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Original Article

Efficacy of calcaneal quantitative ultrasound and bone turnover markers for assessing fracture risk in patients undergoing hemodialysis

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Abstract: Aims: To explore risk factors for fractures in maintenance hemodialysis patients and develop a diagnostic model for clinically predicting fracture risk. Materials and Methods: This single-center retrospective study included 166 hemodialysis patients. General data, clinical indicators, calcaneal quantitative ultrasound (QUS)-bone mineral density (BMD) results, and bone turnover markers were collected. Univariate and multivariate logistic regression identified independent risk factors. A nomogram prediction model was constructed using R software and evaluated by receiver operating characteristic curve, calibration curve, and decision curve analysis (DCA). Results: 43 patients (25.90%) had fractures. Multivariate analysis identified BMD T-score as an independent fracture predictor (OR = 2.822, 95% CI: 1.105-7.206, P = 0.030). A BMD T-score < -2.88 and a procollagen type I N-propeptide (PINP) β-terminal crosslinking telopeptide of type I collagen (β-CTX) product > 843.53 were significant predictive thresholds. The nomogram model incorporated 8 variables (gender, bed rest, age, OSTA, BMD, PINP, β-CTX, PINP β-CTX product), demonstrating good discrimination (C-index = 0.8287), calibration (H-L test P = 0.9006), and clinical utility by DCA. This multifactor model outperformed the single-factor model using BMD alone, demonstrating high clinical utility, as well as robust and stable performance. Conclusion: Regular QUS-BMD monitoring combined with BTMs (PINP and β-CTX) is crucial for assessing fracture risk in hemodialysis patients. The comprehensive prediction model proposed in this study was superior to single-marker evaluation, enabling clinicians to perform risk stratification, early diagnosis, and personalized management. This should reduce fracture incidence and improve patient outcome.

Keywords: Bone mineral density, bone turnover markers, β-CTX, PINP, fracture, hemodialysis, quantitative ultrasound

Introduction

Chronic kidney disease (CKD) is a high-prevalence disease that has evolved into a public health problem. One of the main reasons for the increased risk of fractures in hemodialysis patients is changes in bone microstructure and bone mineral density (BMD), related to mineral and bone disorders, commonly known as chronic kidney disease-mineral and bone disorder (CKD-MBD) [1]. It is a complex disease caused by disturbances in metabolism and hormone levels (e.g., changes in calcium, phosphorus, parathyroid hormone (PTH), and vitamin D levels) [1]. It can lead to bone quality damage and abnormal bone remodeling [1]. The prevalence of low BMD in CKD patients is as high as 24.5% (95% Confidence Interval (CI): 21.3-27.8%), especially in dialysis patients (30%, 95% CI: 25-35%) [2]. The rate of hip fractures in hemodialysis patients is higher than that of spinal fractures, and the rate of cortical bone fractures is higher than that of trabecular bone fractures [3-5]. For every 1.0 unit decrease in total hip BMD T-score, the risk of fracture significantly increases by 1.46 times (95% CI: 1.12-1.89) [6]. In non-dialysis CKD patients, low BMD is related to a higher rate of fractures and overall mortality [7, 8].

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CKD-MBD is the core pathophysiologic basis of skeletal fragility in hemodialysis patients. The loss of renal phosphorus excretion function leads to hyperphosphatemia, which not only directly stimulates parathyroid cell hyperplasia and PTH secretion, but also indirectly exacerbates PTH release by lowering blood calcium levels [9]. Hypocalcemia, synergizing with insufficient active vitamin D synthesis, persistently activates the calcium-sensing receptor of the parathyroid glands, becoming a key driver for the occurrence and maintenance of secondary hyperparathyroidism. Persistently abnormally elevated PTH levels lead to a significant acceleration of bone turnover, resulting in high-turnover bone disease. In this state, osteoclast activity is excessively enhanced, and bone resorption exceeds bone formation. Although bone formation also increases, the newly formed bone tissue exhibits disordered collagen arrangement and incomplete mineralization, ultimately leading to a significant decrease in bone strength [5]. In patients on hemodialysis, there are higher levels of the more specific markers of bone turnover, namely bone-specific alkaline phosphatase, which are the best independent predictors of fracture risk [5]. This highlights the central role of high bone turnover driven by secondary hyperparathyroidism in compromising skeletal structural integrity.

In recent years, with a deepening understanding of the pathophysiologic mechanisms of CKD-MBD and the application of novel biomarkers and imaging techniques, the comprehension of fracture risk factors in hemodialysis patients has become more comprehensive. Abnormal serum phosphorus levels [9], fluctuations in parathyroid hormone, and elevated fibroblast growth factor 23 are all associated with an increased risk of fracture in maintenance hemodialysis patients [9-11]. Among these, PTH levels exhibit a “U”-shaped curve relationship with fracture risk: chronically excessive levels overstimulate osteoclast activity, leading to hyperactive bone resorption and the formation of woven bone with poor mechanical properties; conversely, excessively low PTH levels (< 150 pg/mL) often indicate adynamic bone disease, where bone repair capacity is severely impaired, also significantly increasing fracture risk [10]. When tertiary hyperparathyroidism develops, the fracture risk further escalates [12].

Furthermore, non-traditional risk factors also crucially increase fracture risk: long dialysis vintage [13], peritoneal dialysis potentially being superior to hemodialysis [14], low Geriatric Nutritional Risk Index (GNRI) and low albumin indicating malnutrition [15], and the use of opioids [16] and erythropoietin [17]. Low handgrip strength is significantly associated with an elevated 10-year fracture probability, while femoral artery calcification is an independent predictor of hip fracture [18]. Therefore, fracture risk management in maintenance hemodialysis patients requires a comprehensive assessment of bone turnover status, biochemical markers, and various clinical factors.

The relationship of vascular calcification to bone fragility in hemodialysis is strong and bidirectional. Several factors like hyperphosphatemia, elevated Ca-P product, and deregulated RANKL/osteoprotegerin (OPG) signaling pathway induce vascular smooth muscle cell phenotype switching towards an osteoblastic cell-type, simultaneously impairing bone homeostasis [18]. Of note, the presence of calcifications within the femoral arteries was independently associated with hip fracture development among these patients. A higher score was found to predict not only a greater risk but also worse outcomes following hip fracture [18]. This phenomenon results in calcium-phosphorous being taken away from the bone matrix damage. This is known as “vascular bone steal”, and it is considered a two-part problem which can lead to an increased risk of fractures [18].

Our study assumes that quantitative ultrasound (QUS) bone density measurement and bone turnover markers (BTMs) can independently predict fracture risk by reflecting the balance between bone formation and resorption. Through early diagnosis, appropriate treatment, and lifestyle adjustments, fracture risks can be effectively reduced, improving quality of life.

Materials and methods

Inclusion and exclusion criteria

This was a retrospective analysis. The study enrolled patients who underwent hemodialysis - either as inpatients or outpatients - in the Department of Nephrology at Shanghai Tianyou

Hospital between April 2020 and February 2024.

Inclusion criteria: (a) Diagnosis and treatment status: Confirmed diagnosis of end-stage renal disease and currently receiving regular maintenance hemodialysis (e.g., three sessions per week, each lasting ≥4 hours). Patients were required to have a dialysis vintage of at least three months and to be on a stable, established dialysis regimen. (b) Participant's age: Age ranged from 18 to 90 years old. (c) Informed consent: The study protocol was approved by the Ethics Committee of Shanghai Tianyou Hospital (Approval No: 2023-007). All participants provided voluntary, written informed consent after demonstrating full understanding of the study objectives, procedures, risks, and benefits. (d) Clinical stability and baseline requirements: Dry weight remained relatively stable (e.g., fluctuation < 5% over the preceding month). Patients possessed a functional vascular access suitable for the study - either a mature arteriovenous fistula or a well-maintained central venous catheter.

Exclusion criteria: (a) Concurrent serious illness: current, life-threatening infection (e.g., blood stream infection, active TB); progressive neoplasm not adequately controlled; recent (within the past six months) history of myocardial infarction, unstable angina pectoris, or Stroke; Severe hepatic dysfunction (Child-Pugh score C); or Severe heart failure (New York Heart Association class IV). (b) Medical contraindications for treatment, expected kidney transplant or planned change to peritoneal dialysis within three to six months; recent (within one month) participation in another drug or device experiment; or current use of drugs with significant contraindications or interactions for the investigational product. (c) Dialyzer-related exclusion criteria: patients with severe coagulopathy and significant hemorrhagic diathesis; history of known allergy to dialysate membranes, anticoagulants, or study drug. (d) Inability to participate in study due to major cognitive deficit, current mental health condition, or less than six months of expected life expectancy; and subjects in the investigator's judgment are noncompliant or for practical, social, or other barriers that prevent completion of the studies.

Demographic characteristics

Demographic data included age, sex, smoking status, alcohol abuse, and history of hypertension or diabetes. Patient height (m) and dry weight (kg) were recorded to calculate body mass index (BMI) using the following formula: dry weight/height^2 (kg/m^2). Detailed information regarding hemodialysis treatment was recorded, including dialysis vintage (months), blood flow rate, vascular access, and ultrafiltration volume, to calculate dialysis adequacy (urea clearance index [Kt/V]). Any history of fractures, along with their locations (e.g. lumbar spine, hip or other sites), were documented.

Blood test assay

The blood values acquired during the study included serum urea nitrogen(BUN), creatinine(Scr), total calcium, ionized calcium, inorganic phosphorus, alkaline phosphatase (ALP), bone alkaline phosphatase (B-ALP), PTH, total 25-hydroxyvitamin D (25(OH)D), total procollagen type I N-pro-peptide (PINP), β-terminal crosslinking telopeptide of type I collagen (β-CTX), and osteocalcin levels.

Osteoporosis self-assessment tool for Asians (OSTA)

OSTA is based on research from eight Asian countries and regions focusing on postmenopausal women. The calculation equation is as follows: OSTA index = (body weight [kg] - age [years]) × 0.2.

Quantitative ultrasound bone mineral density (QUS-BMD)

The QUS BMD measurement system is a non-invasive technology used to evaluate bone health. It operates on two principles: the speed of sound (SOS) and broadband ultrasound attenuation (BUA) [19]. BMD results evaluation is the process of measuring mineral content in bones to help diagnose osteoporosis or assess bone health. T-score compares a patient's BMD to the average BMD of young adults. A higher T-score indicates higher BMD and greater bone mass, while a lower T-score suggests lower BMD and risk of osteoporosis.

Statistical methods

Data analysis was performed using the SPSS software (version 27.0, IBM Corporation, Armonk, NY, USA). Measured data were expressed as mean ± SD and counted data as frequency (percentage). Participants were divided into fracture and non-fracture groups based on the presence of fractures. Comparisons of normally distributed measured data between groups were performed using independent sample t-tests, while non-parametric tests were used for data that were not normally distributed. Pearson's chi-square test was used to compare the counted data. Differences were considered significant at $P < 0.05$.

Univariate logistic regression analysis was performed with fracture status as the dependent variable, and sex, diabetes history, hypertension history, bedridden, smoking history, alcohol abuse, age, dialysis vintage, dry weight, BMI, OSTA index, BMD indicators, and various biochemical markers as covariates. *P*-values, odds ratio (OR), and the corresponding upper and lower limits of the 95% CI were calculated. Significant factors from univariate analysis were subsequently incorporated into a multivariate logistic regression model using a backward elimination method to identify the main relevant factors. *P*-value, OR, and the corresponding 95% CI were computed.

Additionally, receiver operating characteristic (ROC) curves were generated for the main relevant factors, and area under curve (AUC) was calculated to determine the optimal cutoff point, along with its sensitivity and specificity. Differences were considered significant at $P < 0.05$. Figures were generated using Origin 2021 9.8.0 and Prism version 9.5.1 (GraphPad Inc., San Diego, CA, USA).

We further used R software (version 4.4.2) for Nomogram model construction and validation. Initially, we selected the best predictive factors for the risk of fracture in hemodialysis patients through previous univariate and multivariate regression analysis as independent variables. The dataset was split into a training set and a validation set, with the validation set at 15%. The area under the ROC curve provided good discriminative ability to separate true positives from false positives. We plotted and calculated calibration curves using the rms and Resource Selection packages to assess the calibration of the forest plot of fracture risk in hemodialysis patients, supplemented by the Hosmer-Lemeshow test. Decision curve analysis (DCA) was conducted using the rmda package to determine the clinical utility of the forest plot in the hemodialysis patient population, based on the net benefit at different threshold probabilities.

Results

Epidemiologic data from patients undergoing maintenance hemodialysis with fractures

Flow diagram of study participants

As shown in **Figure 1**, 166 maintenance hemodialysis patients were included in this study through retrospective screening, and 43 patients (25.90%) had fractures. According to the OSTA scale, 53.61% of patients were at low risk, 27.11% were at medium risk, and 19.28% were at high risk. Fractures occurred in 43 (25.90%) patients. Based on the fracture site, they were divided into lumbar spine, hip, and other fractures. There were 15 cases of lumbar spine fracture (9.04%), 20 cases of hip fracture (12.05%), and the remaining fracture (4.82%).

Correlation between fractures and clinical outcome in hemodialysis patients

Of 166 patients undergoing hemodialysis, 84 died during the follow-up period. The death rate of patients with fractures was 74.42% (n = 32), which was significantly higher than that of the non-fracture group (n = 52, 42.28%) ($P < 0.05$). Hip fractures accounted for the largest number of deaths. Univariate Logistic regression analysis showed that the risk of death was 3.972 times higher in the fracture group than in the non-fracture group ($P < 0.001$) (**Table 1**). When lumbar spine, hip, and other fractures were included as covariates, multivariate logistic regression analysis showed that hip fracture was the strongest independent risk factor for death (OR = 5.462, 95% CI: 1.725-17.293, P = 0.004) (**Table 1**).

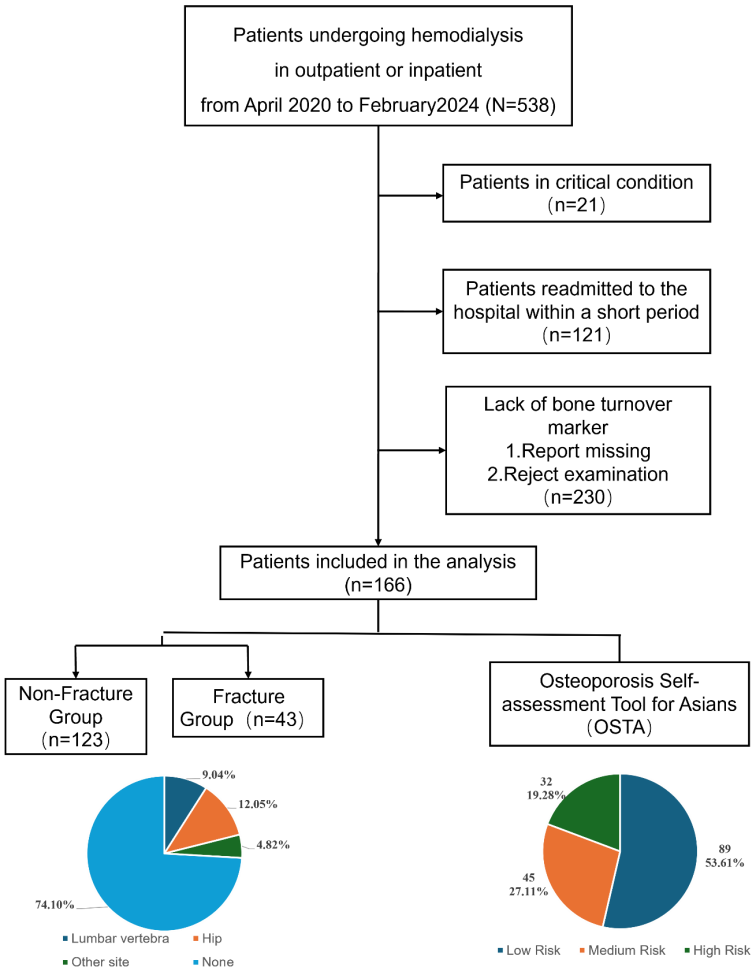

Figure 1. Flow chart of study participants.

Statistical analysis of fracture-related factors in patients undergoing hemodialysis

Multivariate logistic analysis of fracture risk

Following univariate analysis, multivariate logistic regression analysis was performed, incorporating variables such as sex, bedridden status, age, BMD T-score, OSTA index, β-CTX, PINP, and PINP β-CTX product as covariates. The results revealed that a 0.1-unit increase in BMD T-score was associated with an 18.22% increase in fracture risk ($P < 0.05$). BMD T-score (OR 2.822, 95% CI: 1.105-7.206; $P = 0.030$) emerged as an independent risk factor for fractures in hemodialysis patients. In contrast, bedridden status (OR 12.462, 95% CI: 0.363-427.506; $P = 0.162$) was no longer significant by multivariate analysis ($P > 0.05$), possibly due to confounding factors (**Table 2**).

Clinical characteristics and univariate logistic analysis of fracture risk in patients undergoing hemodialysis

This study included 110 male cases and 56 female cases. The incidence of fractures in female hemodialysis patients was 35.71% (20/56), which was much higher than that in males (20.91%, 23/110), and there was a significant difference between the two groups ($P < 0.05$). Among the cases with fractures, 58.14% (25/43) were bedridden, which was significantly higher than that of the non-fracture group ($P < 0.001$). Conversely, no significant differences were observed between the fracture and non-fracture groups in the presence of diabetes, hypertension, smoking history, or long-term alcohol consumption ($P > 0.05$). The average age of the subjects in this study was 65.48±12.16 years, with an average dialysis vintage of 43.8±49.33 months. The average age of patients in the fracture group was significantly higher than that in the non-fracture group (70.63±9.35 versus 63.68±12.54; $P = 0.001$). The OSTA index, BMD T-score, BMD SoS, and BMD BUA were significantly lower in the fracture group than in the non-fracture group ($P < 0.05$). Additionally, the levels of β-CTX, PINP, and PINP β-CTX product were considerably higher in the fracture group than in the non-fracture group ($P < 0.05$). No significant differences were found between the two groups in terms of dialysis vintage, Kt/V, URR, albumin, total calcium, corrected calcium, ionized calcium, phosphorus, PTH, ALP, BALP, 25(OH)D, or osteocalcin ($P > 0.05$) (**Table 3**).

Univariate logistic regression analysis revealed that female patients undergoing hemodialysis had a 2.101 times higher risk of fractures than their male counterparts ($P < 0.05$). The risk of fracture in bedridden patients was 5.444 times

Table 1. Univariate and multivariate logistic regression analysis of fracture site and death in hemodialysis patients

Fracture site	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR_1	95% CI_1	P_1 value	OR_2 value	95% CI_2	P_2 value
Total	3.972	1.834-8.603	< 0.001			
Lumbar vertebra	2.081	0.679-6.378	0.200	2.731	0.881-8.467	0.082
Hips	4.588	1.463-14.388	0.009	5.462	1.725-17.293	0.004
Other sites	3.077	0.603-15.711	0.177	4.096	0.795-21.112	0.092

Note: OR, Odds Ratio; CI, Confidence Interval.

Table 2. Multifactorial logistic analysis of fracture risk in hemodialysis patients

	P value	OR	95% Lower CI	95% Upper CI
Female sex	0.759	1.403	0.162	12.189
Age	0.137	1.110	0.967	1.273
Bed ridden	0.162	12.462	0.363	427.506
BMD |T score|	0.030	2.822	1.105	7.206
OSTA index	0.480	1.153	0.776	1.715
β-CTX ng/ml	0.557	0.524	0.061	4.519
PINP ng/ml	0.222	0.993	0.981	1.004
P1NP * β-CTX	0.096	1.006	0.999	1.012

Note: OR, Odds Ratio; CI, Confidence Interval; BMD, Bone Mineral Density; OSTA, Osteoporosis Self-assessment Tool for Asians; β-CTX, β-terminal crosslinking telopeptide of type I collagen; PINP, procollagen type I N-propeptide.

higher than that in non-bedridden patients (P < 0.05). Each additional year of age increased fracture risk by 5.4%. For every 1-unit increase in the absolute value of the OSTA index, fracture risk increased by 17%. A 0.1-unit increase in the absolute value of the BMD T-score increased fracture risk by 13.20%. Each 1 ng/mL increase in β-CTX level was associated with a 62.2% increase in fracture risk, while every 10 ng/mL increase in PINP level led to a 2% increase in fracture risk. Additionally, every 10-unit increase in the PINP β-CTX product level corresponded to a 1% increase in fracture risk (**Table 3**).

ROC curve analysis of factors influencing fracture risk in hemodialysis

As shown in **Table 4** and **Figure 2**, ROC curve analysis revealed that BMD T-score, OSTA index, age, β-CTX, and PINP β-CTX product were all effective in predicting fracture risk in hemodialysis patients. Specifically, BMD T-score was entered as its absolute value to facilitate interpretation of OR > 1 as indicating increased risk with lower bone mineral density. Accordingly, an OR of 2.822 means that each 1-unit increase in |T-score| (i.e., more negative T-score) was associated with a 182% higher fracture risk. The OSTA index had an AUC of 0.674 (95% CI: 0.581-0.766), with an optimal cut-off point of -1.40, sensitivity of 67.4%, and specificity of 65.0% (P = 0.001). Age had an AUC of 0.663 (95% CI: 0.576-0.751), with an optimal cut-off point of 62.5 years, sensitivity of 88.4%, and specificity of 39.0% (P = 0.001). β-CTX exhibited an AUC of 0.645 (95% CI: 0.548-0.741), with an optimal cutoff point of 1.765, sensitivity of 58.1%, and specificity of 65.9% (P = 0.005). Finally, PINP β-CTX product exhibited an AUC of 0.668 (95% CI: 0.563-0.773), with an optimal cutoff point of 843.53, sensitivity of 55.8%, and specificity of 80.5% (P = 0.001).

Clinical predictive model of related factors for combined fractures in hemodialysis patients

This study developed and validated a clinical prediction model for predicting the risk of fractures in this population [20]. The model was based on eight variables: gender, bedridden status, age, OSTA index, BMD T-score, serum PINP, β-CTX, and PINP β-CTX product. A nomogram is constructed through multiple logistic regression analysis. The scores for each variable were calculated based on the regression coefficients, and the total score, which is the sum of individual scores, can be used to calculate the probability of fracture occurrence in individual patients [20]. The model converts the total score into fracture risk probability using a third-degree polynomial function, with

Table 3. Analysis of clinical characteristics and univariate logistic regression of fracture risk in hemodialysis patients

Variable	Total group	Fracture group (N = 43)	Non fracture group (N = 123)	P_1	Univariate logistic regression analysis		
					OR	95% CI	P_2
Male	110	23 (53.49%)	87 (70.73%)				
Female	56	20 (46.51%)	36 (29.27%)	0.040	2.101	1.029-4.292	0.042
Diabetes	88	26 (60.47%)	62 (50.41%)	0.255	1.505	0.743-3.049	0.257
Hypertension	147	40 (93.02%)	107 (86.99%)	0.285	1.994	0.551-7.210	0.293
Bedridden	50	25(58.14%)	25 (20.33%)	< 0.001	5.444	2.576-11.506	< 0.001
Smoking	55	11 (25.58%)	44 (35.77%)	0.222	0.617	0.284-1.344	0.224
Alcohol history	10	1 (2.32%)	9 (7.32%)	0.236	0.302	0.037-2.453	0.262
Age	65.48±12.16	70.63±9.35	63.68±12.54	0.001	1.054	1.020-1.090	0.002
Dialysis duration (months)	43.80±49.33	47.81±51.79	42.39±48.57	0.403	1.002	0.995-1.009	0.535
Dry weight (kg)	63.29±13.48	60.53±16.14	64.26±12.35	0.119	0.978	0.950-1.006	0.121
BMI	22.80±5.57	21.95±4.74	23.10±5.82	0.136	0.952	0.877-1.034	0.243
OSTA index	-0.44±3.84	-2.02±3.76	0.12±3.73	0.002	1.170	1.058-1.294	0.002
BMD T-score	-2.20±1.14	-2.93±1.20	-1.95±1.01	0.003	2.320	1.236-4.353	0.009
BMD SOS m/s	1481.92±49.75	1470.03±49.01	1485.97±49.90	0.015	0.994	0.983-1.005	0.289
BMD BUA	71.08±28.78	59.77±30.51	74.94±27.47	0.047	0.983	0.963-1.002	0.086
Kt/V	1.14±0.53	1.16±0.54	1.14±0.53	0.790	1.103	0.538-2.263	0.788
UUR%	58.52±17.34	58.82±18.60	58.42±16.99	0.907	1.001	0.979-1.024	0.906
Total calcium mmol/l	2.25±0.22	2.27±0.23	2.25±0.21	0.485	1.776	0.364-8.675	0.478
Corrected Calcium mmol/l	2.34±0.23	2.36±0.25	2.34±0.23	0.557	1.544	0.355-6.724	0.563
Ionized calcium mmol/l	1.13±0.09	1.13±0.10	1.12±0.09	0.624	2.898	0.050-167.90	0.607
Phosphorus mmol/l	1.77±0.65	1.70±0.42	1.80±0.71	0.272	0.783	0.451-1.358	0.384
PTH pg/ml	272.76±441.09	349.12±761.54	246.69±252.89	0.602	1.000	1.000-1.001	0.254
ALP u/l	81.78±80.18	104.04±147.77	74.00±30.70	0.114	1.008	0.997-1.018	0.143
Bone ALP u/l	12.72±13.49	17.08±22.31	10.74±5.69	0.173	1.050	0.984-1.121	0.141
Total 25 (OH) D ng/ml	10.46±6.46	8.76±4.48	11.05±6.94	0.067	0.929	0.863-1.000	0.051
β-CTX ng/ml	1.80±1.08	2.25±1.31	1.64±0.95	0.005	1.622	1.179-2.231	0.003
Osteocalcin ng/ml	111.75±76.66	112.88±83.59	111.35±74.45	0.911	1.000	0.996-1.005	0.910
PINP ng/ml	400.38±305.10	537.38±380.87	352.49±258.89	0.011	1.002	1.001-1.003	0.001
PINP * β CTX	833.73±1087.87	1492.72±1729.94	603.35±603.10	0.001	1.001	1.000-1.001	< 0.001

Note: OR, Odds Ratio; CI, Confidence Interval; BMI, body mass index; OSTA, Osteoporosis Self-assessment Tool for Asians; BMD, Bone mineral density; SOS, speed of sound; BUA, broadband ultrasound attenuation; UUR, Urea Reduction Ratio; PTH, parathyroid hormone; ALP, alkaline phosphatase; β-CTX, β-terminal crosslinking telopeptide of body mass index type I collagen; PINP, procollagen type I N-propeptide.

Table 4. Receiver operating characteristic curve analysis of fracture risk in hemodialysis patients

Variable	AUC	95% CI	*P*-value	Cut-off value	Sensitivity	Specificity
BMD|T-score|	0.761	0.607-0.916	0.003	2.88	0.600	0.886
OSTA index	0.674	0.581-0.766	0.001	-1.40	0.674	0.650
Age	0.663	0.576-0.751	0.001	62.5	0.884	0.390
β-CTX	0.645	0.548-0.741	0.005	1.765	0.581	0.659
PINP	0.631	0.525-0.736	0.011	447.85	0.535	0.740
PINP * β-CTX	0.668	0.563-0.773	0.001	843.53	0.558	0.805

Note: AUC, area under curve; CI, Confidence Interval; BMD, Bone Mineral Density; OSTA, Osteoporosis Self-assessment Tool for Asians; β-CTX, β-terminal crosslinking telopeptide of type I collagen; PINP, procollagen type I N-propeptide.

total scores of 162 and 220 corresponding to 50% and 95% risk thresholds, respectively (Shown in **Figures 3** and **4**).

Based on this framework, patients are stratified into low-, moderate-, and high-risk groups. This multifactorial model demonstrates superi-

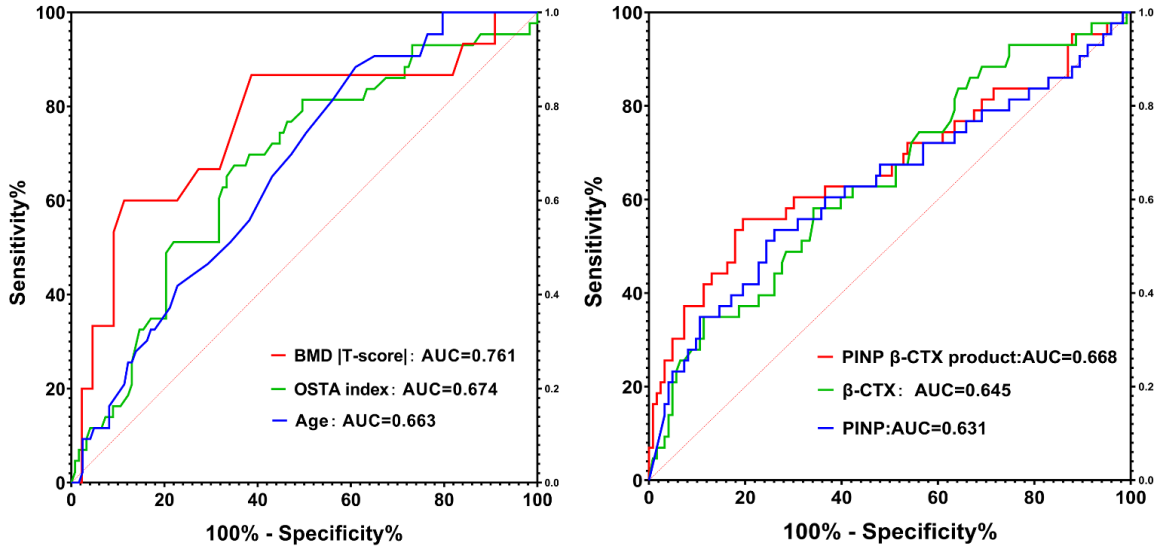

Figure 2. Receiver operating characteristic curve analysis of fracture risk in hemodialysis patients. Note: AUC, area under curve; BMD, Bone Mineral Density; OSTA, Osteoporosis Self-assessment Tool for Asians; β-CTX, β-terminal crosslinking telopeptide of type I collagen; PINP, procollagen type I N-propeptide.

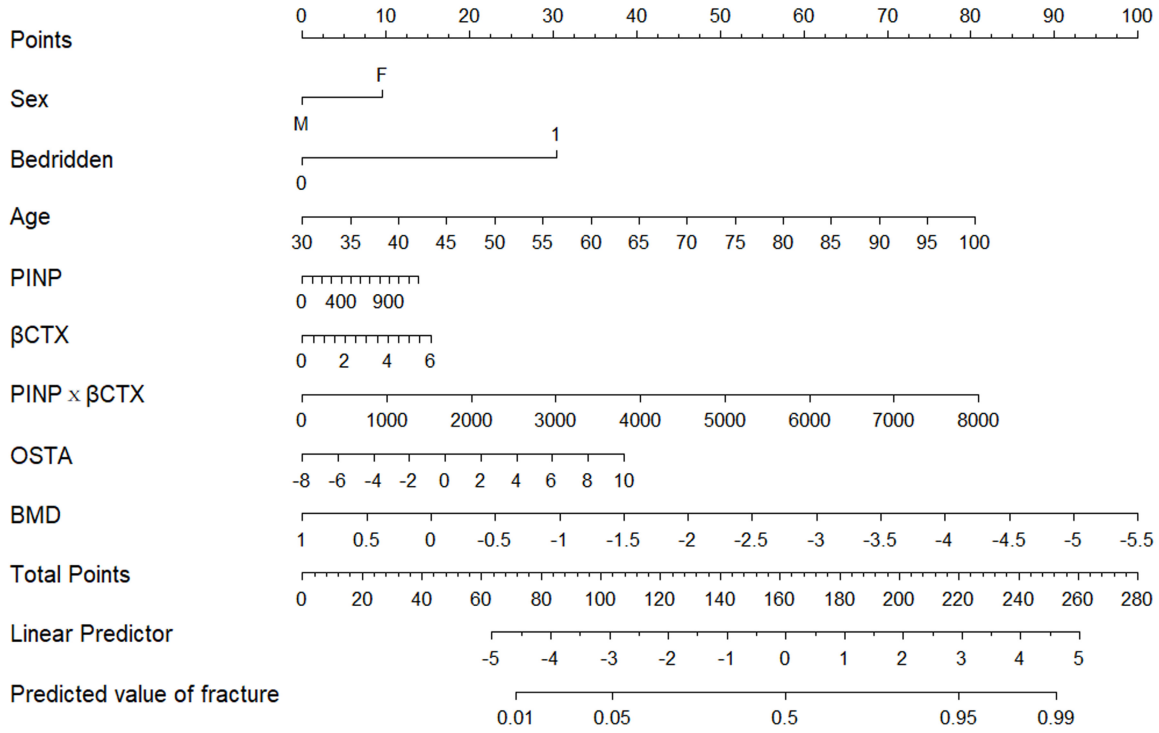

Figure 3. Constructed nomogram model for predicting the probability of fracture in hemodialysis patients. Note: BMD, Bone Mineral Density; OSTA, Osteoporosis Self-assessment Tool for Asians; β-CTX, β-terminal crosslinking telopeptide of type I collagen; PINP, procollagen type I N-propeptide.

or performance compared to a single-factor model relying solely on BMD, exhibiting high clinical utility and translational potential, as well as robust and stable predictive performance.

Discussion

This study explored the risk factors for fractures in hemodialysis patients and established

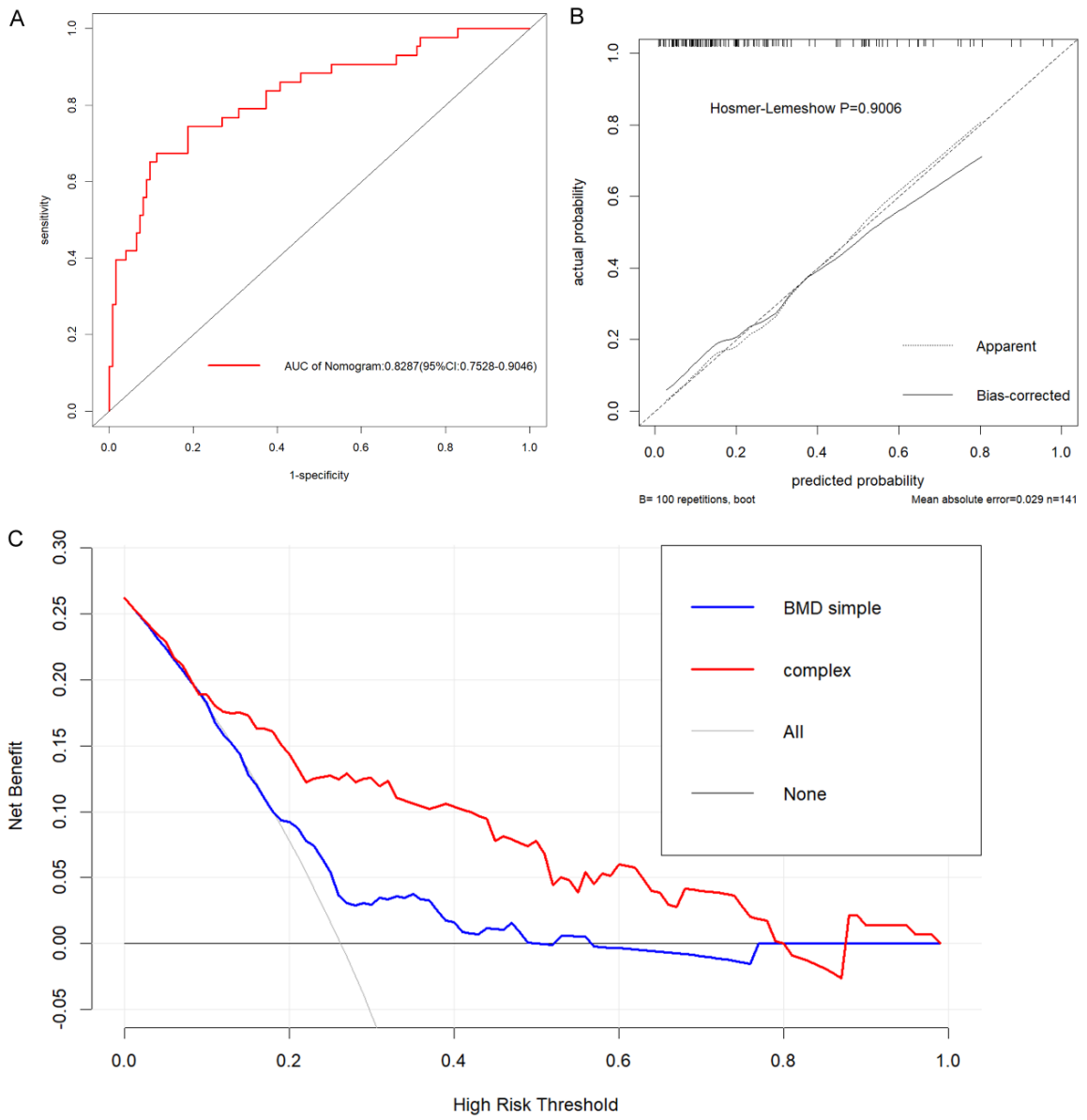

Figure 4. Internal validation of the clinical prediction model for predicting the probability of fracture in hemodialysis patients. A. Discrimination of the constructed nomogram. Nomogram's receiver operating characteristic curve. B. Calibration curve of the nomogram. C. Decision curve analyses of the nomogram. Note: BMD, Bone Mineral Density.

a practical clinical prediction model. The study identified multiple significant risk factors through univariate analysis, including being female, bedridden, advanced age, low OSTA index, low BMD T-score, high β-CTX, and high PINP β-CTX product. Multivariable logistic regression further confirmed that a BMD T-score below -2.88 had the highest predictive value, while a PINP β-CTX product exceeding 843.53 also significantly indicated fracture risk with high specificity. Hemodialysis patients over the age of 62.5 have a higher sensitivity to osteoporosis and fractures, emphasizing the importance of screening to avoid underdiagnosis. Based on these factors, the researchers successfully constructed a column line prediction model with 8 variables, demonstrating excellent discrimination (C-index = 0.8287), good calibration, and high clinical value. Therefore, regular QUS-BMD and PINP β-CTX product are essential for assessing fracture risk in hemodialysis patients.

Traditional risk factors for bone disease in CKD patients

As in the general population, traditional factors such as advanced age, female sex, malnutrition, being sedentary, smoking, and alcohol abuse also play important roles in the skeletal changes of CKD patients [21, 22]. Diabetes, low BMI, previous history of corticosteroid use, and proteinuria are all related to the risk of fractures in patients with chronic kidney disease [23]. In this study, the incidence of fractures in women (35.71%) was significantly higher than in men (20.91%), with the average age of fracture patients being higher compared to the non-fracture group (70.63±9.35 vs 63.68±12.54, P = 0.001). Univariate analysis showed that the risk of fractures in female hemodialysis patients was 2.101 times that of male hemodialysis patients (P < 0.05). Bedridden patients were 5.444 times more likely to experience fractures than non-bedridden patients (P < 0.05), and for every 1-year increase in age, the risk of fractures increased by 5.4% (P < 0.05). However, the results of the multivariate analysis did not show significant differences in gender, sedentary status, or advanced age. ROC curve analysis revealed that an age over 62.5 years was significant for predicting fractures in hemodialysis patients, with a sensitivity of 88.4%, but low specificity. Hence, routine necessary follow-up examinations and treatments should be conducted for hemodialysis patients over 62.5 years old to reduce misdiagnosis rates. Additionally, this study in hemodialysis patients did not find any association of fractures with diabetes, hypertension, smoking, chronic alcohol abuse, or low BMI.

Vitamin D deficiency can lead to secondary hyperparathyroidism, bone mineralization defects, and also affect neuromuscular function, increasing the risk of falls [24, 25]. Serum 25(OH)D level < 27 ng/ml is one of risk factors for low BMD in chronic kidney disease [25]. Inadequate intake of vitamin D results in a higher area of low mineralization, highlighting the crucial role of vitamin D in ensuring proper mineralization of bone cells [26]. Correction should be considered for serum 25(OH)D concentrations below 15 ng/mL regardless of PTH levels [27, 28]. Vitamin D deficiency is common in 86.6% peritoneal dialysis patients, but no significant correlation was found between 25(OH)D levels and BMD [29]. Similarly, low vitamin D levels were not found to be associated with fractures in hemodialysis patients in this study, possibly due to the majority of the study population being deficient in vitamin D (25(OH)D < 10 ng/ml). Clinical studies on the effects of vitamin D supplementation have conflicting conclusions, influenced by various factors such as dosage, frequency, type of vitamin D used, body fat content affecting vitamin D requirements, and baseline vitamin D levels of the study subjects.

PTH is the most used bone turnover biomarker in CKD-MBD, but it does not indicate bone metabolism itself. Currently, the clinical target range for PTH is derived from the perspective of mortality risk, rather than fracture risk. It is necessary to reassess the target range of PTH in hemodialysis patients [30], rather than aiming for complete normalization of PTH levels [31]. Different guidelines recommend early identification and treatment of vitamin D deficiency, as well as proactive intervention, instead of waiting until severe secondary hyperparathyroidism occurs [31]. Sclerostin, a protein produced by bone cells, inhibits the differentiation and activity of osteoblasts, reducing bone formation [32]. It is negatively correlated with renal function and may be related to early low turnover bone disease in CKD [32]. As CKD progresses, the vicious cycle of PTH resistance followed by increasing PTH levels pushes a breakthrough in peripheral tissue resistance, leading to high-turnover bone disease [32]. Sclerostin/iPTH ratio is the best marker of low turnover disease, while iPTH performs best in diagnosing high turnover disease [33]. ALP, especially BALP, can also be used to evaluate bone metabolism in CKD [34]. In contrast, circulating BALP is mainly derived from active osteoblasts, more directly reflecting bone metabolism. Elevated BALP is the most important predictor of fracture incidence in hemodialysis patients, with a critical value of 96.6 μg/L predicting fractures with sensitivity and specificity of 81.8% and 49%, respectively [5]. The mean levels of PTH, ALP, and BALP in the fracture group of hemodialysis patients in our study were higher than those of the non-fracture group without significant differences. Serum phosphorus levels > 6.1 mg/dL (4.3-6.1 mg/dL) were significantly associat-

ed with a higher risk of brittle bone fractures, suggesting that elevated phosphorus may be a new risk factor for fractures in hemodialysis patients [35]. However, this study found no significant difference in the serum phosphorus levels between the fracture and non-fracture groups.

Non-traditional risk factors for bone disorders in CKD patients

Imaging examinations

Compared to the general population, trabecular and cortical bone changes appear to be different in patients with CKD. Specifically, cortical bone loss progresses more rapidly in CKD patients. Studies using both high-resolution peripheral quantitative computed tomography and bone biopsy have confirmed that the trabecular bone is better preserved than the cortical bone in these patients [8]. Elevated PTH levels promote bone formation in the trabecular bone, leading to resorption in the cortical bone, thereby inhibiting trabecular bone loss [8]. As a result, bone deterioration in patients undergoing dialysis is typically more severe than that of non-dialysis patients [8].

Despite being the most widely used technique for assessing BMD, dual-energy X-ray absorptiometry (DXA) has specific limitations when applied to patients with CKD. First, patients with CKD5D exhibit unique bone microstructural changes, with abdominal aortic calcification being particularly common, and artifacts and local structural changes can affect DXA measurement results [36]. Second, CKD patients present with abnormalities in bone mineralization and metabolism, with high-turnover bone disease being the most common, but DXA can only statically assess the degree of bone destruction [5, 8]. Third, as a two-dimensional technique, DXA does not measure the true volumetric BMD or bone size and cannot differentiate between trabecular and cortical bones. Even with the same measured BMD, larger bones had a higher actual BMD than smaller bones [19]. Finally, the high cost of DXA imposes a financial burden on patients, thus limiting its clinical use.

Quantitative ultrasound is an innovative, non-invasive technology that uses ultrasound to measure bone density. This technology can assess cortical and trabecular bone in different bone sites, including the calcaneus, tibia, and phalanges [19]. It has a significant advantage of avoiding exposure to ionizing radiation, is safe, and can quickly detect the BMD of the calcaneus to reflect the overall health of the skeleton. Therefore, this study used the more widely spread QUS to determine BMD.

Although QUS cannot completely replace DXA for the definitive diagnosis of osteoporosis, it has a clear role in risk stratification and identifying high-risk individuals who require further DXA examination [37]. A meta-analysis targeting elderly women showed that the pooled sensitivity of QUS for diagnosing osteoporosis was 0.69, the specificity was 0.67, and the AUC was 0.7523, indicating acceptable diagnostic value and suggesting its use as a prescreening tool to determine the need for DXA measurement [38]. Furthermore, research has focused on optimizing the diagnostic performance of QUS, such as by establishing device-specific diagnostic thresholds to improve its accuracy in identifying osteoporosis and osteopenia [39]. In recent years, with the integration of artificial intelligence technology, multi-channel convolutional neural network models based on QUS radiofrequency signals have been developed, and their diagnostic accuracy is significantly superior to traditional SOS methods, opening new directions for the future development of QUS technology [40, 41].

The ability of calcaneal QUS in predicting fracture risk: Prospective cohort studies have confirmed that calcaneal QUS measurements are independent predictors of fracture risk beyond BMD measured by DXA. A prospective study conducted in elderly women demonstrated that each standard deviation decrease in calcaneal BUA was associated with a 15% higher risk of all-cause mortality and a 20% higher risk of cardiovascular disease-related mortality. These associations remained significant after adjustment for hip BMD and established cardiovascular risk factors [42], underscoring that skeletal properties assessed by QUS are closely linked to long-term health outcomes. Regarding the prediction of fragility fractures, compelling evidence comes from the cohort study. After adjusting for clinical risk factors incorporated in the Fracture Risk Assessment Tool (FRAX), use of anti-osteoporotic medication,

DXA-derived BMD, and trabecular bone score, each standard deviation decrease in the calcaneal QUS-derived stiffness index and SOS was associated with a 43% and 52% increase in the risk of major osteoporotic fractures, respectively [43]. This finding highlights the incremental value of QUS beyond conventional BMD measurements and clinical risk assessment in fracture risk prediction. The predictive capacity of QUS for fractures likely stems from its sensitivity to bone microstructural features and material properties - factors that directly influence bone strength - rather than reflecting bone mass alone. For instance, studies have reported moderate correlations between calcaneal QUS parameters and trabecular volumetric BMD as well as microstructural measurements (e.g., trabecular number, thickness, and separation) at the radius and tibia, as quantified by high-resolution peripheral quantitative computed tomography (HR-pQCT). In contrast, correlations with cortical bone measurements were weaker [44]. This pattern suggests that calcaneal QUS is particularly sensitive to the integrity and architecture of the trabecular network. In summary, calcaneal QUS not only provides robust prediction of fracture risk but also offers complementary information on bone quality relative to DXA. As such, it represents a valuable tool for fracture risk assessment - particularly in resource-limited settings or where access to DXA is restricted [37].

Clinical application of calcaneal QUS: With its advantages of being radiation-free, low-cost, portable, and easy to operate, calcaneal QUS has become an ideal tool for large-scale community screening of osteoporosis, particularly suitable for primary healthcare institutions and physical examination centers [45]. Multiple studies have confirmed its effectiveness as a pre-screening tool. A study on postmenopausal women in Taiwan found that when screening for primary osteoporosis, AUC for calcaneal QUS was 0.737, outperforming the OSTA, demonstrating good screening capability [45]. Another meta-analysis, pooling data from 12 studies involving a total of 2260 elderly women, showed that the pooled sensitivity and specificity of calcaneal QUS for diagnosing osteoporosis were 0.69 and 0.67, respectively, with an AUC of 0.7523. This indicates acceptable diagnostic value, supporting its use as a pre-screening tool to determine the need for further DXA measurement [38]. In areas lacking DXA equipment, this stratified screening strategy is highly cost-effective.

Note, however, that QUS and DXA provide fundamentally different kinds of measurement, with the results showing that there is little or modest agreement in their evaluation [45, 46]. Therefore, it cannot be used interchangeably with DXA for final diagnosis of osteoporosis. However, it is proven useful for the assessment of risk in primary care settings or in screening programs with populations. Recent research is exploring more sensitive QUS-derived measurements or dynamic measurement modes to enhance its utility in efficacy monitoring. For example, a study developed a multi-channel convolutional neural network model based on ultrasound radiofrequency signals, achieving a diagnostic accuracy for osteoporosis of 83.05%, significantly higher than the traditional speed of sound method (66.67%). This demonstrates the potential to improve QUS performance through advanced signal processing techniques [32]. In addition, novel ultrasound treatment and assessment modes, such as pulse frequency modulation ultrasound, are being explored to better promote bone formation [47]. Although QUS is not yet considered as the gold standard technique for longitudinal monitoring of treatment response. It has great promise to expand their use in the future of healthcare.

Our results of the study indicated that hemodialysis patients with a history of fracture had significantly lower BUA, SOS, and T-scores measured by DXA compared to no fracture history. Multivariable logistic regression models revealed that for each unit reduction of the BMD T-score, the incidence risk of fracture increased by 18.22% ($P < 0.05$). ROC analysis suggested that the optimal threshold for predicting fracture risk among these patients was at a BMD T-score of -2.88, where the maximum detection accuracy is obtained as 60.0%, 88.6%. Taken together, these findings suggest that the use of quantitative ultrasound to routinely assess BMD T-score is clinically useful because it is simple, non-invasive tool for the classification of fracture risk in hemodialysis patients that could allow early intervention aimed at reducing fracture incidence and enhancing clinical outcome.

Bone turnover markers (BTM)

BTMs, which are components of the bone matrix or enzymes and their metabolic products secreted by bone cells during bone remodeling, offer a dynamic view of bone remodeling [48]. Despite their importance, BTMs are not routinely emphasized or tested in clinical practice [26]. PINP, a marker of bone formation primarily secreted by osteoblasts, reflects bone generation activity. Elevated PINP typically indicate active bone formation, making them useful for monitoring bone metabolic status and evaluating treatment effectiveness, especially in patients undergoing bone-forming therapies [49]. Notably, only intact PINP measurements remain unaffected by declining renal function in patients with CKD [34]. β-CTX, a marker of bone resorption, indicates bone breakdown and remodeling activity and is mainly secreted by osteoclasts, reflecting the level of bone resorption activity. Elevated β-CTX levels are usually associated with an increased risk of osteoporosis or fractures, making β-CTX valuable in assessing bone resorption status [50]. In the elderly, total PINP and β-CTX serve as independent risk factors for poor prognosis in patients with osteoporotic fractures. In this study, while PINP levels were significantly elevated in hemodialysis patients with fractures, ROC curve analysis indicated that PINP had no predictive utility for fracture risk [50]. In contrast, β-CTX levels were markedly higher in patients who experienced fractures, and ROC curve analysis suggested that β-CTX levels > 1.765 ng/mL could predict fracture risk in patients undergoing hemodialysis. These findings indicate that β-CTX has a greater clinical utility than PINP. Nevertheless, the use of CTX in patients with CKD is generally not recommended because of its subjectivity in renal impairment [51].

Bone disorders caused by CKD are complex and multifaceted, encompassing conditions such as osteoporosis, osteomalacia, adynamic bone disease, fibrous osteitis, secondary hyperparathyroidism, and mixed uremic osteodystrophy [52]. Elevated BTM levels may indicate accelerated bone remodeling, suggesting disruption in bone metabolism and an increased risk of fractures. Conversely, lower BTM levels may reflect reduced bone remodeling, which can also be associated with fragile bone structures and higher fracture risk [53]. High bone turnover states are more prevalent among predialysis patients, whereas low turnover states are prevalent among patients actively undergoing dialysis. Both conditions involve impairments in bone mineralization that persist despite attempts to correct the serum phosphorus or PTH levels. Therefore, understanding intrinsic bone turnover status is crucial for addressing CKD-related bone disorders [54]. Although both high- and low-turnover states can lead to reduced bone mass and increased fracture risk, different treatment approaches are required. Generally, anti-resorptive agents are used to treat bone diseases with normal or high turnover rates, while synthetic metabolic agents are used to treat bone diseases with low turnover rates [55]. Teriparatide and Denosumab are the preferred choices for preventing fractures and increasing bone density in CKD patients [55]. Therefore, an accurate assessment of the type of bone turnover remains critical in managing CKD-MBD [56].

To better assess the balance between bone resorption and formation, this study introduced the concept of PINP β-CTX product to comprehensively evaluate bone metabolic status. The findings revealed that hemodialysis patients with fractures exhibited significantly higher PINP β-CTX product levels than those without fractures. Additionally, ROC curve analysis indicated that a PINP β-CTX product value of > 843.53 was a significant predictor of fracture risk in hemodialysis patients, with a specificity of 80.5%. Collectively, these results suggest that the PINP β-CTX product is highly effective in identifying fracture risk in hemodialysis patients, making it a valuable tool for clinical diagnosis. Its application can enhance diagnostic accuracy, reduce misdiagnoses, and optimize treatment strategies, thereby improving clinical outcomes.

Clinical predictive model

Our study considered the following eight factors: gender, disability (unable to walk), age, OSTA score, BMD, PINP, β-CTX or their product - to best define a model predicting fracture risk in hemodialysis patients. Based on this scorecard, < 162: low-risk; 162-220: moderate-risk where values above 220 are considered to be high risk, this scoring system has good discri-

minative power and validity, suggesting that they may be clinically more useful than BMD alone. Currently, there is no validated clinical prediction rule that assesses the risk of fractures in this group of patients. Our developed risk score allows clinicians to determine the risk of fractures in hemodialysis patients: allowing us to detect and intervene in our most vulnerable populations earlier than we ever have before.

Limitations and shortcomings

This study still has many limitations and shortcomings: First, the study design and data source were based on a single-center retrospective analysis, which may have selection bias and missing information; only 166 patients (43 in the fracture group) were included, with a relatively small sample size limiting statistical power and subgroup analysis, and posing a risk of overfitting. Second, variable selection was incomplete, failing to include known important confounding factors such as vascular calcification score, sclerostin, fall history, and use of glucocorticoids and anticoagulants, which may affect the predictive accuracy of the model. Third, the interpretation of bone turnover markers requires caution: β-CTX is cleared by the kidneys, and its levels in dialysis patients are affected by residual renal function, so it cannot fully and accurately reflect true bone resorption status. Fourth, inherent limitations of QUS bone density measurement: QUS and the DXA gold standard are not interchangeable, and QUS is affected by soft tissue factors, making it suitable only for risk screening rather than diagnosis. Fifth, at the statistical analysis level, only a simple internal validation (15% validation set) was used, without bootstrap or cross-validation, possibly leading to optimistic estimates of model discrimination; moreover, the cross-sectional design cannot establish causal relationships or assess the longitudinal association between dynamic changes in indicators and fracture risk. Sixth, there is a lack of independent external validation, and the model's generalizability requires validation in multicenter, prospective cohorts. Additionally, the economic costs and intervention effects of clinical application of the model have not been evaluated. In summary, the conclusions of this study should be interpreted with caution, and future large-sample, multicenter prospective studies are needed to validate and optimize this predictive model.

Future research should focus on conducting multicenter prospective cohort studies, performing independent external validation of the prediction model developed in this study, and constructing dynamically updatable longitudinal prediction models. At the same time, predictive factors (such as vascular calcification scores, sclerostin, functional status, and medication history) should be expanded to optimize bone metabolism assessment strategies and explore the use of artificial intelligence to enhance QUS technology. Additionally, stricter modeling and validation methods (such as bootstrapping and cross-validation) should be adopted to develop simplified clinical scoring tools. Ultimately, risk-stratified intervention studies, health economic evaluations, and post-fracture management research should be advanced to confirm the clinical value of the model and effectively reduce the risk of fractures in dialysis patients.

Summary

Calcaneus quantitative ultrasound bone mineral density and PINP β-CTX product index were both effective assessment tools in the assessment of fracture risk in hemodialysis patients, suggesting their application value in routine clinical practice. The clinical prediction model based on the above indicators combined with traditional risk factors has broad practical application prospects. However, use of this model still faces challenges such as data collection, external validation, and demonstration of universality, so future studies are needed to ensure its accuracy and safety.

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Disclosure of conflict of interest

None.

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