Association Between Bone Mineral Density of the Distal Third of the Radius and Mortality in Patients on Hemodialysis, a Retrospective Cohort Study

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Original Paper

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Introduction. Although several investigators have reported the relationship between bone mineral density (BMD) and mortality in patients on hemodialysis, it is unclear BMD of which site is most strongly associated with mortality.
Methods. We examined the factors related to fractures in patients on hemodialysis in 2009. Based on these data, we investigated the influence of BMD of different sites on mortality in this cohort of 81 patients on hemodialysis. BMD was measured at the distal third of the radius (1/3 Rad), lumbar spine, and total hip. Fifteen patients had prevalent vertebral fractures and seven had prevalent hip fractures. The influences of age, body mass index (BMI), serum creatinine (Cr), serum albumin (Alb), dialysis vintage, and parathyroid hormone (PTH, measured as whole PTH) on mortality were also studied.
Results. Fifty-two patients died by August 31, 2018. BMD was significantly higher in the survival group than in the deceased group only for the 1/3 Rad group ($P < .001$). Although patients with prevalent hip or vertebral fractures showed a higher mortality rate than those without fractures, no significant difference was observed. In the deceased group, age was significantly higher, and BMI and Cr levels were significantly lower than those in the survival group ($P < .001$, $P < .05$, and $P < .01$; respectively). After adjustment for these parameters, BMD of the 1/3 Rad remained a significant prognostic factor.
Conclusion. Although this was a study with a limited number of patients, BMD of the 1/3 Rad appears to be associated with mortality in patients on hemodialysis.

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INTRODUCTION

Fractures reduce survival in the general population[1,2] as well as in patients on dialysis.[3,4] Decreased bone mineral density (BMD) is associated with fractures[5,6] and mortality[7,8] in the general population. However, in patients with chronic kidney disease (CKD), pathological conditions such as hyperphosphatemia, hypocalcemia, elevated parathyroid hormone (PTH) levels, vitamin D deficiency, chronic metabolic acidosis, and chronic inflammation may affect bone quality and bone mass.[9] Therefore, the association between BMD and fractures and mortality in these patients could be different from that in the general population. However, there are several recent reports on the relationship between BMD and fractures in patients

with CKD,[10,11] and BMD testing appears to be useful for evaluating fracture risk in patients with CKD, including those on dialysis.[12]

The relationship between low BMD and mortality in patients undergoing dialysis has not been thoroughly studied. BMD of the hip,[13,14] forearm,[15,16] and spine[17] were reported to be associated with mortality. In those reports, however, BMD was measured at different sites, leaving the question of which site is the most useful for predicting mortality unanswered. Therefore, it is crucial to elucidate the BMD measurement site that is most relevant to the mortality of patients on dialysis. We examined the association between BMD and prevalent fractures in 81 patients on hemodialysis in 2009. BMD was measured at the distal third of the radius (1/3 Rad), lumbar spine, and total hip. Fifty-two patients died by August 31, 2018. In the present study, we compared the impact of different BMD measurement sites on mortality.

MATERIALS AND METHODS

Study Design

We examined factors related to fractures in patients on hemodialysis in 2009. They were 81 maintenance hemodialysis patients treated at Konan Medical Center, Kobe, Japan. Patients with unstable conditions or temporarily treated in our hospital were excluded. Based on these data, we investigated the influence of BMD on mortality in these patients through a retrospective cohort study. The data consisted of BMD of the 1/3 Rad, lumbar spine (L1 to L4, vertebrae with compression fractures were excluded), and total hip as well as information on the prevalent hip and vertebral fractures of 81 patients on hemodialysis. BMD was expressed as the percentage of young adult mean (%YAM) in order to evaluate the data of both sexes simultaneously. Data on body mass index (BMI) and levels of plasma PTH (measured as whole PTH using a chemiluminescent enzyme immunoassay kit from SB Bioscience Co., Ltd, Tokyo, Japan), serum creatinine (Cr), and serum albumin (Alb). Prevalent vertebral and hip fractures were determined using history-taking and X-ray films. BMD was determined by dual-energy X-ray absorptiometry using DPX BRAVO (General Electric, Fairfield, CT, USA). This study was performed according to the principles of the Declaration of Helsinki and was approved by the ethics committee of the facility (approval number 2019–04). The information on this clinical study was disclosed on our website, where it was clarified that the use of data could be suspended if desired.

Statistics

Data are presented as medians with the 25th and 75th percentiles. The difference between the survival group and deceased group was analyzed using a Mann-Whitney U test or chi-squared test. Spearman's rank correlation coefficient was used to evaluate the relationship between BMD and PTH levels. Since the time of death of patients who were transferred and died in other facilities was unknown, factors related to mortality were examined using logistic regression analysis. Statistical analysis was performed using Stata15 (StataCorp LLC, College Station, TX, USA). *P* values less than .05 were considered statistically significant.

RESULTS

The baseline characteristics of the patients are shown in Table 1. The cohort comprised 51 men and 30 women. There were 31 patients with diabetes and 51 non-diabetics. Their median age was 71.8 years, and median dialysis vintage was 5.2 years. Fifteen patients had prevalent vertebral fractures, and seven had prevalent hip fractures. The median BMD (%YAM) of the 1/3 Rad, lumbar spine, and total hip was 79.6%, 93.3% and 80.3 %, respectively. The median BMI was 20.4 kg/m^2; Cr level, 10.4 mg/dL; Alb level, 3.6 g/dL; and whole PTH level, 70.5 pg/mL.

Fifty-two patients died by August 31, 2018. BMD

Table 1. Baseline Characteristics of the Patients

Male / Female	51 / 30
DM / non-DM	30 / 51
Age, y	71.8 (64.2, 76.8)
Dialysis Vintage, y	5.2 (2.3, 10.6)
Prevalent Fractures	Vertebra 15 / hip 7
BMD (% YAM)	
1/3 Rad	79.6 (62.1, 90.9)
Lumbar Spine	93.3 (83.1, 103.8)
Hip	80.3 (66.0, 90.2)
BMI, kg/m^2	20.4 (19.1, 21.6)
Cr Level, mg/dL	10.4 (8.23, 11.69)
Alb Level, g/dL	3.6 (3.3, 3.8)
Whole PTH Level, pg/mL	70.5 (34.4, 109.0)

Medians with the 25th and the 75th percentiles are shown for continuous variables. Abbreviations: DM, diabetes mellitus; BMD, bone mineral density; YAM, young adult mean; 1/3 Rad, distal third of the radius; BMI, body mass index; Cr, creatinine; Alb, Albumin; PTH, parathyroid hormone.

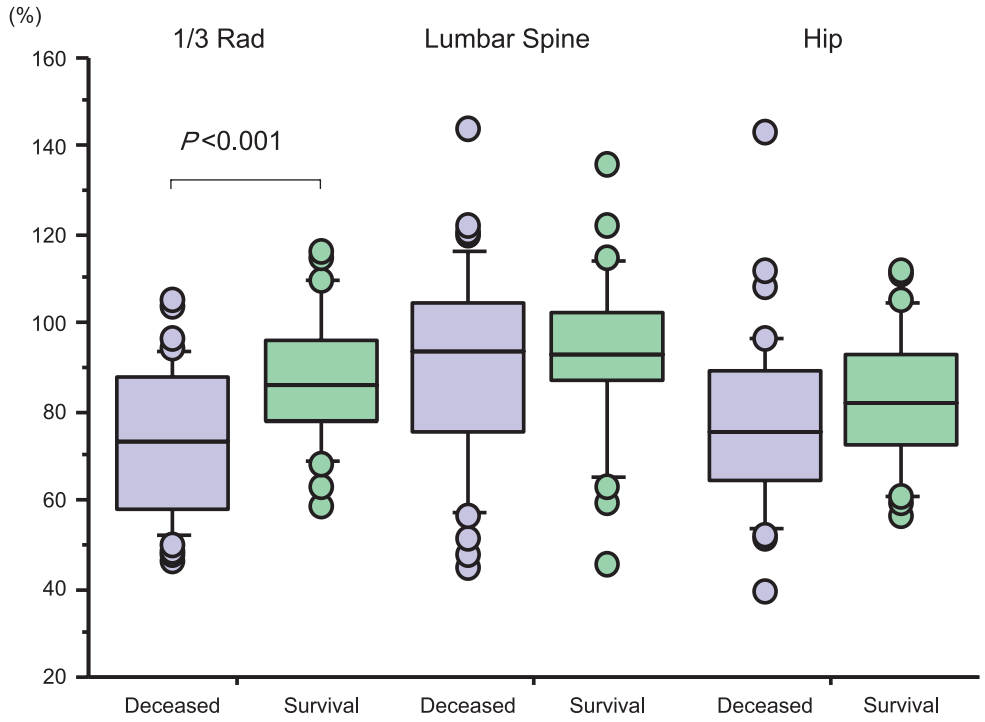

Figure 1. Comparison of BMD Between the Survival and Deceased Groups
The medians with the 25th and 75th percentiles are shown. BMD of the 1/3 Rad in the survival group was significantly higher than that in the deceased group ($P < .001$, Mann-Whitney U test). No significant differences were found in either the spine or hip (Abbreviation: 1/3 Rad, distal third of the radius).

was compared between the survival and deceased groups (Figure 1). The median BMD of the 1/3 Rad was 85.8% in the survival group, which was significantly higher than 73.3% in the deceased group. BMD of the lumbar spine was 93.0% in the survival group and 93.4% in the deceased group. BMD of the total hip was 81.8% in the survival group and 75.7% in the deceased group. No statistically significant differences were found in BMD of the lumbar spine or total hip. The patients were categorized into three groups: BMD < 70% (osteoporosis), 70 ≤ BMD < 80% (osteopenia), and 80% ≥ BMD (normal BMD); mortality was higher in the osteoporosis group than those in the other groups. However, a statistically significant difference was noted only in the BMD of the 1/3 Rad (Table S1).

The prognostic influence of prevalent fractures was evaluated using the chi-squared test (Table 2). The odds ratio for death was 3.65 and 2.60 in patients with vertebral and hip fractures, respectively. However, no statistical significance was found (95% CI: 0.42 to 31.94 and 0.67 to 10.11; respectively).

Age, BMI, dialysis vintage, and Cr, Alb, and whole PTH levels were compared between the deceased and survival groups (Figure 2). The median age in the deceased group was 75.2 years, which was significantly higher than 62.8 years in the survival group. BMI (20.0 kg/m^2 in the deceased

Table S1. Prognostic Influence of BMD Divided in 3 Categories

	BMD (%) of the 1/3 Rad				BMD (%) of the Lumbar Spine				BMD (%) of the Hip			
	< 70	70 ≤ < 80	80 ≤		< 70	70 ≤ < 80	80 ≤		< 70	70 ≤ < 80	80 ≤	
Deceased	20	8	16	44	10	2	32	44	16	8	19	43
Survival	3	6	18	27	3	1	23	27	5	5	17	27
	23	14	34		13	3	55		21	13	36	
	P < .05				N.S.				N.S.			

Patients were categorized into 3 groups, BMD < 70% (osteoporosis), 70 ≤ BMD < 80% (osteopenia), and 80% ≤ BMD (normal BMD) groups. Although mortality was higher in groups with BMD < 70% than those in other groups, a statistically significant difference was found only in BMD of the 1/3 Rad (a chi-square test using js-STAR version 9.8.7j).
Note: BMD data were collected from 71 patients. In one patient, BMD of the hip was not measured.
Abbreviations: BMD, bone mineral density; 1/3 Rad, distal third of the radius; N.S., not significant.

Table 2. Prognostic Influences of Prevalent Fractures

	Hip Fx +	Hip Fx -	
Deceased	6	46	52
Survival	1	28	29
	7	74	

Odds Ratio	3.65	
95% CI	Lower	Upper
	0.42	31.94

	Vertebral Fx +	Vertebral Fx -	
Deceased	12	40	52
Survival	3	26	29
	15	66	

Odds Ratio	2.60	
95% CI	Lower	Upper
	0.67	10.11

Although odds ratios for mortality were higher in patients with prevalent hip or vertebral fractures than that in patients without fractures (they were not statistically significant (a chi-square test).
Abbreviations: Fx, fracture.

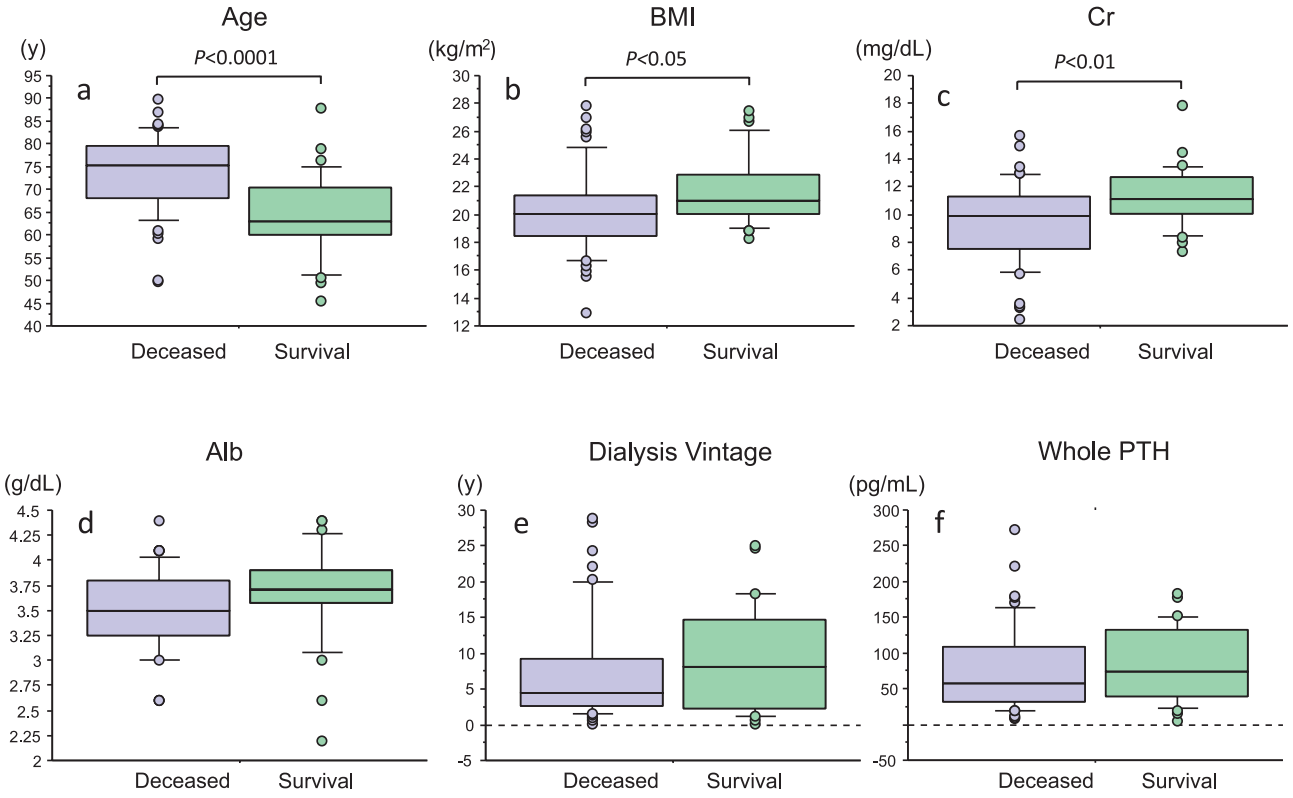

Figure 2. Comparison of Age, BMI, Dialysis Vintage, and Cr, Alb, and Whole PTH Levels Between the Survival and Deceased Groups
The medians with the 25th and 75th percentiles are shown. In the survival group, age was significantly lower, while BMI and Cr level were significantly higher (Mann-Whitney U test) compared to those in the deceased group. There were no significant differences in dialysis vintage, or Alb or whole PTH levels (Abbreviations: BMI, body mass index; Cr, creatinine; Alb, albumin; PTH, parathyroid hormone).

group, 21.0 kg/m^2 in the survival group), and Cr level (9.9 mg/dL in the deceased group, 11.1 mg/dL in the survival group) were significantly lower in the deceased group. Alb level was slightly higher in the survival group, but the difference was not significant. Neither dialysis vintage nor whole PTH level was significantly different between the survival and deceased groups. There were no significant differences in mortality between patients with and without diabetes or between men and women (Tables S2 and S3).

Table S2. The Prognostic Influence of DM

	DM +	DM -	
Deceased	23	29	52
Survival	7	22	29
	30	51	

Odds Ratio	2.49	
95% CI	Lower	Upper
	0.91	6.85

Although odds ratio for mortality was higher in diabetic patients than that in patients without diabetes (it was not statistically).
significant measures as chi-square test.

Table S3. Prognostic Influence of Sex

	Male	Female	
Deceased	35	17	52
Survival	16	13	29
	51	30	
Odds Ratio	1.67		
95% CI	Lower	Upper	
	0.66	4.25	

Although odds ratio for mortality was higher in male patients than that in female patients (it was not statistically).
significant measures as chi-square test.

The relationship between whole PTH level and BMD of the 1/3 Rad is shown in Figure 3. No significant correlations were observed. Similarly, whole PTH levels did not significantly correlate with the BMD of the lumbar spine or total hip (Figures S1 and S2). A logistic regression analysis was performed to evaluate the effects of age, BMI, Cr level, and BMD of the 1/3 Rad on mortality (Table 3). After adjusting for age, BMI, and Cr level, BMD of the 1/3 Rad was shown to be a statistically significant prognostic factor (OR = 0.954, 95% CI: 0.915 to 0.995; $P < .05$). Age was also a significant prognostic factor (OR = 1.09, 95% CI: 1.00 to 1.18; $P < .05$).

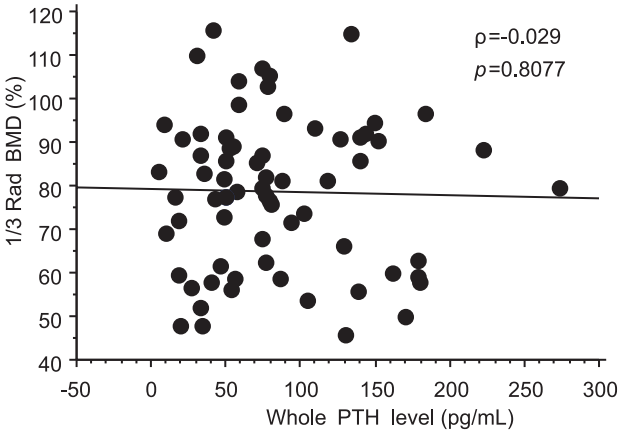

Figure 3. Relationship Between Whole PTH Level and BMD of the 1/3 Rad
Whole PTH levels did not correlate with BMD of the 1/3 Rad ($\rho = -0.029$, $P > .05$) (Abbreviations: 1/3, right distal third of the radius; BMD, bone mineral density; PTH, parathyroid hormone).

Table 3. Results of a Logistic Regression Analysis

	Odds Ratio	CI	*P*
Age	1.09	1.00 to 1.18	< .05
BMI	0.95	0.75 to 1.21	> .05
Cr Level	0.84	0.63 to 1.10	> .05
Rad 1/3 BMD	0.954	0.915 to 0.995	< .05

Rad 1/3 BMD and age were significant prognostic factors.
Abbreviations: BMI, body mass index; Cr, creatinine; Rad 1/3 BMD, bone mineral density of the distal third of the radius.

DISCUSSION

Few studies have reported the relationship between BMD and mortality in patients on hemodialysis, and it is unclear BMD of which site is appropriate as a prognostic factor. In the present study, BMD was measured at three different sites (the total hip, lumbar spine, and 1/3 Rad) to compare the impact on mortality. BMD was

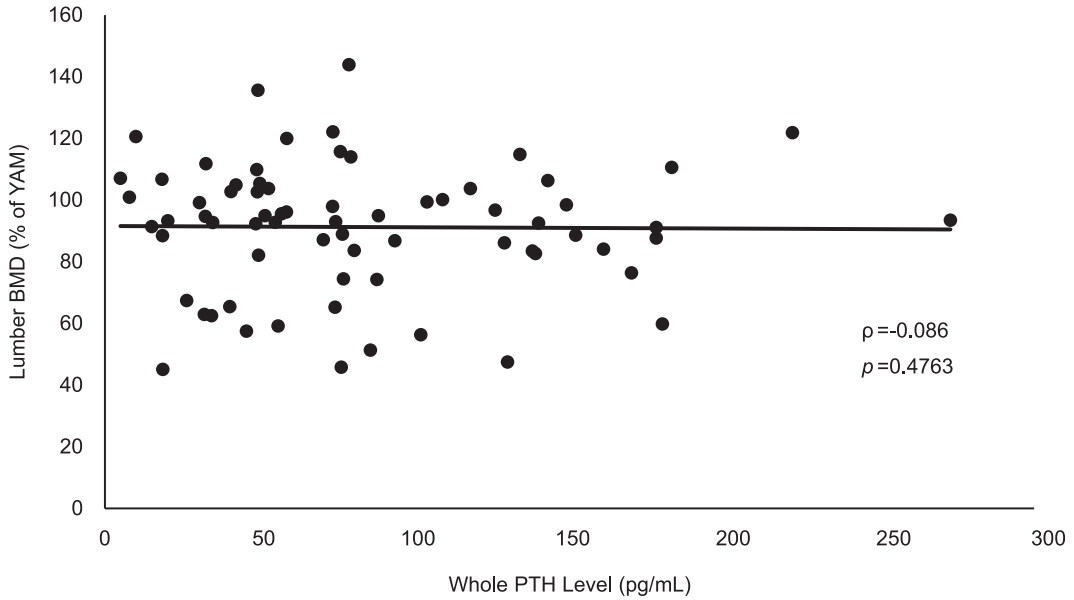

Figure S1. Relationship Between Whole PTH Level and Lumbar BMD (There was no correlation between Whole PTH level and lumbar BMD. Abbreviations: BMD, bone mineral density; PTH, parathyroid hormone).

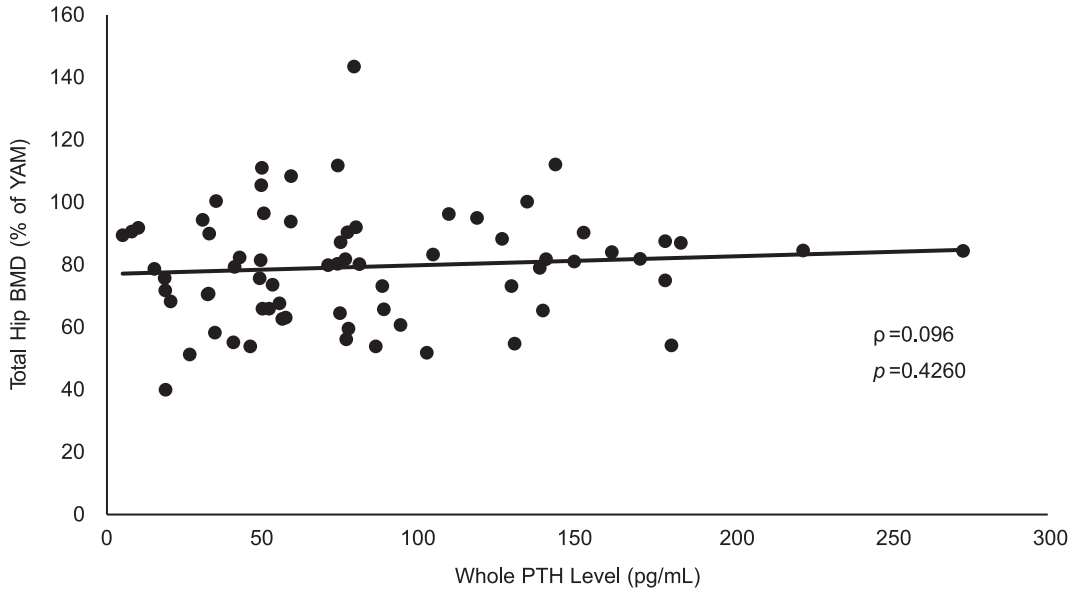

Figure S2. Relationship Between Whole PTH Level and Total Hip BMD (There was no correlation between Whole PTH level and total hip BMD. Abbreviations: BMD, bone mineral density; PTH, parathyroid hormone)

significantly higher in the survival group than in the deceased group only in the 1/3 Rad site. Age and BMI were also significantly higher in the survival group, and the Cr levels were significantly lower. Although BMD could be affected by age, BMI, and/or nutritional status, the logistic regression analysis demonstrated that BMD of the 1/3 Rad was independently associated with mortality in patients on hemodialysis. Although the cause of death was not examined in the present study because some of the patients died after being transferred to other facilities, cardiovascular death could have increased in the patients with decreased BMD of the 1/3 Rad. In the general population, low thoracic BMD is independently associated with coronary calcification and mortality.[18] Low BMD in the femur also exacerbates coronary atherosclerosis.[19] In CKD patients with elevated PTH levels, vascular calcification is strongly enhanced[20] with peculiar manners of bone loss. Secondary hyperparathyroidism due to renal failure progression promotes bone resorption, mainly in the bone cortex, and induces the release of calcium and phosphorus. Since cortical bone is abundant in the 1/3 Rad, a decrease in BMD here is more evident than that in the lumbar spine or hip. BMD of the lumbar spine may be affected by osteosclerotic changes and be higher than it actually is owing to aortic calcification. The increased load of calcium and phosphorus could facilitate a transformation of vascular smooth muscle cells into osteoblast-like cells and cause medial calcification of arteries.[21,22] As vascular calcification develops, incidence of cardiovascular event increases, and then mortality worsens. As reported by Soleymanian *et al.*,[23] elevated PTH levels and disorders of mineral metabolism are associated with mortality. Conversely, suppression of PTH inhibits ectopic calcification and improves survival in patients receiving hemodialysis.[24,25] In the present study, however, there was no correlation between whole PTH level and BMD of the 1/3 Rad. This discrepancy could be explained by a "Legacy Effect". In most of the patients, PTH level was within the target range defined by the guideline of the Japanese Society for Dialysis Therapy.[26] Low BMD of the 1/3 Rad would indicate long-term exposure to high levels of PTH in the past, which has been associated with advanced vascular calcification. Prevalent fractures increase mortality in the general population.[1,2] Also, in hemodialysis patients, it has been reported that prevalent hip and vertebral fractures are associated with mortality.[3] In addition, vertebral fractures are associated with vascular calcification and mortality in patients on hemodialysis.[4] However, in the present study, although the odds ratio for death increased in patients with prevalent fractures, the increase was not statistically significant. This inconsistency appears to be due to the small number of patients with fractures. This single-center cohort study

has several limitations. Owing to the small size of the cohort, significant differences could not be observed. As some patients had been transferred to other facilities, analysis including the time of death was not possible. Additionally, it was not possible to confirm the cause of death. This study had limited data because we used prior collected data. The effect of BMD of the 1/3 Rad was adjusted for Cr level, BMI, and age, but there could be other important confounding factors.

CONCLUSION

In conclusion, low BMD, especially in the 1/3 Rad, could be an independent prognostic factor in patients receiving hemodialysis.

DECLARATIONS

Funding

The authors declare that there is no funding related to this manuscript.

Competing Interest

All the authors declare that they have no competing interests.

Availability of Data and Materials

All data generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

TK performed the statistical analysis and wrote the manuscript. AF designed the study and edited the manuscript. SO and NH contributed to data acquisition. TK reviewed the manuscript and provided scientific comments. All authors read and approved the final manuscript.

Ethical Approval, Consent to Participate, and Consent for Publication

This study was performed in accordance with the principles of the Declaration of Helsinki, and approved by the ethics committee of the facility with an approval number of 2019–04. The information on this clinical study was disclosed on our website, where it was clarified that the use of data could be suspended if desired.

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