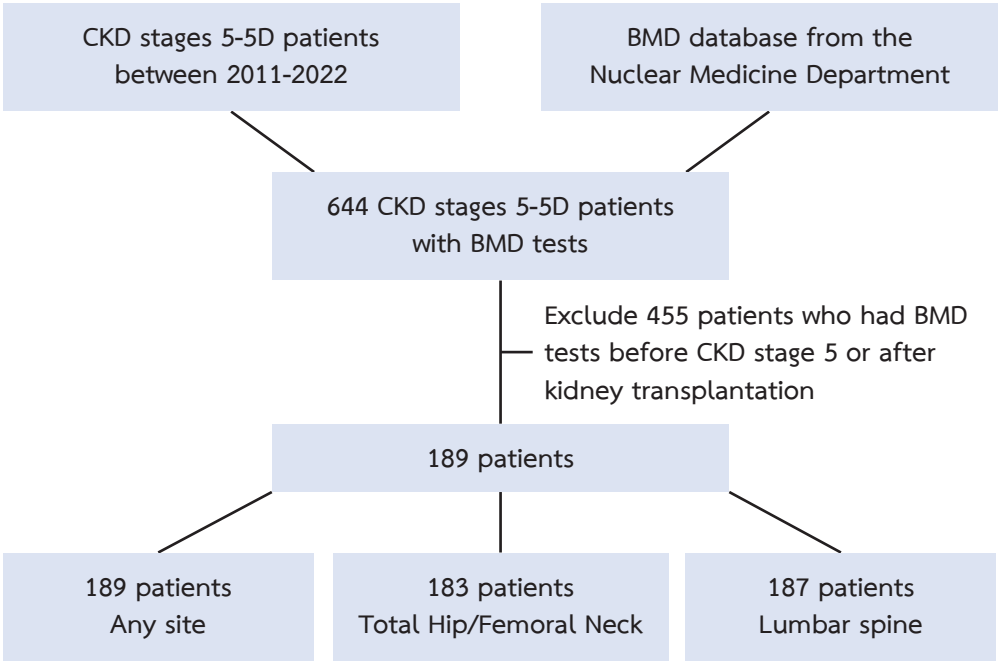

Figure 1 Study flow diagram
CKD, chronic kidney disease; BMD, bone mineral density

Bone Mineral Density

BMD was determined by dual-energy X-ray absorptiometry (Hologic A, software 12.6.1, Bedford, MA, USA). Osteopenia and osteoporosis were defined using the World Health Organization criteria[12]. In this study, osteopenia and osteoporosis at any site indicate that a patient had a T-score between -2.5 to -1 and below -2.5, respectively, at one or more of the following skeletal sites: total hip, femoral neck, or lumbar spine. Thus, the presence of osteopenia or osteoporosis at any site was defined by the lowest T-score among these skeletal sites.

Outcomes and follow-up

The outcomes included examining the associations between BMD, T-score, and osteoporosis with baseline factors, as well as evaluating their ability to predict all-cause mortality. The study began at the time of the BMD test, with follow-ups continuing until the patient's death, kidney transplantation, or the end of 2024. For patients lost to follow-up, survival data were obtained through phone contact.

Biochemical data

Demographic and laboratory data were obtained from the electronic medical record system. Cardiovascular disease (CVD) was defined as a history of coronary artery disease, cerebrovascular disease, or peripheral vascular disease. Baseline biochemical data were calculated as the 12-month average values preceding the BMD test. Serum calcium levels were corrected using the following equation: corrected calcium (mg/dl) = serum calcium (mg/dl) + [(40 – serum albumin (g/l))/10 × 0.8].

Statistical methods

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). Group differences were assessed using one-way ANOVA with Bonferroni correction, the Kruskal–Wallis test, or the Chi-square test, as appropriate. Baseline demographic and laboratory data associated with BMD and T-scores were analyzed using linear regression, while associations with osteoporosis were assessed using logistic regression. Cox proportional hazards regression was applied to identify predictors of all-cause mortality. Multivariate analyses were conducted using stepwise regression with backward elimination. All statistical analyses were performed using Stata 18 software (StataCorp LLC, College Station, Texas, USA).

Results

Baseline demographic and laboratory data stratified by osteopenia/osteoporosis status

Baseline characteristics and laboratory data for all patients (N=189), stratified by T-score category for osteopenia and osteoporosis at any skeletal site, are summarized in **Table 1 and Figure 2**. Among 143 patients with CKD stage 5D, 6 were on peritoneal dialysis, and 137 were on hemodialysis. Twenty-five patients (13.2%) had normal BMD, 68 (36.0%) had osteopenia, and 95 (50.8%) had osteoporosis. Declining T-scores at any site were associated with older age, female sex, and lower body mass index (BMI). Patients with osteoporosis more frequently had CVD and a history of fractures. Use of active vitamin D was also more common in the osteoporosis group. Additionally, lower serum creatinine, calcium, and phosphate levels were linked to greater declines in T-scores.

Baseline biochemical data stratified by osteopenia/osteoporosis status at the total hip are presented in **Supplementary Table 1 and Figure 2**. Among 183 patients, 58 (31.7%) had normal BMD, 79 (43.2%) had osteopenia, and 46 (25.1%) had osteoporosis. In addition to the above relationships, osteoporosis at the total hip was more frequent in CKD stage 5D compared with stage 5. Declining total hip T-score was also associated with hematologic indices, including higher mean corpuscular volume (MCV) and lower platelet counts. No significant association was observed between total hip T-score and serum calcium.

Table 1 Baseline characteristics and laboratory findings of all patients categorized by osteopenia/osteoporosis status at any skeletal site

Factors	All N=189	Normal N=25	Osteopenia N=68	Osteoporosis N=96	P
Age (years)	64.7±14.9	56.6±14.4	62±15.4	68.7±13.5[b,d]	<0.001
Sex (female)	152 (80.4)	13 (52)	52 (76.5)[a]	87 (90.6)[c,d]	<0.001
Height (cm)	154.1±8.6	163.4±7.4	155.8±7.6[c]	150.6±7.5[c,f]	<0.001
Weight (kg)	57.4±13.8	73.3±18.8	58.1±10.6[c]	52.8±10.8[c,d]	<0.001
Body mass index (kg/m^2)	24.1±4.77	27.4±8.2	24±4.47[b]	23.4±4.21[c]	<0.001
Diabetes (n/%)	77 (40.7)	12 (48)	23 (33.8)	42 (43.8)	0.324
CVD (n/%)	60 (31.8)	7 (28)	15 (22.1)	38 (39.6)[d]	0.054
Dyslipidemia (n/%)	178 (94.2)	25 (14)	61 (89.7)	92 (95.8)	0.105
Fracture (n/%)	17 (8.99)	0 (0)	3 (4.41)	14 (14.6)[a,d]	0.019
Parathyroidectomy (n/%)	17 (8.99)	4 (16)	7 (10.3)	6 (6.25)	0.283
CKD stages (n/%)					0.863
5	46 (24.3)	5 (20)	17 (25)	24 (25)	
5D	143 (75.7)	20 (80)	51 (75)	72 (75)	
Dialysis vintage (months)	45.3 (6.47-93.6)	36.8 (12.3-98.1)	51.2 (1.5-111)	43.1 (3.23-88.8)	0.846
Medications					
Steroids (n/%)	17 (8.99)	5 (20)	4 (5.88)[a]	8 (8.33)	0.103
PO_4 Binders (n/%)					0.309
Calcium (n/%)	110 (58.2)	14 (56)	40 (58.8)	56 (58.3)	

Table 1 Baseline characteristics and laboratory findings of all patients categorized by osteopenia/osteoporosis status at any skeletal site (continued)

Factors	All N=189	Normal N=25	Osteopenia N=68	Osteoporosis N=96	P
Non-Calcium (n/%)	11 (5.82)	1 (4)	7 (10.3)	3 (3.12)	
Natural vitamin D (n/%)	60 (31.8)	9 (36)	16 (23.5)	35 (36.5)	0.191
Active vitamin D (n/%)	67 (35.5)	3 (12)	21 (30.9)	43 (44.8)[b]	0.006
Calcimimetics (n/%)	14 (7.41)	2 (8)	3 (4.41)	9 (9.38)	0.486
Denosumab (n/%)	12 (6.35)	0 (0)	5 (7.35)	7 (7.29)	0.377
$NaHCO_3$ (n/%)	160 (84.7)	22 (88)	56 (82.4)	82 (85.4)	0.765
PPI (n/%)	84 (44.4)	11 (44)	27 (39.7)	46 (47.9)	0.58
Laboratory data					
Hemoglobin (g/dL)	10.6±1.48	10.7±1.89	10.6±1.44	10.7±1.41	0.89
MCV (μm^3)	86.6±10.4	88.6±9.05	84.9±10.4	87.3±10.7	0.21
TLC (cells)	1438±497	1597±513	1419±463	1409±512	0.272
Platelets (cells x 10^3)	223±70.3	234±65.1	219±62.1	223±76.9	0.645
MPV (μm^3)	9.52±0.94	9.32±1.01	9.48±0.95	9.59±0.92	0.427
NLR	3 (2.32-4.17)	3.45 (2.76-4.1)	2.81 (2.26-4.18)	2.81 (2.41-3.9)	0.311
PLR	9.85 (7.79-14)	11.5 (7.99, 14.6)	9.67 (7.54-12.6)	9.89 (7.96-14.3)	0.463
Sodium (mmol/L)	138.9±2.94	139.4±2.38	139±2.27	138.9±3.46	0.557
Potassium (mmol/L)	4.52±0.52	4.54±0.58	4.48±0.54	4.54±0.5	0.776
Chloride (mmol/L)	101.3±4.57	100.3±4.64	101.4±4.28	101.5±4.76	0.517
Bicarbonate (mmol/L)	23±2.94	22.6±2.59	23.1±3.11	23±2.94	0.776
BUN (mg/dL)	50.1±15.9	52.6±15.2	51.6±15.8	48.3±16.2	0.324
Creatinine (mg/dL)	7.36±3.34	9.36±3.95	7.89±3.58	6.46±2.66[c,d]	<0.001
Albumin (g/L)	34.1±4.06	33.6±2.26	34.5±4.02	34±4.46	0.565
Cholesterol (mg/dL)	169.9±43.5	172.6±38.5	166.9±46.2	171.3±43.2	0.794
Calcium (mg/dL)	9.82±0.85	9.77±0.88	10.1±0.89	9.67±0.77[d]	0.015
Phosphate (mg/dL)	4.6±1.21	4.85±1.31	4.83±1.16	4.37±1.18	0.034
PTH (pg/mL)	283 (137-621)	213 (129-539)	319 (136-654)	311 (152-605)	0.472
ALP (unit/L)	98.2 (72.3-132)	93 (65.8-107)	95 (71.5-124)	103 (78.3-160)	0.246
25-OH D (ng/mL)	28.8±16.5	25.8±7.04	24.8±6.75	31.2±20.1	0.293

[a]P<0.05, [b]P<0.01, [c]P<0.001 vs. normal [d]P<0.05, [e]P<0.01, [f]P<0.001 vs. osteopenia; CVD, cardiovascular disease; PTX, parathyroidectomy; CKD , chronic kidney disease; PO_4, phosphate; $NaHCO_3$, sodium bicarbonate; PPI, proton pump inhibitors; MCV, mean corpuscular volume; TLC, total lymphocyte count; MPV, mean platelet volume; NLR, neutrophil: lymphocyte ratio; PLR, platelet: lymphocyte ratio; BUN, blood urea nitrogen; Ca, calcium; PTH, parathyroid hormone; ALP, alkaline phosphatase; 25-OH-D, 25 hydroxy vitamin D; BMD, bone mineral density

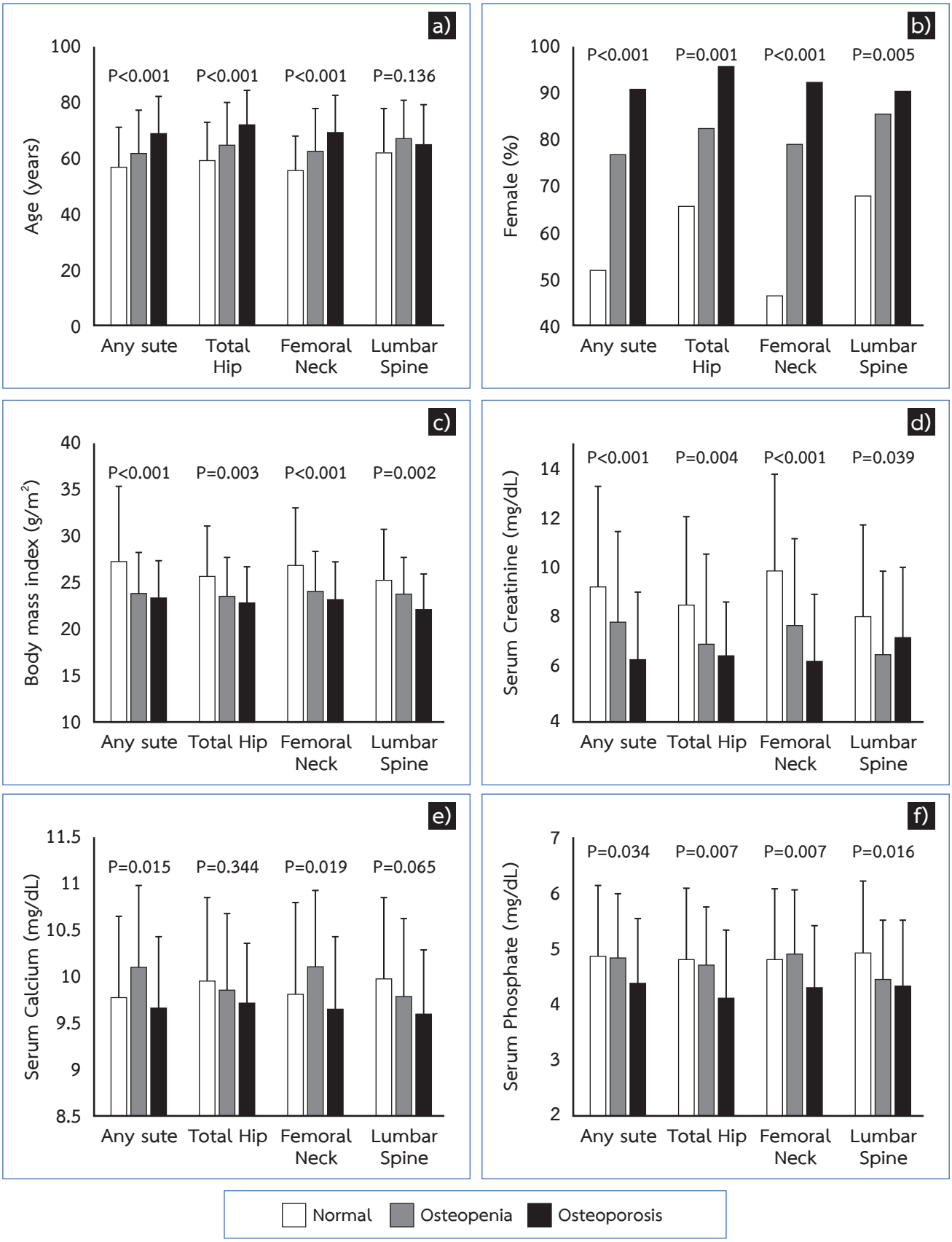

Figure 2 Baseline characteristics stratified by osteopenia/osteoporosis status

a) age; b) female sex; c) body mass index; d) Serum creatinine; e) Serum calcium; f) Serum phosphate

Baseline biochemical data for the femoral neck are presented in **Supplementary Table 2 and Figure 2.** Among 183 patients, 28 (15.3%) had normal BMD, 66 (36.0%) had osteopenia, and 89 (48.6%) had osteoporosis. Dyslipidemia emerged as a risk factor for reduced femoral neck T-score, whereas parathyroidectomy (PTX) was protective against osteoporosis. In contrast to the total hip, the femoral neck T-score was not associated with CKD stage. In addition to active vitamin D, calcium-based phosphate binders were more frequently prescribed in the osteoporosis group. No significant associations were found between femoral neck T-score and hematologic indices.

Baseline demographic and laboratory data for the lumbar spine are shown in S**upplementary Table 3 and Figure 2.** Unlike the total hip and femoral neck, lumbar spine T-score was not associated with age, CVD, or dyslipidemia. Similar to the total hip, osteoporosis at the lumbar spine was more frequent in CKD stage 5D. Declining lumbar spine T-score was also associated with lower total lymphocyte count (TLC) as well as higher parathyroid hormone (PTH) and alkaline phosphatase (ALP) levels.

Multivariate analysis of baseline factors associated with bone mineral density

Variables with a P-value < 0.2 in the univariate analysis were included in the multivariate model. The use of calcium, natural and active vitamin D, and calcimimetics was more common in the osteoporosis group, likely reflecting treatment prescription; therefore, these variables were excluded from the analysis. Serum 25-OH-D was also excluded due to a high proportion of missing values (59%). Multivariate analyses were conducted using stepwise regression with backward elimination. The least significant variables were sequentially removed until only those with P-values <0.05 remained in the final model **(Table 2)**.

Multivariate regression analyses identified several factors associated with BMD and T-scores. Female sex and lower BMI were consistently associated with reduced BMD and T-scores across all skeletal sites. Older age was associated with lower BMD and T-scores at all sites, except the lumbar spine. At the total hip, reduced BMD and T-scores were associated with CKD stage 5D and elevated ALP levels. Lower total hip BMD was also related to a history of fracture and higher MCV. At the lumbar spine, reduced BMD and T-scores were associated with a history of fracture, lower TLC, and lower serum calcium. Lower lumbar spine T-scores were also associated with higher ALP levels.

Multivariate logistic regression analyses demonstrated that female sex was an independent predictor of osteoporosis at all skeletal sites. Age was an independent predictor of osteoporosis at all sites except the lumbar spine. Higher BMI was protective against osteoporosis at any site and at the femoral neck. At the total hip, CKD stage 5D was associated with osteoporosis, while higher ALP and lower platelet counts also emerged as significant predictors. At the femoral neck, CVD and lower serum calcium were independently associated with an increased risk of osteoporosis. At the lumbar spine, osteoporosis was associated with a history of fracture, CKD stage 5D, lower TLC, and reduced serum calcium.

Table 2 Multivariate linear and logistic regression analyses of baseline factors associated with bone mineral density

Variables	Any site		Total hip		Femoral neck		Lumbar	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
BMD								
Age	-	-	-0.006 (-0.008, -0.004)	<0.001	-0.004 (-0.005,-0.003)	<0.001	-	-
Female sex	-	-	-0.124 (-0.176, -0.072)	<0.001	-0.139 (-0.183,-0.095)	<0.001	-0.131 (-0.192, -0.07)	<0.001
BMI	-	-	0.011 (0.006, 0.015)	<0.001	0.008 (0.004,0.012)	<0.001	0.009 (0.004, 0.015)	0.001
Fracture	-	-	-0.092 (-0.178, -0.006)	0.035	-	-	-0.109 (-0.198, -0.02)	0.016
CKD stage 5D	-	-	-0.11 (-0.169, -0.051)	<0.001	-	-	-0.083 (-0.144, -0.022)	0.008
TLC (x1000)	-	-	-	-	-	-	0.059 (0.004, 0.114)	0.036
MCV (x100)	-	-	-0.22 (-0.43, -0.002)	0.048	-	-	-	-
Calcium	-	-	-	-	-	-	0.044 (0.014, 0.074)	0.005
ALP (x100)	-	-	-0.012 (-0.021, -0.003)	0.007	-	-	-	-
T-score								
Age	-0.024 (-0.037, -0.012)	<0.001	-0.056 (-0.071, -0.042)	<0.001	-0.036 (-0.047,-0.025)	<0.001	-	-
Female sex	-0.817 (-1.272, -0.361)	0.001	-0.622 (-1.072, -0.172)	0.007	-1.138 (-1.544,-0.733)	<0.001	-0.765 (-1.304, -0.226)	0.006
BMI	0.076 (0.038, 0.114)	<0.001	0.092 (0.054, 0.131)	<0.001	0.071 (0.037,0.105)	<0.001	0.07 (0.018, 0.121)	0.008
Fracture	-	-	-	-	-	-	-0.893 (-1.749, -0.036)	0.041
CKD stage 5D	-	-	-1.02 (-1.516, -0.523)	<0.001	-	-	-	-
TLC (x100)	-	-	-	-	-	-	0.069 (0.017, 0.122)	0.01
Calcium	-	-	-	-	-	-	0.344 (0.073, 0.614)	0.013
ALP (x100)	-	-	-0.113 (-0.188, -0.038)	0.003	-	-	-0.112 (-0.209, -0.016)	0.023

Table 2 Multivariate linear and logistic regression analyses of baseline factors associated with bone mineral density (continued)

Variables	Any site		Total hip		Femoral neck		Lumbar	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Osteoporosis								
	Odds ratio (95%CI)	P	Odds ratio (95%CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age	1.03 (1.01, 1.06)	0.011	1.12 (1.07, 1.19)	<0.001	1.04 (1.01, 1.06)	0.005	-	
Female sex	4.26 (1.77, 10.2)	0.001	15.8 (2.69, 92.6)	0.002	5.93 (2.24, 15.7)	<0.004	5.01 (1.52, 16.6)	0.008
BMI	0.9 (0.84, 0.97)	0.008	-	-	0.91 (0.84, 0.98)	0.017	-	-
CVD	-	-	-	-	2.26 (1.07, 4.78)	0.034	-	-
Fracture	-	-	-	-	-	-	8.98 (2.24, 36)	0.002
CKD stage 5D	-	-	18.5 (3.98, 86.3)	<0.001	-	-	4.82 (1.53, 15.2)	0.007
TLC (x100)	-	-	-	-	-	-	0.88 (0.8, 0.97)	0.009
Platelets (x10^5)	-	-	0.32 (0.13,0.81)	0.016	-	-	-	-
Calcium	0.6 (0.39, 0.91)	0.018		-	0.61 (0.39,0.94)	0.026	0.42 (0.25, 0.72)	0.001
ALP (x100)	-	-	1.39 (1.12, 1.75)	0.003	-	-	-	-

Multivariate analyses were performed by backward elimination. Variables with a p-value < 0.2 from Tables 1 or Supplementary Tables 2 or 3 were entered into the model, and only those with a P-value < 0.05 were retained in the final model.

Variables included were as follows: for any site—age, sex, BMI, DLP, fracture, serum creatinine, calcium, and phosphate; total hip—age, sex, BMI, CVD, fracture, CKD stages, PPI, MCV, TLC, platelets, serum creatinine, phosphate, and ALP; for femoral neck—age, sex, BMI, CVD, dyslipidemia, fracture, PTX, NLR, serum creatinine, calcium, and phosphate; and for the lumbar spine—age, sex, BMI, fracture, CKD stages, DV, TLC, MPV, NLR, serum potassium, creatinine, calcium, phosphate, and ALP.

BMD, bone mineral density; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; BMI, body mass index; PTX, parathyroidectomy; CKD, chronic kidney disease; DV, dialysis vintage; PPI, proton pump inhibitor; NLR, neutrophil-to-lymphocyte ratio; MCV, mean corpuscular volume; TLC, total lymphocyte count; PTH, parathyroid hormone; ALP, alkaline phosphatase

Bone Mineral Density and all-cause mortality

The median follow-up time was 51.2 months (interquartile range: 33.4–75.6). During this period, 93 patients (49.2%) died. Univariate Cox proportional hazards regression analyses of baseline factors associated with all-cause mortality are presented in **Table 3**. Older age, CVD, history of fracture, and higher neutrophil-to-lymphocyte ratio (NLR) were positively associated with mortality. In contrast, a history of parathyroidectomy, as well as higher serum bicarbonate, creatinine, albumin, phosphate, and PTH levels, were negatively associated with mortality.

Table 3 Univariate Cox proportional hazards regression analysis of baseline factors for all-cause mortality

Variables	HR (95% CI)	P	Variables	HR (95% CI)	P
Age (years)	1.04 (1.03, 1.06)	<0.001	Laboratory data		
Female sex	0.91 (0.55, 1.51)	0.721	Hemoglobin	0.99 (0.87, 1.15)	0.963
BMI	0.97 (0.93, 1.02)	0.212	MCV (x10)	0.92 (0.75, 1.12)	0.394
Diabetes	1.51 (1, 2.29)	0.049	TLC (x 100)	0.98 (0.94, 1.03)	0.476
Cardiovascular disease	1.74 (1.14, 2.65)	0.01	Platelets (x 10^5)	0.81 (0.72, 1.35)	0.936
Dyslipidemia	2 (0.63, 6.33)	0.237	MPV	1.08 (0.86, 1.36)	0.496
Fracture	1.85 (1.04, 3.27)	0.035	NLR	1.07 (1.02, 1.12)	0.009
Parathyroidectomy	0.41 (0.22, 0.77)	0.006	PLR	1.01 (0.99, 1.03)	0.293
CKD stage 5D	0.78 (0.5, 1.22)	0.276	Sodium	0.94 (0.87, 1.01)	0.098
Dialysis vintage (years)	0.99 (0.97, 1.03)	0.935	Potassium	0.71 (0.47, 1.08)	0.11
Medications			Chloride	1.01 (0.97, 1.05)	0.696
Steroids	1.1 (0.53, 2.27)	0.807	Bicarbonate	0.93 (0.87, 1)	0.05
Phosphate Binders	0.97 (0.64, 1.48)	0.886	BUN	0.99 (0.98, 1.01)	0.629
Calcium	0.99 (0.64, 1.53)	0.971	Creatinine	0.93 (0.87, 0.99)	0.029
Non-Calcium	1.2 (0.5, 2.87)	0.679	Albumin	0.94 (0.89, 0.99)	0.024
Natural vitamin D	1.32 (0.86, 2.03)	0.205	Cholesterol	0.99 (0.99, 1)	0.055
Active vitamin D	0.84 (0.54, 1.29)	0.421	Calcium	0.85 (0.67, 1.09)	0.209
Calcimimetics	0.87 (0.35, 2.15)	0.767	Phosphate	0.83 (0.69, 0.98)	0.03
Denosumab	1.04 (0.48, 2.25)	0.916	PTH (x 100 pg/mL)	0.95 (0.91, 0.99)	0.014
Sodium bicarbonate	0.88 (0.51, 1.51)	0.644	ALP (x100 U/L)	0.84 (0.69, 1.02)	0.08
Proton pump inhibitors	1.41 (0.94, 2.12)	0.099	25-hydroxy vitamin D	1 (0.98, 1.02)	0.862

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; MCV, mean corpuscular volume; TLC, total lymphocyte count; MPV, mean platelet volume; NLR, neutrophil: lymphocyte ratio; PLR, platelet: lymphocyte ratio; BUN, blood urea nitrogen; PTH, parathyroid hormone; ALP, alkaline phosphatase

Univariate Cox proportional hazards regression analyses of BMD, T-score, and osteoporosis in relation to all-cause mortality are shown in **Table 4**. The Kaplan–Meier survival curves comparing osteoporosis and non-osteoporosis groups are presented in **Figure 3**. Lower BMD and T-scores at the total hip and femoral neck were significantly associated with higher mortality risk. Osteoporosis at all skeletal sites was associated with increased mortality.

Table 4 Univariate Cox proportional hazards regression analysis of bone mineral density for all-cause mortality

Parameters	Any site		Total hip		Femoral neck		Lumbar spine	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
BMD	-	-	0.17 (0.04, 0.66)	0.011	0.16 (0.03, 0.78)	0.024	0.5 (0.16, 1.59)	0.239
T-score	0.87 (0.74, 1.02)	0.091	0.79 (0.67, 0.93)	0.005	0.82 (0.69, 0.98)	0.026	0.92 (0.8, 1.05)	0.222
Osteoporosis (vs. No osteoporosis)	1.83 (1.28, 2.79)	0.004	1.65 (1.05, 2.58)	0.029	1.8 (1.18, 2.75)	0.007	1.71 (1.09, 2.7)	0.021

HR, hazard ratio; CI, confidence interval; BMD, bone mineral density

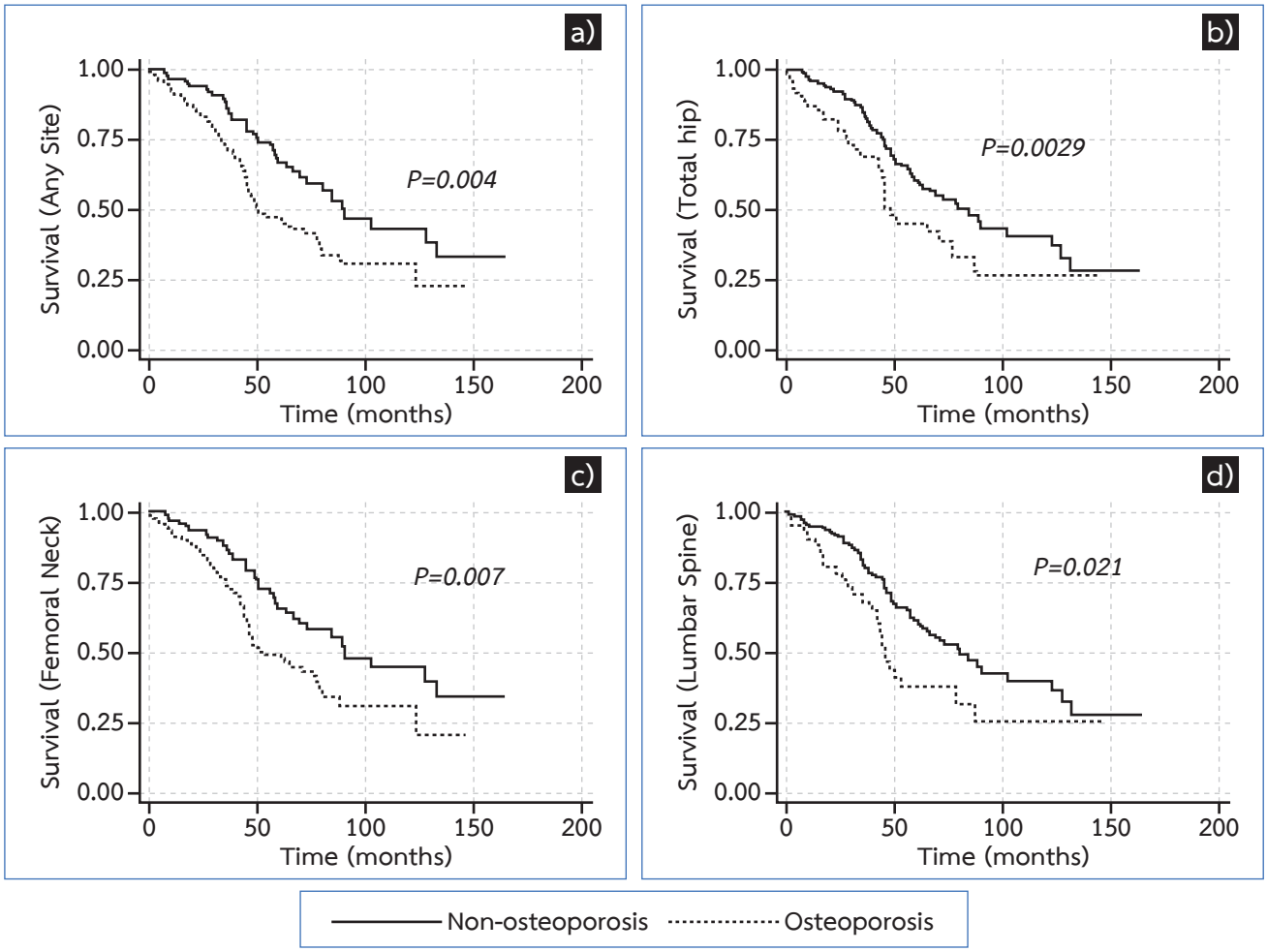

Figure 3 Kaplan–Meier survival analysis comparing osteoporosis and non-osteoporosis groups. a) Any site; b) Total hip; c) Femoral neck; d) Lumbar spine

Multivariate Cox proportional hazards regression analyses were conducted using stepwise regression with backward elimination. Variables with a P-value < 0.1 in the univariate analyses were included, and the least significant variables were sequentially removed until only those with P-values < 0.05 remained in the final model **(Table 5)**. Age was excluded because its strong association with the outcome rendered the other variables non-significant. Across all skeletal sites, only NLR and PTH remained in the final model, with higher NLR and lower PTH levels emerging as independent predictors of all-cause mortality. In addition, reduced BMD and T-scores at the total hip, reduced BMD at the femoral neck, and osteoporosis at all sites except the total hip were also independent predictors of all-cause mortality.

Table 5 Multivariate Cox proportional hazards regression analysis of bone mineral density for all-cause mortality

Parameters	Any site		Total hip		Femoral neck		Lumbar spine	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
BMD								
NLR	-	-	1.1 (1.03, 1.17)	0.007	1.09 (1.02, 1.17)	0.008	1.08 (1, 1.15)	0.042
PTH (x 100 pg/mL)	-	-	0.95 (0.91, 0.99)	0.022	0.95 (0.92, 0.99)	0.026	0.95 (0.91, 0.99)	0.01
BMD	-	-	0.18 (0.04, 0.82)	0.026	0.18 (0.03, 0.98)	0.048	0.38 (0.1,1.36)	0.137
T-score								
NLR	1.08 (1.01, 1.16)	0.026	1.1 (1.03, 1.17)	0.007	1.1 (1.02, 1.17)	0.008	1.08 (1, 1.15)	0.042
PTH (x 100 pg/mL)	0.94 (0.9, 0.98)	0.006	0.95 (0.91, 0.99)	0.022	0.95 (0.92, 0.99)	0.026	0.95 (0.91, 0.89)	0.01
T-Score	0.87 (0.73, 1.03)	0.117	0.8 (0.67, 0.96)	0.016	0.84 (0.7, 1)	0.056	0.89 (0.76, 1.04)	0.128
Osteoporosis								
NLR	1.09 (1.01, 1.16)	0.019	1.1 (1.03, 1.18)	0.007	1.1 (1.03, 1.17)	0.006	1.07 (1, 1.15)	0.048
PTH (x 100 pg/mL)	0.94 (0.9, 0.98)	0.006	0.95 (0.91, 0.99)	0.025	0.96 (0.92, 0.99)	0.031	0.94 (0.9, 0.99)	0.009
Osteoporosis (vs. No osteoporosis)	1.79 (1.13, 2.85)	0.014	1.6 (0.97, 2.65)	0.064	1.73 (1.08, 2.76)	0.022	1.82 (1.11, 2.99)	0.017

Multivariate analyses were performed by backward elimination. Variables with a p-value < 0.1 from Table 3 excluding age were entered into the model, and only those with a P-value < 0.05 were retained in the final model.

Variables included were diabetes, cardiovascular disease, parathyroidectomy, proton pump inhibitor, neutrophil-to-lymphocyte ratio, serum sodium, bicarbonate, creatinine, albumin, cholesterol, phosphate, parathyroid hormone, and alkaline phosphatase

HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PTH, parathyroid hormone

Discussion

This study assessed BMD at the total hip, femoral neck, and lumbar spine in patients with CKD stages 5–5D. Lower BMD and osteoporosis were associated with traditional risk factors, including older age, lower BMI, and female sex. Biochemical abnormalities, such as reduced serum calcium and elevated ALP, reduced TLC and platelet count, as well as increased MCV, were associated with lower BMD and osteoporosis. Patients with CKD stage 5D demonstrated greater BMD loss compared with those in stage 5. Importantly, reduced BMD across all skeletal sites independently predicted all-cause mortality.

The associations between lower BMD and osteoporosis with aging, lower BMI, and female sex have been well established in both the general and dialysis populations[11,13], and the present study confirms these findings. The link between lower serum calcium and higher ALP with reduced BMD and osteoporosis likely reflects inadequate calcium storage. A previous study on the effects of different dialysate calcium concentrations (1.25 mmol/L vs. 1.75 mmol/L) on BMD changes reported lower serum calcium levels in association with increased PTH and ALP in the low-dialysate calcium group, with a more significant reduction in BMD over two years[14]. Similarly, a recent small study found that lower serum corrected calcium was associated with an increased risk of asymptomatic vertebral fractures[15]. Other studies have also reported that calcium-based phosphate binders help reduce BMD loss and lower osteoporosis risk[16,17].

Although this study found an association between lower BMD and elevated ALP, the relationship with PTH was suggested only at the lumbar spine. In advanced CKD and dialysis patients, PTH levels appear to have a weaker association with bone health than ALP[18]. Similarly, a study on osteoporosis in pre-dialysis CKD found that higher bone ALP levels were associated with osteoporosis, while increased PTH levels had a protective effect[19]. These findings suggest that ALP may better reflect bone changes than PTH. Moreover, other CKD-related factors can influence PTH independently of bone metabolism. For instance, decreased serum phosphate and the use of active vitamin D supplements can directly suppress PTH secretion[20,21]. In advanced CKD, reductions in serum phosphate and PTH often indicate malnutrition[22], which is also linked to sarcopenia, reduced BMD, and osteoporosis[13,23]. This study further supports the connection between malnutrition and osteoporosis, as evidenced by the association of lower serum creatinine and phosphate with reduced BMD and osteoporosis.

Lower BMD and a higher prevalence of osteoporosis at the total hip and lumbar spine were observed in CKD stage 5D compared with stage 5. Prior research in CKD stages 2–4 has shown that declining kidney function is linked to lower BMD and higher osteoporosis risk[24,25]. A systematic review and meta-analysis on osteoporosis prevalence in CKD found that dialysis patients had lower BMD compared to non-dialysis CKD patients, particularly at cortical bone sites[26]. These findings confirm significant bone loss in dialysis patients. In addition to alterations in serum calcium, phosphate, and PTH, other factors, such as the accumulation of uremic toxins and inhibitors of the Wnt signaling pathway, metabolic acidosis, and yet unidentified factors, likely contribute to bone deterioration in dialysis patients[3].

This study also found that increased MCV was associated with lower BMD at the total hip, consistent with previous reports[27]. It has been suggested that elevated MCV, as a marker of bone marrow microenvironment injury or ineffective hematopoiesis, may reflect reduced hematopoietic stem cell stimulation by osteoblasts in dialysis patients[28]. Additionally, increased MCV is linked to nutritional deficiencies, particularly folate and vitamin B12, which are common in dialysis patients. Recent studies have suggested a connection between reduced circulating folate/vitamin B12 levels and decreased BMD/bone strength in postmenopausal women[29].

The associations between decreased TLC and platelet count with osteoporosis are likely related to nutritional deficiencies and inflammation[30,31]. The association between reduced platelet count and osteoporosis has not been widely investigated. Micronutrients, folate, and B12 deficiencies can lead to reduced lymphocyte and platelet production[32]. In this study, the high prevalence of osteoporosis in CKD stage 5D raises the possibility

that lower platelet counts may also be influenced by dialysis-related factors such as membrane effects, heparin use, and mechanical stress.

In univariate analyses, decreased BMD, lower T-scores, and osteoporosis at all skeletal sites were associated with increased all-cause mortality. Additional baseline parameters that predicted higher mortality included older age, diabetes, CVD, history of fracture, elevated NLR, and lower levels of serum bicarbonate, creatinine, albumin, phosphate, and PTH, reflecting the impact of inflammation and impaired nutrition on adverse outcomes[22,33]. In contrast, a history of PTX was protective against mortality. Previous studies have consistently demonstrated improved outcomes after PTX in dialysis patients, attributed to enhanced bone mass, quality of life, and nutritional status[34,35]. These findings underscore the importance of addressing malnutrition and inflammation to achieve better outcomes.

In the multivariate model, reduced BMD, lower T-scores, and osteoporosis at all skeletal sites remained significant predictors of all-cause mortality. Increased NLR and lower PTH levels were the only other independent predictors. The association between lower PTH levels and poor outcomes was likely related to impaired nutrition[22] A prior study that examined BMD at the femoral neck, lumbar spine, arm, head, pelvis, and total body in dialysis patients reported an association only between decreased femoral neck BMD and all-cause mortality[11] Other studies have shown an association only between decreased forearm BMD and increased mortality[10,36]. These discrepancies are likely attributable to differences in study populations. Moreover, beyond metabolic derangements, the decline in BMD in CKD stages 5–5D may also reflect systemic conditions such as heightened inflammation and nutritional impairment, which contribute to adverse outcomes.

This study had some limitations. The indications for the BMD test are lacking, which could lead to selection bias. The absence of cardiovascular event data prevented the evaluation of the association between reduced BMD and cardiovascular outcomes. Prior studies have established links between reduced BMD, increased vascular calcification, and possibly worse cardiovascular outcomes[37,38]. Additionally, a lack of forearm BMD data prevents its analysis in relation to mortality.

In conclusion, lower BMD in CKD stages 5–5D was linked to traditional risk factors, insufficient calcium storage, elevated bone turnover, inflammation, and nutritional deficiencies. Reduced BMD and osteoporosis were independently predictive of all-cause mortality. Thus, optimizing bone health in advanced CKD requires addressing not only mineral metabolism but also systemic inflammation and nutritional status.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, SD utilized ChatGPT and Grammarly to enhance the language by correcting grammar and revising sentences for clarity. SD has reviewed and edited the content and takes full responsibility for the content of the publication.

References

1. Neto R, Pereira L, Magalhaes J, Quelhas-Santos J, Frazao J. Low bone turnover is associated with plain X-ray vascular calcification in predialysis patients. PloS one 2021;16 (10):e0258284. doi: 10.1371/journal.pone.0258284.
2. El-Husseini A, Abdalbary M, Lima F, Issa M, Ahmed MT, Winkler M, et al. Low Turnover Renal Osteodystrophy With Abnormal Bone Quality and Vascular Calcification in Patients With Mild-to-Moderate CKD. Kidney Int Rep 2022;7(5):1016–26. doi: 10.1016/j.ekir.2022.02.022.
3. Drueke TB, Massy ZA. Changing bone patterns with progression of chronic kidney disease. Kidney Int 2016;89(2):289–302. doi: 10.1016/j.kint.2015.12.004.
4. Sprague SM, Bellorin-Font E, Jorgetti V, Carvalho AB, Malluche HH, Ferreira A, et al. Diagnostic Accuracy of Bone Turnover Markers and Bone Histology in Patients With CKD Treated by Dialysis. Am J Kidney Dis 2016;67(4):559–66. doi: 10.1053/j.ajkd.2015.06.023.
5. Salam S, Gallagher O, Gossiel F, Paggiosi M, Khwaja A, Eastell R. Diagnostic Accuracy of Biomarkers and Imaging

for Bone Turnover in Renal Osteodystrophy. J Am Soc Nephrol 2018;29(5):1557–65. doi: 10.1681/ASN.2017050584.

6. Jorgensen HS, Behets G, Viaene L, Bammens B, Claes K, Meijers B, et al. Diagnostic Accuracy of Noninvasive Bone Turnover Markers in Renal Osteodystrophy. Am J Kidney Dis 2022;79(5):667–76 e1. doi: 10.1053/j.ajkd.2021.07.027.
7. Kidney Disease: Improving Global Outcomes CKDMBDWG. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009(113):S1–130. doi: 10.1038/ki.2009.188.
8. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney Int 2017;92(1):26–36. doi: 10.1016/j.kint.2017.04.006.
9. Bucur RC, Panjwani DD, Turner L, Rader T, West SL, Jamal SA. Low bone mineral density and fractures in stages 3-5 CKD: an updated systematic review and meta-analysis. Osteoporos Int 2015;26(2):449–58. doi: 10.1007/s00198-014-2813-3.
10. Iwasaki T, Fujimori A, Okada S, Hanawa N, Kuragano T. Association Between Bone Mineral Density of the Distal Third of the Radius and Mortality in Patients on Hemodialysis, a Retrospective Cohort Study. Iran J Kidney Dis 2021;15(4):306–13.
11. Jaques DA, Henderson S, Davenport A. Association between bone mineral density at different anatomical sites and both mortality and fracture risk in patients receiving renal replacement therapy: a longitudinal study. Clin Kidney J 2022;15(6):1188–95. doi: 10.1093/ckj/sfac034.
12. Organization WH. Guidelines for preclinical evaluation and clinical trials in osteoporosis Switzerland1998 [Available from: https://apps.who.int/iris/bitstream/handle/10665/42088/9241545224_eng.pdf.
13. Davenport A. Frailty, appendicular lean mass, osteoporosis and osteosarcopenia in peritoneal dialysis patients. J Nephrol 2022;35(9):2333–40. doi: 10.1007/s40620-022-01390-1.
14. Kang SH, Cho KH, Park JW, Yoon KW, Do JY. Low-calcium dialysate as a risk factor for decline in bone mineral density in peritoneal dialysis patients. Scand J Urol Nephrol 2012;46(6):454–60. doi: 10.3109/00365599.2012.700643.
15. Jirasiririrak S, Disthabanchong S, Ongphiphadhanakul B, Arj-Ong Vallibhakara S, Nimitphong H. Prevalence and predictors of asymptomatic vertebral fracture in patients with end-stage renal disease. Heliyon 2022;8(3):e09158. doi: 10.1016/j.heliyon.2022.e09158.
16. Hashimoto H, Shikuma S, Mandai S, Adachi S, Uchida S. Calcium-based phosphate binder use is associated with lower risk of osteoporosis in hemodialysis patients. Sci Rep 2021;11(1):1648. doi: 10.1038/s41598-021-81287-4.
17. Kato K, Nakashima A, Morishita M, Ohkido I, Yokoo T. Calcium-based phosphate binders and bone mineral density in patients undergoing hemodialysis: a retrospective cohort study. Clin Exp Nephrol 2024;28(9):917–24. doi: 10.1007/s10157-024-02493-8.
18. Yamamoto S, Jorgensen HS, Zhao J, Karaboyas A, Komaba H, Vervloet M, et al. Alkaline Phosphatase and Parathyroid Hormone Levels: International Variation and Associations With Clinical Outcomes in the DOPPS. Kidney Int Rep 2024;9(4):863–76. doi: 10.1016/j.ekir.2024.01.002.
19. Kuang C, Shang J, Ma M, Huang S, Yan B, Zhong Y, et al. Risk factors and clinical prediction models for osteoporosis in pre-dialysis chronic kidney disease patients. Ren Fail 2024;46(2):2361802. doi: 10.1080/0886022X.2024.2361802.
20. Brown AJ, Zhong M, Finch J, Ritter C, Slatopolsky E. The roles of calcium and 1,25-dihydroxyvitamin D3 in the regulation of vitamin D receptor expression by rat parathyroid glands. Endocrinology 1995;136(4):1419–25. doi: 10.1210/endo.136.4.7895652.
21. Centeno PP, Herberger A, Mun HC, Tu C, Nemeth EF, Chang W, et al. Phosphate acts directly on the calcium-sensing receptor to stimulate parathyroid hormone secretion. Nat Commun 2019;10(1):4693. doi: 10.1038/s41467-019-12399-9.
22. Raj R, Kadiyala A, Patel C. Malnutrition-Inflammation Complex Syndrome: A Cause of Low Parathyroid Hormone in Patients With Chronic Kidney Disease. Cureus 2021;13(12):e20324. doi: 10.7759/cureus.20324.
23. Rashid A, Chaudhary Hauge S, Suetta C, Hansen D. "Sarcopenia and risk of osteoporosis, falls and bone fractures in patients with chronic kidney disease: A systematic review". PloS one 2022;17(1):e0262572. doi: 10.1371/journal.pone.0262572.

24. Kang DH, Park CH, Kim HW, Park JT, Han SH, Kim J, et al. Kidney function and bone mineral density in chronic kidney disease patients. Clin Kidney J 2024;17(9):sfae248. doi: 10.1093/ckj/sfae248.
25. Huang JF, Zheng XQ, Sun XL, Zhou X, Liu J, Li YM, et al. Association between Bone Mineral Density and Severity of Chronic Kidney Disease. Int J Endocrinol 2020;2020:8852690. doi: 10.1155/2020/8852690.
26. Duarte MP, Ribeiro HS, Neri SGR, Almeida LS, Oliveira JS, Viana JL, et al. Prevalence of low bone mineral density (T-score </= - 2.5) in the whole spectrum of chronic kidney disease: a systematic review and meta-analysis. Osteoporos Int 2023;34(3):467–77. doi: 10.1007/s00198-022-06598-2.
27. Chiang MH, Yang CY, Kuo YJ, Cheng CY, Huang SW, Chen YP. Inverse Relationship between Mean Corpuscular Volume and T-Score in Chronic Dialysis Patients. Medicina (Kaunas) 2022;58(4). doi: 10.3390/medicina58040497.
28. Calvi LM, Adams GB, Weibrecht KW, Weber JM, Olson DP, Knight MC, et al. Osteoblastic cells regulate the haematopoietic stem cell niche. Nature 2003;425(6960):841–6. doi: 10.1038/nature02040.
29. Kalimeri M, Leek F, Wang NX, Koh HR, Roy NC, Cameron-Smith D, et al. Folate and Vitamin B-12 Status Is Associated With Bone Mineral Density and Hip Strength of Postmenopausal Chinese-Singaporean Women. JBMR Plus 2020;4(10):e10399. doi: 10.1002/jbm4.10399.
30. Reddan DN, Klassen PS, Szczech LA, Coladonato JA, O'Shea S, Owen WF, Jr., et al. White blood cells as a novel mortality predictor in haemodialysis patients. Nephrol Dial Transplant 2003;18(6):1167–73. doi: 10.1093/ndt/gfg066.
31. Yousif DE, Ye X, Stuard S, Berbessi J, Guinsburg AM, Usvyat LA, et al. Biphasic Dynamics of Inflammatory Markers Following Hemodialysis Initiation: Results From the International MONitoring Dialysis Outcome Initiative. Kidney Int Rep 2023;8(1):75–80. doi: 10.1016/j.ekir.2022.10.020.
32. Xie Y, Liu F, Zhang X, Jin Y, Li Q, Shen H, et al. Benefits and risks of essential trace elements in chronic kidney disease: a narrative review. Ann Transl Med 2022;10(24):1400. doi: 10.21037/atm-22-5969.
33. Zheng CM, Wu CC, Lu CL, Hou YC, Wu MS, Hsu YH, et al. Hypoalbuminemia differently affects the serum bone turnover markers in hemodialysis patients. Int J Med Sci 2019;16(12):1583–92. doi: 10.7150/ijms.39158.
34. Zhou X, Kong Y, Ma Z, Liu T, Wan T, Zhang W, et al. Evaluation of malnutrition and inflammation after total parathyroidectomy in patients on maintenance dialysis. Int Urol Nephrol 2023;55(5):1301–9. doi: 10.1007/s11255-022-03436-6.
35. Disthabanchong S, Saeseow S, Khunapornphairote S, Suvikapakornkul R, Wasutit Y, Tungkeeratichai J. Improvement of nutritional status after parathyroidectomy in patients receiving maintenance hemodialysis. Front Med (Lausanne) 2023;10:1132566. doi: 10.3389/fmed.2023.1132566.
36. Orlic L, Mikolasevic I, Crncevic-Orlic Z, Jakopcic I, Josipovic J, Pavlovic D. Forearm bone mass predicts mortality in chronic hemodialysis patients. J Bone Miner Metab 2017;35(4):396–404. doi: 10.1007/s00774-016-0766-7.
37. Chen Z, Qureshi AR, Ripsweden J, Wennberg L, Heimburger O, Lindholm B, et al. Vertebral bone density associates with coronary artery calcification and is an independent predictor of poor outcome in end-stage renal disease patients. Bone 2016;92:50–7. doi: 10.1016/j.bone.2016.08.007.
38. Huang J, Bao L, Pan Y, Lu Q, Huang Y, Ding Q, et al. The predictive value of coronary artery calcification score combined with bone mineral density for the 2-year risk of cardiovascular events in maintenance hemodialysis patients. Int Urol Nephrol 2022;54(4):883–93. doi: 10.1007/s11255-021-02961-0.