



Research article

Prevalence and predictors of asymptomatic vertebral fracture in patients with end-stage renal disease

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ABSTRACT

Objective: This study aimed to investigate the prevalence and predictors of asymptomatic vertebral fracture in patients with end-stage renal disease undergoing hemodialysis.**Methods:** This cross-sectional study included 80 patients with end-stage renal disease undergoing hemodialysis. Medical history, Fracture Risk Assessment Tool and anteroposterior and lateral radiographs of the thoracolumbar and lumbosacral spine were obtained. Vertebral fractures were identified using the Genant semiquantitative assessment.**Results:** Radiography demonstrated asymptomatic vertebral fracture in 22 patients (27.5%). FRAX[®] results for major osteoporotic fracture (area under the curve, 0.64) and hip fracture (area under the curve, 0.62) were able to discriminate patients with prevalent asymptomatic vertebral fracture. A multivariate analysis demonstrated that a 1-year average corrected calcium (odds ratio, 0.38), steroid use (odds ratio, 8.99), and a serum albumin concentration <25 g/dL (odds ratio, 28.82) significantly predicted prevalent asymptomatic vertebral fracture (clinical model; area under the curve, 0.82). Combining the 1-year average corrected calcium and serum albumin concentration <25 g/dL with FRAX[®] results for major osteoporotic fracture (area under the curve, 0.78) and FRAX[®] results for hip (area under the curve, 0.75) produced a significantly greater area under the curve value to predict fracture when compared with FRAX[®] result for major osteoporotic fracture and FRAX[®] result for hip (P = 0.022).**Conclusion:** Asymptomatic vertebral fracture is prevalent. FRAX[®] results for major osteoporotic fracture and hip provided lower ability in predicting asymptomatic vertebral fracture when compared to the clinical model. Combining a 1-year average corrected calcium and serum albumin concentration <25 g/dL with FRAX[®] result for major osteoporotic fracture or hip improved the model's performance and provided comparable area under the curve to the clinical model.

1. Introduction

Fractures are 2- to 14-fold more common in patients with chronic kidney disease (CKD) compared with the general population [1], and the incidence of fracture progressively increases as kidney function worsens [2]. For example, in patients undergoing long-term hemodialysis, there were an increase in the age-standardized incidence ratio of hip fracture [3] and higher mortality and morbidity rates after hip fracture [4, 5]. Conversely, vertebral fracture has received much less attention. The

prevalence of vertebral fracture may be underestimated since the majority of vertebral fractures are silent and spinal X-ray is not performed on a routine basis. A varying prevalence of vertebral fracture (8–20%) has been reported, and the prevalence depends on the methods used to detect fracture [6, 7, 8]. Collectively, the high incidence of fracture and adverse outcomes that follow fracture pose a significant health burden for patients. Data on the prevalence and predictors of vertebral fracture in Thai patients with end-stage renal disease (ESRD) undergoing hemodialysis are also lacking.

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A combination of classic risk factors for osteoporotic fracture, such as age, sex, medical history of fracture, diabetes, and glucocorticoid use, and risk factors associated with CKD, explain the higher risk of fracture in patients with CKD [9]. It is well established that systemic disorder of mineral and bone metabolism due to CKD, also known as CKD-mineral and bone disorder (CKD-MBD), affects bone strength and quality [10, 11]. In previous studies in patients with CKD, advanced age; low bone mineral density (BMD); low body mass index (BMI); narcotic and psychoactive medication use; low 25-hydroxyvitamin D [25(OH)D]; abnormal parathyroid hormone (PTH), phosphorus, calcium, and total alkaline phosphatase (ALP) concentrations; and high Fracture Risk Assessment Tool (FRAX[®]) for major osteoporotic fracture were associated with low-trauma fracture [12, 13, 14, 15, 16]. Long-term dialysis vintage was correlated with hip and vertebral fracture in studies with small sample sizes [7, 17]. In the general population, the FRAX[®] with or without dual-energy X-ray absorptiometry (DXA) result is commonly used to predict the 10-year probability of hip and vertebral fracture. However, the clinical utility of FRAX[®] in patients with CKD is controversial, and no definite cut-off point to suggest a high risk of fracture exists [18].

This study aimed to investigate the prevalence of asymptomatic (morphometric) vertebral fracture and identify predictors of prevalent asymptomatic vertebral fracture in patients with ESRD undergoing hemodialysis.

2. Results

This study included 80 participants and the results should be considered as preliminary. Baseline clinical characteristics are shown in Table 1. The mean age of patients was 68.7 ± 14.0 years, mean body mass index was 23.7 ± 4.8 kg/m², and 52.5% of patients were male. The duration of hemodialysis ranged from 3 months to 19 years with a median of 4 years and the mean frequency of visits was 5.0 ± 1.8 times/year. Diabetes, hypertension, and dyslipidemia were reported in 58.75%, 90%, and 77.5% of the patients, respectively. Steroid use, with the median duration of 6 (3–84) months, was reported in 13.75% of the patients. The number of patients receiving other drugs associated with fracture risk [19] can be found in Table 1. A total of 53%, 44%, and 29% of the patients received calcium, and supplementation of active forms of vitamin D and ergocalciferol (vitamin D₂), respectively. A parental history of hip fracture was reported in 1 patient (1.3%). All laboratory results are also shown in Table 1.

Twenty-two patients (27.5%) had asymptomatic vertebral fracture detected by spine radiographs with 12, 7, and 3 patients had 1, 2, and 3 vertebral fractures, respectively. With regards to the severity of fracture [20], 3, 11, and 8 patients had mild, moderate, and severe vertebral fractures, respectively. Although most patients with vertebral fracture belonged to the older age group, the difference in the fracture prevalence compared to the lower age group did not reach statistical significance (<70 years vs. ≥ 70 years: 18.4% vs. 35.7%, $P = 0.084$). The majority of patients with fracture had shorter hemodialysis duration (<4 years vs. ≥ 4 years: 40% vs. 17.8%; $P = 0.027$) and a history of steroid use (non-user vs. user: 21.7% vs. 63.6%; $P = 0.004$). Although, the medians of the FRAX[®] results for MOF and hip fracture were higher in the group with fracture, the difference between two groups did not reach statistical significance (fracture vs. no fracture: 9% (1.2–22) vs. 4.3% [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16]; $P = 0.066$ for MOF and 3.8% (0.1–17) vs. 1.9% (0.1–12); $P = 0.102$ for hip fracture (Table 1). Comparisons of current laboratory values revealed no differences in serum albumin-corrected calcium, phosphate, ALP, PTH, bicarbonate, and hemoglobin concentrations between the two groups. The average values over the 1-year period were also largely similar among the two groups (data not shown), except, for lower serum albumin-corrected calcium in the group with fracture (Table 1). Most patients with fracture had serum albumin <25 g/dL (<25 vs. ≥ 25 g/dL: 80% vs. 24%; $P = 0.019$). The 25(OH)D concentration, which was assessed in only 27 patients, was

significantly lower in the group with fracture (14.2 vs. 35 ng/mL; $P = 0.013$). Of note, 25(OH)D concentration was not further analyzed because of limiting data availability.

Table 2 shows the pairwise Spearman's correlation between parameters that were significantly associated with prevalent vertebral fracture obtained from Table 1. Because the duration of hemodialysis was highly correlated to the 1-year average serum calcium, therefore, the duration of hemodialysis was excluded from further analyses in order to avoid the statistical issue of multicollinearity.

2.1. Logistic regression and ROC area under the curve (AUC) for models predicting asymptomatic vertebral fracture

Simple logistic regression was used to determine the ability of FRAX[®] scores to predict the prevalence of asymptomatic vertebral fracture. FRAX[®] result for MOF was significantly associated with prevalent asymptomatic vertebral fracture (OR 1.16, 95%CI 1.04–1.30; $P = 0.007$) with the AUC of 0.64 (95% CI 0.47–0.81). In addition, FRAX[®] result for hip fracture was efficient in predicting prevalent asymptomatic vertebral fracture (OR 1.19, 95% CI 1.01–1.40; $P = 0.035$) with the AUC of 0.62 (95% CI 0.46–0.79).

We performed a multiple logistic regression analysis to determine clinical factors that could possibly predict the prevalence of vertebral fracture. The 1-year average corrected calcium (OR 0.38, 95% CI 0.15–0.93; $P = 0.035$), the history of steroid use (OR 8.99, 95% CI 2.12–38.13; $P = 0.003$), and serum albumin <25 g/dL (OR 28.82, 95% CI 2.49–333.33; $P = 0.007$) were associated with prevalent asymptomatic vertebral fracture (Table 3). The AUC of the clinical model (model 1) was 0.82 (95% CI 0.70–0.93) (Table 3). Model 2 which included clinical risk factors to the FRAX[®] result for MOF showed significant associations between FRAX[®] result for MOF (OR 1.21, 95% CI 1.07–1.37; $P = 0.003$), 1-year average corrected calcium (OR 0.33, 95% CI 0.13–0.88; $P = 0.026$), and serum albumin <25 g/dL (OR 27.73, 95% CI 1.70–451.92; $P = 0.020$) with prevalent asymptomatic vertebral fracture with the AUC of 0.77 (95% CI 0.66–0.89; Table 4). Model 3, which included clinical risk factors to FRAX[®] result for hip fracture also significantly correlated with the prevalence of vertebral fracture with the AUC of 0.75 (95% CI 0.63–0.87) (Table 4).

Comparison of AUCs among different FRAX[®] results with or without clinical risk factors and clinical risk factors alone for predicting prevalent vertebral fracture is shown in Table 5. The models derived from clinical risk factors alone (Model 1) (AUC 0.80, 95% CI 0.68–0.93), FRAX[®] result for MOF + clinical risk factors (Model 2) (AUC 0.78, 95% CI 0.66–0.89), and FRAX[®] result for hip + clinical risk factors (Model 3) (AUC 0.75, 95% CI 0.63–0.87) provided significantly higher AUC values when compared to FRAX[®] result for MOF and FRAX[®] result for hip alone ($P = 0.022$).

3. Discussion

This study demonstrates that the prevalence of asymptomatic vertebral fracture in Thai patients with ESRD undergoing hemodialysis is as high as 27.5%. FRAX[®] results for both MOF and hip fracture were significantly correlated with the prevalence of vertebral fracture in this study cohort. The preliminary results demonstrated that a combination of clinical factors (the clinical model), including a 1-year average corrected calcium, history of steroid use, and serum albumin concentration of <25 g/dL, were also able to predict the prevalence of vertebral fracture. The ability to predict vertebral fracture was higher in a model derived from clinical risk factors when compared with FRAX[®] results for both MOF and hip alone. Combining FRAX[®] results with other clinical risk factors not already included in FRAX[®] did improve the ability to predict the prevalence of asymptomatic vertebral fracture but performed no better than having clinical risk factors alone. Because of the small number of participants, these observations are preliminary and should not lead to clinical application. A confirmation in a large prospective cohort is mandatory. Our data emphasize that vertebral fracture is clinically silent

Table 1. Baseline characteristic of participants according to fracture status (n = 80).

	Total (n = 80)	No vertebral fracture (n = 58)	Vertebral fracture (n = 22)	P value
Age, n (%)				0.084
<70 years	38 (47.5)	31 (81.6)	7 (18.4)	
≥70 years	42 (52.5)	27 (64.3)	15 (35.7)	
Female, n (%)	38 (47.5)	26 (68.4)	12 (31.6)	0.437
Duration of hemodialysis, n (%)				0.027
<4 years	35 (43.8)	21 (60)	14 (40)	
≥4 years	45 (56.2)	37 (82.2)	8 (17.8)	
Mean BMI (kg/m ²)	23.7 ± 4.8	23.3 ± 4.8	24.7 ± 4.8	0.238
Current smoking, n (%)	1 (1.3)	0	1 (100)	0.275 ^a
Current alcohol use, n (%)	1 (1.3)	0	1 (100)	0.275 ^a
Drug-related fracture risk, n (%)				
Glucocorticoid	11 (13.8)	4 (36.4)	7 (63.6)	0.004
Furosemide	40 (50)	30 (75)	10 (25)	0.617
PPI	33 (41.3)	25 (75.8)	8 (24.2)	0.494
TZD	4 (5)	4 (100)	0	0.571 ^a
SSRI	2 (2.5)	1 (50)	1 (50)	0.477 ^a
Anticoagulant	8 (10)	5 (62.5)	3 (37.5)	1 ^a
Androgen deprivation therapy	1 (1.3)	1 (1.7)	0	1 ^a
Aromatase inhibitor	1 (1.3)	1 (1.7)	0	1 ^a
Antiepileptic	4 (5)	3 (75)	1 (25)	1 ^a
Calcium				
Number receiving supplementation, n (%)	42 (52.5)	27 (64.3)	15 (35.7)	0.084
Elemental calcium, median (mg/day)	140 (0–3000)	720 (0–3000)	360 (0–2000)	0.263
Active vitamin D, n (%)				
Number receiving supplementation, n (%)	35 (43.8)	25 (71.4)	10 (28.6)	0.850
Ergocalciferol (vitamin D ₂)				
Number receiving supplementation, n (%)	23 (28.8)	16 (69.6)	7 (30.4)	0.709
Vitamin D dosage, median (IU/week)	0 (0–40000)	0 (0–40000)	0 (0–40000)	0.486
Parental history of hip fracture, n (%)	1 (1.3)	1 (100)	0	1.000
FRAX ^b				
Major osteoporotic fracture, median (%)	4.5 (1–22)	4.3 (1–16)	9 (1.2–22)	0.066
Hip, median (%)	2.3 (0.1–17)	1.9 (0.1–12)	3.8 (0.1–17)	0.102
Laboratory results ^c				
Albumin, n (%)				0.019 ^a
<25 g/dL	5	1 (20%)	4 (80%)	
≥25 g/dL	75	57 (76%)	18 (24%)	
Corrected calcium (mg/dL)	9.7 ± 0.8	9.7 ± 0.8	9.7 ± 0.7	0.989
1-year average corrected calcium (mg/dL)	9.7 ± 0.7	9.8 ± 0.7	9.5 ± 0.5	0.016
Phosphate (mg/dL)	4.6 ± 1.3	4.6 ± 1.2	4.5 ± 1.3	0.690
Alkaline phosphatase, median (mg/dL)	95 (30–383)	89.5 (30–317)	113.5 (44–383)	0.267
iPTH, median (pg/mL)	250.8 (32.4–3388)	257.4 (32.4–3388)	207.1 (39.7–1509)	0.821
25(OH)D, median (ng/mL) ^d	31.3 (4.3–117)	35 (4.3–83)	14.2 (7–26)	0.013
HCO ₃ (mmol/L)	23.3 ± 2.6	23.1 ± 2.6	23.8 ± 2.3	0.263
Hemoglobin (g/dL)	10.7 ± 1.6	10.7 ± 1.6	10.9 ± 1.7	0.559

^a, Fisher's exact test; ^b, n = 75; ^c, all were reported as the current values except corrected calcium; ^d n = 27.

BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; PAD, peripheral arterial disease; CVA, cerebrovascular disease; PPI, proton pump inhibitor; TZD, thiazolidinedione; SSRI, selective serotonin reuptake inhibitor; iPTH, intact parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; HCO₃, bicarbonate.

in patients with ESRD undergoing hemodialysis. The prevalence of asymptomatic vertebral fracture in this study was higher compared with prior studies; specifically, the prevalence was 8% in Caucasian individuals (detected by standard radiography, computerized tomography, and Tc-99bone scintigraphy) [7]; 11.76% in Chinese individuals [8]; and 20% in Japanese individuals [6] (detected by thoracic and lumbar spine radiography). Differences in ethnicity and age may explain the discrepancies. Of note, our patients were older when compared to those in other studies (the mean age were 68.74, 60.5, 59 and 54.2 years in the present study, Caucasian, Chinese and Japanese studies, respectively) [6, 7, 8].

Originally, FRAX[®] was developed to estimate the 10-year absolute risk of osteoporotic fracture among the general population, but evidence supporting its use in patients undergoing long-term hemodialysis is limited and inconclusive. In this study, high FRAX[®] scores for MOF and hip fracture were correlated with the prevalence of asymptomatic vertebral fracture. However, the accuracy of FRAX[®] alone for prediction of prevalent vertebral fracture is poor, as demonstrated by the low AUC. The prior study in Chinese patients undergoing hemodialysis reported that FRAX[®] results were associated with the prevalence of fracture (both clinical non-vertebral and morphometric vertebral fracture) with the

Table 2. Spearman's correlation of clinical parameters that were significantly associated with prevalent vertebral fracture.

	Hemodialysis duration <4 years	Steroid use	Albumin concentration <25 g/dL	1-year average corrected calcium (mg/dL)
Hemodialysis duration <4 years	1			
Steroid use	0.01 P = 0.90	1		
Albumin concentration <25 g/dL	-0.02 P = 0.86	-0.10 P = 0.36	1	
1-year average corrected calcium (mg/dL)	-0.31 P < 0.01	-0.06 P = 0.58	0.02 P = 0.88	1

Table 3. Multiple logistic regression analysis of clinical risk factors associated with prevalent vertebral fracture.

	OR	95% CI	P value
N = 80			
1-year average corrected calcium (mg/dL)	0.38	0.15–0.93	0.035
Steroid use	8.99	2.12–38.13	0.003
Albumin concentration <25 g/dL	28.82	2.49–333.33	0.007
AUC to predict vertebral fracture	0.82 (0.70–0.93)		

OR, odds ratio; 95% CI, 95% confidence interval; AUC, area under the curve.

AUC of 0.715 [8]. Another study on Canadian patients with CKD reported that FRAX[®] was able to discriminate among those with morphometric vertebral fracture with an AUC of 0.66 [21]. Many clinical risk factors associated with fracture risk in patients with CKD were not included in FRAX[®], and this could explain the limited ability of FRAX[®] to predict the prevalence of fracture.

Older age, steroid use, and hypoalbuminemia were associated with a higher prevalence of vertebral fracture in the present study. The proposed mechanism is a decrease in sex hormones in older patients. In addition, malnutrition and chronic illness are associated with frailty and sarcopenia, and nutritional deficiencies can eventually increase age-related bone loss. Nutrients are directly linked to spine, hip and whole-body bone density in postmenopausal women [22] and patients on hemodialysis [23, 24]. In contrast to previous study, a shorter duration of hemodialysis was inversely associated with vertebral fracture in this study [7, 25]. Despite these observations, the duration of hemodialysis has not been consistently correlated with fracture. Urena et al. reported that patients with fractures were undergoing hemodialysis for longer period compared with patients without fractures (fracture group: 10.4 years vs. no fracture group: 5 years), and the relative risk of fracture was significantly increased after 5 years of hemodialysis [7]. On the other hand, among Japanese patients who underwent hemodialysis for an average of 12 years, no significant difference in hemodialysis duration was observed between the vertebral fracture and non-vertebral fracture group [6]. Our patients had a relatively shorter duration of hemodialysis

Table 5. Comparison of AUCs between FRAX[®] results and different clinical models.

	AUC	95% CI
N = 75		
FRAX [®] result for MOF	0.64	0.47–0.81
FRAX [®] result for hip fracture	0.62	0.46–0.79
Clinical risk factors (model 1)	0.80	0.68–0.93
FRAX [®] result for MOF + clinical risk factors (model 2)	0.78	0.66–0.89
FRAX [®] result for hip fracture + clinical risk factors (model 3)	0.75	0.63–0.87

P value = 0.022.

AUC, area under the curve; 95% CI, 95% confidence interval; MOF, major osteoporotic fracture.

(median duration, 4 years) than those from the above studies and there was a significant correlation between albumin-corrected calcium and hemodialysis duration. The relatively low serum calcium during the first few years of hemodialysis initiation could represent the reduced calcium balance that occurred since prior to hemodialysis from inadequate dietary calcium intake and absorption [26]. The reduced calcium balance as well as the abnormalities of other mineral parameters prior to hemodialysis initiation could be responsible for the increased fracture risk during the first few years. After receiving additional calcium from dialysis fluid, the calcium balance became neutral or even positive in the later years of dialysis vintage. The restoration of calcium balance could be responsible for the subsequent reduction in fracture risk [27]. Moreover, PTH level in the present study population is relatively low suggesting that low-turnover bone disease which is increasingly common among patients with ESRD could be responsible for the changes in bone architecture especially among those with shorter dialysis vintage [28]. Lower 25(OH)D concentrations was observed among patients with vertebral fracture in this study. However, over 2/3 of the patients were not assessed for vitamin D status and the significance of this finding could not be ascertained.

Table 4. Multiple logistic regression analysis of different FRAX[®] result with clinical risk factors for prediction of prevalent vertebral fracture.

N = 75	Model 2: FRAX [®] result for MOF and clinical risk factors			Model 3: FRAX [®] result for hip fracture and clinical risk factors		
	OR	95% CI	P value	OR	95% CI	P value
FRAX [®] result for MOF	1.21	1.07–1.37	0.003			
FRAX [®] result for hip fracture				1.23	1.03–1.46	0.020
1-year average corrected calcium (mg/dL)	0.33	0.13–0.88	0.026	0.38	0.15–0.95	0.038
Albumin concentration <25 g/dL	27.73	1.70–451.92	0.020	19.80	1.41–278.25	0.027
AUC to predict vertebral fracture	0.78 (0.66–0.89)			0.75 (0.63–0.87)		

MOF, major osteoporotic fracture; OR, odds ratio; 95% CI, 95% confidence interval; AUC, area under the curve.

Finally, we demonstrated that combining clinical FRAX[®] result for MOF with relevant clinical factors not already included in FRAX[®] significantly improved the ability of the model to determine the prevalence of asymptomatic vertebral fracture. This data suggests the necessity to identify relevant risk factors among patients with CKD in order to develop a more appropriate CKD-specific risk score for fracture prediction.

To the best of our knowledge, this is the first study to explore the prevalence and clinical predictors of asymptomatic vertebral fracture in patients with ESRD undergoing hemodialysis in Thailand. In addition, the ability of FRAX[®] results, clinical risk factors, and the combined models of both FRAX[®] and clinical risk factors for prediction of prevalent asymptomatic vertebral fracture were assessed. These findings are valuable because the risk of fracture varies among patients with different condition and different ethnic groups. However, the limitations of this study included the small sample size and the lack of data on height and vitamin D status. In our country, the assessment of 25(OH)D and 1,25(OH)₂D concentrations are not routinely performed in patients with ESRD. Another concern was the lack of the data on BMD resulting in the lower-than-expected performance of FRAX[®]. The duration of hemodialysis in this study was relatively short; therefore, the results should not be generalized to patients with longer dialysis vintage. Since this is a cross-sectional study; the ability of FRAX[®] without BMD was used to determine the prevalence of asymptomatic vertebral fracture rather than to predict the 10-year fracture risk.

4. Conclusion

Asymptomatic vertebral fracture is prevalent and clinically silent in patients with ESRD undergoing hemodialysis. The clinical model was more accurate compared with the FRAX[®] results in the determination of prevalent vertebral fracture. Combine d FRAX[®] and clinical predictors improved the accuracy of fracture prediction but performed no better than clinical predictors alone.

5. Material and methods

This was a cross-sectional study and performed during May 2019 to October 2019. Eligible participants were patients with ESRD undergoing hemodialysis for >3 months with a regular visit to the hemodialysis clinic, Ramathibodi Hospital. Patients were ≥18 years of age. Patients who fulfilled the following criteria were excluded: 1) bedridden, 2) tube feeding, 3) post-parathyroidectomy, 4) receiving anti-osteoporosis medications (i.e., bisphosphonates, denosumab, hormonal therapy, selective estrogen receptor modulators, parathyroid hormone analogues) or cinacalcet. All patients provided written informed consent. The protocol was approved by the institutional review board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University. All participants were assessed for CKD history, medical records, and fracture risk using a questionnaire, the FRAX[®] risk assessment, and anteroposterior and lateral radiographs of the thoracolumbar and lumbosacral spine.

5.1. Questionnaire, medical record review, and FRAX[®] risk assessment

We administered a questionnaire (by phone or direct interview; in Supplementary Material) upon study entry and performed a review of each participant's medical records. Data included age, hemodialysis duration, current alcohol drinking, current smoking status, history of osteoporotic fracture (see below), history of parental hip fracture, other underlying diseases (diabetes, coronary artery disease, peripheral arterial disease, cerebrovascular disease, hypertension, dyslipidemia), and current medications (calcium, vitamin D, glucocorticoids, furosemide, proton pump inhibitors, thiazolidinediones, selective serotonin reuptake inhibitors, anticoagulants, androgen deprivation therapy, aromatase inhibitors, antiepileptic drugs). The laboratory parameters associated with ESRD included in the analysis were albumin, albumin-corrected calcium, phosphate, ALP, PTH, 25(OH)D, bicarbonate, and hemoglobin. All these parameters, except albumin-corrected calcium, were reported as the

current values. Albumin-corrected calcium was reported as the current value and 1-year average value. The current value was defined as the latest values at the time of inclusion. All laboratory tests were assessed at the central laboratory of Ramathibodi Hospital.

For our FRAX[®] assessment, 11 clinical risk factors required by FRAX[®] (age, sex, weight, height, history of previous osteoporotic fracture, history of parenteral hip fracture, current smoking status, current use and/or exposure to glucocorticoids [>5 mg of prednisone or equivalent per day for ≥ 3 months], rheumatoid arthritis, known secondary osteoporosis, and alcohol intake of ≥ 3 units per day) were incorporated into the web-based Thailand-specific FRAX[®] assessment tool [29]. Thirteen participants in this study had a history of non-vertebral fracture, and none of them had known clinical or asymptomatic vertebral fracture. With regard to the type of fracture, three patients had multiple fracture sites (one had fractures at the wrist, tibia and fibula; one had fractures at the forearm and fibula; and one had fractures at the forearm, tibia, and fibula), six participants had hip fractures, and each participant had a fracture at one of the following sites: humerus, elbow, radius, and fibula. There was no BMD data in this study, therefore we calculated FRAX[®] without BMD and reported as FRAX[®] results for major osteoporotic fracture (MOF) and FRAX[®] results for hip fracture. Because the FRAX algorithm was developed for use within a specific age range (i.e., between 40 and 90 years of age) and there were five participants aged <40 or >90 years in this study, we reported the results related to FRAX in 75 patients.

5.2. Fracture ascertainment

5.2.1. History of non-vertebral fracture

We defined osteoporotic non-vertebral fracture as fractures at the hip, distal forearm, pelvis, humerus and proximal tibia that occurs from minimal trauma (such as a fall from equal to or less than standing height) according to the World Health Organization's definition [30]. Non-vertebral fractures were self-reported.

5.2.2. Prevalence of asymptomatic vertebral fracture

None of the patients had known clinical or asymptomatic vertebral fracture. To investigate the prevalence of asymptomatic vertebral fracture, anteroposterior and lateral radiographs of the thoracolumbar and lumbosacral spine were obtained upon study entry, and vertebral fractures were identified using the Genant semiquantitative assessment [20]. In brief, mild, moderate, and severe vertebral fracture (collapse) were defined as 20%–25%, 26%–40%, and $>40\%$ of vertebral height loss, respectively. If a participant had ≥ 2 vertebral fractures within different severity classes, the most severe vertebral fracture class was used. Films were interpreted by two physicians by using the same criteria, and differences in interpretation were resolved by consensus.

5.3. Statistical analysis

Continuous variables are presented as mean \pm standard deviation or median (range) depending on their distribution, and categorical variables are presented as number (percent). Age was categorized as ≥ 70 years versus <70 years based on the mean age of patients. The duration of hemodialysis was categorized as ≥ 4 years versus <4 years based on the median duration of hemodialysis. Since hypoalbuminemia is independently associated with osteoporosis [31, 32], and malnutrition, as partly reflected by low circulating albumin, can increase fracture risk [17], serum albumin concentrations were categorized as ≥ 25 g/dL versus <25 g/dL based on the 5th percentile of the serum albumin levels in the study population. Differences in clinical characteristics and laboratory results between patients with and without vertebral fracture were analyzed using the Student's t-test, Chi-squared test, or Fisher's exact test, as appropriate. The pairwise Spearman's correlation was performed to investigate the correlation between parameters different in patients with fractures compared to those without fracture. Simple logistic regression was used to investigate the association between FRAX[®] results for MOF

and hip fracture and prevalent asymptomatic vertebral fracture. Multiple logistic regression was used to investigate the ability of relevant clinical risk factors (model 1), FRAX[®] result for MOF and relevant clinical risk factors (model 2), and FRAX[®] result for hip fracture and relevant clinical risk factors (model 3) to predict vertebral fracture. To determine their ability to discriminate prevalent vertebral fracture (as determined by morphometry), we constructed receiver operating characteristic (ROC) curves for each predictor model. Statistical tests were considered significant at a two-tailed level of 0.05. Data were analyzed using STATA, version 15.0 (StataCorp LLC; College Station, TX, USA).

Declarations

Author contribution statement

Sasipim Jirasirak and Hataikarn Nimitphong: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Since Disthabanchong and Boonsong Ongphiphadhanakul: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Sakda Arj-Ong Vallibhakara: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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