Am J Transl Res 2026;18(10):9408-9420
www.ajtr.org /ISSN:1943-8141/AJTR0174620

Original Article

Real-world determinants of bone mineral density loss and osteoporotic fractures in primary hyperparathyroidism: a retrospective cohort and nested case-control study

Mei Zeng, Bojun Zhang, Lilin Yu, Yarong Yang

Department of Nuclear Medicine, Wuhan Fourth Hospital, Wuhan 430033, Hubei, China

Received June 9, 2026; Accepted August 5, 2026; Epub October 15, 2026; Published October 30, 2026

Abstract: Purpose: To identify real-world determinants of osteoporosis and fragility fractures in primary hyperparathyroidism (PHPT) and to quantify bone mineral density (BMD) recovery after parathyroidectomy (PTX). Methods: This single-center retrospective cohort study with a nested case-control analysis included PHPT patients diagnosed during 2015-2024 who had undergone DXA. The primary endpoint was osteoporosis; the secondary endpoint was fragility fracture. Determinants of osteoporosis were analyzed using propensity-score matching (1:2) followed by multivariable logistic regression; fractures were analyzed using risk-set matched conditional logistic regression. BMD changes after PTX were assessed by paired t-tests. Results: Overall, 300 patients (100 osteoporosis/200 normal bone mass) were included. Older age [adjusted odds ratio (aOR) = 1.28], postmenopausal status (aOR = 1.44), higher corrected calcium (aOR = 1.30), higher parathyroid hormone (PTH) (aOR = 1.95), and vitamin D deficiency (aOR = 2.05) were independently associated with osteoporosis, while higher body mass index (BMI) (aOR = 0.93) and prior PTX (≥ 12 months, aOR = 0.63) were protective. In fracture analysis (92 cases/184 controls), risk increased with age (aOR = 1.45), lower BMD T-score (aOR = 1.62), corrected calcium (aOR = 1.18), PTH (aOR = 1.70), and vitamin D deficiency (aOR = 1.52), whereas higher BMI (aOR = 0.94) and PTX ≥ 6 months (aOR = 0.58) reduced risk. Among 146 PTX patients, BMD increased by 7.7% at lumbar spine, 5.6% at femoral neck, and 5.0% at total hip at 12-24 months post-surgery. Subgroup analyses indicated stronger surgical benefits in vitamin D-sufficient patients; sensitivity analyses confirmed robustness. Conclusions: Skeletal complications in PHPT are driven by metabolic activity, vitamin D status, age, menopausal status, and BMI. PTX is associated with reduced risk and significant BMD recovery.

Keywords: Primary hyperparathyroidism, bone mineral density, osteoporosis, fragility fractures, parathyroidectomy

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder that compromises skeletal integrity through sustained hypersecretion of parathyroid hormone and subsequent disruption of calcium-phosphate homeostasis [1-3]. Although cortical bone is preferentially affected, trabecular compartments may also be involved, ultimately leading to reduced bone mineral density (BMD) and an increased risk of fragility fractures [1-3]. Nevertheless, the full extent and distribution of skeletal morbidity in routine clinical practice remain inadequately characterized. In particular, the relationship between areal BMD and fracture risk can be discordant, as conventional densitometry does not fully capture microarchitectural deterioration or cortical porosity [4, 5]. Therefore, clarifying these real-world skeletal patterns is of clinical importance for refining prevention strategies and optimizing the timing of definitive intervention.

Excess parathyroid hormone accelerates bone remodeling, increases resorption, and promotes cortical thinning with associated porosity, while concomitant disturbances in vitamin D status, renal function, and body composition may further amplify this vulnerability [5]. The degree of metabolic activity is reflected by albumin-corrected calcium and other biochemical

https://doi.org/10.62347/WKCD7486

severity indices [6]. Accordingly, the development of osteoporosis and fractures is influenced by a constellation of clinical and biochemical determinants, including parathyroid hormone concentration, 25-hydroxyvitamin D, estimated glomerular filtration rate, body mass index, menopausal status, and serum calcium and phosphate levels [7]. However, relying solely on areal bone mineral density may underestimate the risk of bone-related diseases, and degenerative changes at the lumbar spine can artifactually elevate density measurements, thereby underscoring the need for more comprehensive and integrated assessment protocols in routine clinical practice.

Current evidence on skeletal outcomes in primary hyperparathyroidism is constrained by several limitations, including small or highly selected cohorts and substantial heterogeneity in disease definitions. Moreover, some studies have conducted within-cohort comparisons of structural outcomes and clinical fractures before and after interventions, which may introduce time-related confounding [8]. The potential benefit of parathyroidectomy on fracture risk remains debated, partly due to time-related biases such as immortal time bias [9]. Comparisons across studies are further hampered by the use of different imaging modalities and reference databases, limiting the generalizability of findings [10]. Data from Asian populations, including Chinese cohorts, remain scarce, which may reflect regional differences in exposure profiles and clinical care pathways [11]. Collectively, these knowledge gaps impede robust risk stratification and the development of contextually appropriate surgical and medical management strategies.

Clinical practice in Chinese tertiary hospitals is characterized by several distinctive features, including a higher prevalence of vitamin D deficiency, a lower average body mass index, variable access to and timing of parathyroidectomy, and distinctive patterns of anti-resorptive therapy use [12-14]. These factors may modify both baseline skeletal risk and the effectiveness of interventions, thereby limiting the generalizability of findings derived from Western cohorts [15]. Consequently, locally anchored observational evidence that integrates comprehensive clinical and biochemical data is essential to guide decision-making regarding surgical timing, optimization of vitamin D status, and the appropriate use of bone-protective therapies [16-18].

Against this background, we designed the present study as a retrospective cohort with a nested case-control analysis for fractures, aiming to quantify real-world determinants of osteoporosis and clinical fragility fractures in PHPT, and to characterize BMD changes over 12 to 24 months following parathyroidectomy (PTX).

Methods

Study design and oversight

A single-center retrospective cohort study was conducted, incorporating a nested case-control analysis to investigate clinical fragility fractures. The study population comprised adults with PHPT who were diagnosed based on biochemical or pathological criteria and underwent dual-energy X-ray absorptiometry (DXA) at our institution between January 2015 and December 2024. The index date was defined as the date of the "index DXA". Laboratory data obtained within ± 90 days of the index date were considered baseline measurements. The study was conducted in accordance with the STROBE guidelines, and all analytical decisions-including endpoints, exposure windows, covariates, and the modeling plan-were prespecified before data extraction. Data were deidentified before analysis and managed under institutional audit procedures.

Setting and participants

Patients were identified through the electronic medical records of endocrinology clinics and inpatient services at a tertiary academic hospital in China. Inclusion criteria were: age ≥ 18 years, confirmed PHPT (defined as elevated albumin-corrected calcium with inappropriately elevated parathyroid hormone (PTH), or postoperative histological confirmation), and at least one valid DXA measurement at the lumbar spine (L1-L4), femoral neck, or total hip. Exclusion criteria included secondary or tertiary hyperparathyroidism, high-energy trauma, metastatic bone disease, advanced dialysis-dependent kidney disease, and other major metabolic bone disorders. For longitudinal analyses of surgical response, patients were required to have paired DXA scans obtained 12-24 months after PTX. For the fracture analysis, eligible cases were those who sustained incident low-

trauma fractures during follow-up and were matched to controls by age, sex, calendar time, and follow-up duration (difference ≤ 1 year).

Exposures, covariates, and outcome indicators

The primary outcome was osteoporosis at baseline, defined as a T-score ≤ -2.5 at any skeletal site. Controls for this analysis were patients with normal bone mass (T-score > -1.0). The secondary outcome was clinical fragility fracture, defined as a non-pathological fracture resulting from a fall from standing height or less, as adjudicated through clinical notes and radiology reports, with vertebral and non-vertebral sites documented. PTX exposure was predefined: for the osteoporosis model, surgery had to be completed ≥ 12 months before the index DXA; for the fracture model, PTX had to be completed ≥ 6 months before the index fracture to mitigate immortal-time bias. When available, cure was recorded as sustained normocalcemia for ≥ 6 months. Prespecified covariates included age, sex, body mass index (BMI), menopausal status, smoking, alcohol use, diabetes, hypertension, estimated glomerular filtration rate (eGFR, calculated using the CKD-EPI equation), albumin-corrected calcium, phosphate, 25-hydroxyvitamin D (25 [OH]D; categorized as < 20, 20 < 30, and ≥ 30 ng/mL), and PTH (analyzed in tertiles). Information on DXA manufacturer and model, reference database (Asian/Chinese), quality control procedures (phantom coefficients of variation), as well as assay platforms and imprecision for PTH and 25(OH)D measurements, was recorded from departmental logs.

Statistical analysis

All analyses were performed using R 4.3+ and Stata 17+. Continuous variables were tested for normality using the Shapiro-Wilk test; normally distributed variables are presented as mean ± SD and compared using t-tests, while non-normally distributed variables are presented as median [Interquartile Range (IQR)] and compared using the Mann-Whitney U test. Categorical variables are presented as n (%) and compared using the χ^2 test or Fisher's exact test. For the primary outcome, propensity scores were estimated using multivariable logistic regression incorporating age, sex, calendar year, BMI, menopausal status, eGFR, 25(OH)D, smoking, alcohol, diabetes, and hypertension; 1:2 nearest-neighbor matching without replacement with a caliper of 0.2 SD of the logit was applied to achieve comparability, with balance assessed by absolute standardized mean differences (SMD < 0.10). Determinants of osteoporosis were analyzed using multivariable logistic regression (maximum likelihood estimation) in the matched set, reporting adjusted odds ratios (aORs) with 95% CIs derived from Wald tests; model discrimination was evaluated by the AUC and calibration by the Hosmer-Lemeshow test. For the secondary outcome (clinical fragility fractures), a risk-set matched nested case-control design was employed, with controls matched to cases on age, sex, calendar time, and follow-up duration; conditional logistic regression was used to estimate associations, adjusting for the prespecified covariates and baseline BMD T-score, with results reported as aORs and 95% CIs with robust standard errors. For the longitudinal analysis of BMD response to parathyroidectomy, percentage change was calculated as [(follow-up BMD - baseline BMD)/baseline BMD] × 100%; within-group changes were assessed using paired t-tests, between-subgroup comparisons were performed using ANCOVA, with type-III sum of squares, adjusting for age, sex, BMI, baseline BMD, eGFR, calendar year, and follow-up interval, and predictors of ΔBMD% were explored using multivariable linear regression with residual diagnostics. Missing data were handled using multiple imputation by chained equations, with continuous variables imputed by predictive mean matching and binary variables by logistic regression, and estimates pooled according to Rubin's rules. Sensitivity analyses were conducted under multiple alternative specifications using the same modelling procedures as the main analyses. Multicollinearity was assessed by variance inflation factors (VIF), with VIF > 5 considered indicative of problematic collinearity (Supplementary Tables 2 and 3). All tests were two-sided with $\alpha = 0.05$; model discrimination (AUC/c-statistic) and calibration (Hosmer-Lemeshow *P*-values) are reported alongside effect estimates.

Results

Baseline characteristics

A total of 300 patients with primary hyperparathyroidism were included in the final analysis. Among them, 100 patients with osteoporosis

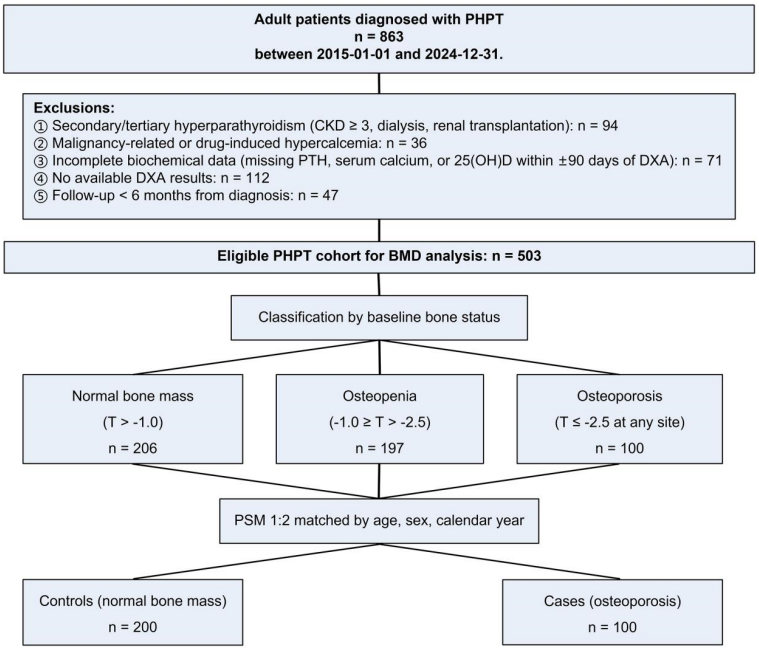

Figure 1. Flow of participants through the study. A total of 863 adult patients with biochemically confirmed primary hyperparathyroidism (PHPT) diagnosed between January 1, 2015, and December 31, 2024, were screened at XX Hospital, China. After excluding patients with secondary or tertiary hyperparathyroidism, malignancy-related or drug-induced hypercalcemia, incomplete biochemical data, missing dual-energy X-ray absorptiometry (DXA) results, or follow-up shorter than 6 months, 503 patients were eligible for bone mineral density (BMD) analysis. Based on baseline DXA T-scores, patients were classified into normal bone mass (T > -1.0), osteopenia (-1.0 ≥ T > -2.5), and osteoporosis (T ≤ -2.5) groups. For the primary case-control analysis, 100 patients with osteoporosis were matched 1:2 with 200 controls with normal bone mass by age, sex, and calendar year.

(T-score ≤ -2.5) were assigned to the osteoporosis group, and 200 patients with normal bone mineral density (T-score > -1.0) served as the control group (**Figure 1**). Compared with the control group, the osteoporosis group had a higher median age (63.0 [57.0-70.0] vs 55.0 [49.0-62.0] years), a greater proportion of females (80% vs 68%), more postmenopausal women (70% vs 52%), and a significantly lower BMI (22.8 [20.6-24.9] vs 24.1 [22.5-26.3] kg/m^2). No statistically significant differences were observed between the two groups regarding smoking history, alcohol consumption, diabetes, or hypertension (**Table 1**).

Laboratory findings revealed that patients with osteoporosis had higher albumin-corrected calcium concentrations (2.8 [2.7-2.9] vs 2.7 [2.6-2.8] mmol/L) and parathyroid hormone (PTH) levels (215 [152-290] vs 155 [112-202] pg/mL), along with lower phosphate (0.8 [0.7-0.9] vs 0.9 [0.8-0.9] mmol/L) and 25-hydroxyvitamin D levels (16.5 [12.4-21.0] vs 22.8 [17.2-28.5] ng/mL). Vitamin D deficiency (< 20 ng/mL) was more prevalent in the osteoporosis group (73% vs 48%). Relative to the control group, the osteoporosis group also showed slightly lower renal function (eGFR 78.2 [66.5-89.6] vs 84.1 [74.8-93.5] mL/min/1.73 m^2), higher alkaline phosphatase levels (112 [94-132] vs 98 [83-115] U/L), a higher frequency of low-energy fractures (22% vs 9%), and a lower rate of parathyroidectomy (27% vs 41%), while the use of anti-osteoporosis medication was more common (39% vs 27%). After propensity score matching, all matched variables achieved satisfactory balance, with absolute standardized mean differences below 0.10 (Supplementary Table 1), ensuring comparability between groups for subsequent analyses.

Distribution of BMD

The osteoporosis group had visibly lower bone mineral density than the control group across all skeletal sites. Box plots demonstrated clear separation of BMD at the lumbar spine, femoral neck, and total hip between the two groups, with medians and interquartile ranges shifted downward in the osteoporosis group for each site (**Figure 2A**). Density curves of T-scores in the full cohort showed a left-shifted distribution at the lumbar spine compared with the hip sites, indicating greater spinal involvement, while the femoral neck and total hip curves were located to the right of the spinal curve and exhibited a narrower overlap (**Figure 2B**).

The prevalence of osteoporosis varied across clinically relevant strata. It was higher in women than in men (42% vs 21%) and higher in postmenopausal women than in premenopausal women (46% vs 18%). Stratification by vitamin D status revealed a graded pattern: the prevalence was 45% for 25-hydroxyvitamin D < 20 ng/mL, 32% for 20- < 30 ng/mL, and 20% for ≥ 30 ng/mL. Prevalence also differed according

Table 1. Baseline characteristics of patients with primary hyperparathyroidism by osteoporosis status

Variable	Osteoporosis (n = 100)	Controls, T > -1.0 (n = 200)	Statistical test (statistic)	*P* value
Demographics				
Age, years, median (IQR)	63.0 (57.0-70.0)	55.0 (49.0-62.0)	Mann-Whitney U (Z = -4.82)	< 0.001
Female, n (%)	80 (80)	136 (68)	Chi-square (χ^2 = 4.55)	0.033
Postmenopausal (women), n (%)	70 (70)	104 (52)	Chi-square (χ^2 = 8.14)	0.004
BMI, kg/m^2, median (IQR)	22.8 (20.6-24.9)	24.1 (22.5-26.3)	Mann-Whitney U (Z = 3.09)	0.002
Current/ever smoking, n (%)	15 (15)	24 (12)	Chi-square (χ^2 = 0.41)	0.523
Alcohol use, n (%)	13 (13)	22 (11)	Chi-square (χ^2 = 0.24)	0.624
Diabetes, n (%)	16 (16)	26 (13)	Chi-square (χ^2 = 0.39)	0.532
Hypertension, n (%)	47 (47)	84 (42)	Chi-square (χ^2 = 0.57)	0.450
Coronary heart disease, n (%)	12 (12)	20 (10)	Chi-square (χ^2 = 0.28)	0.597
Biochemistry and bone markers				
Albumin-corrected calcium, mmol/L, median (IQR)	2.8 (2.7-2.9)	2.7 (2.6-2.8)	Mann-Whitney U (Z = -5.21)	< 0.001
Phosphate, mmol/L, median (IQR)	0.8 (0.7-0.9)	0.9 (0.8-0.9)	Mann-Whitney U (Z = 3.56)	< 0.001
PTH, pg/mL, median (IQR)	215.0 (152.0-290.0)	155.0 (112.0-202.0)	Mann-Whitney U (Z = -4.12)	< 0.001
25-hydroxyvitamin D, ng/mL, median (IQR)	16.5 (12.4-21.0)	22.8 (17.2-28.5)	Mann-Whitney U (Z = 5.36)	< 0.001
Vitamin D deficiency < 20 ng/mL, n (%)	73 (73)	96 (48)	Chi-square (χ^2 = 16.52)	< 0.001
Creatinine, μmol/L, median (IQR)	78.0 (68.0-90.0)	74.0 (63.0-86.0)	Mann-Whitney U (Z = -1.98)	0.047
eGFR, mL/min/1.73m^2, median (IQR)	78.2 (66.5-89.6)	84.1 (74.8-93.5)	Mann-Whitney U (Z = 2.85)	0.004
ALT, U/L, median (IQR)	22.0 (17.0-28.0)	23.0 (18.0-29.0)	Mann-Whitney U (Z = 0.88)	0.379
AST, U/L, median (IQR)	24.0 (20.0-27.0)	25.0 (21.0-28.0)	Mann-Whitney U (Z = 1.05)	0.294
Alkaline phosphatase, U/L, median (IQR)	112.0 (94.0-132.0)	98.0 (83.0-115.0)	Mann-Whitney U (Z = -3.95)	< 0.001
Clinical and treatment				
Prior low-energy fracture, n (%)	22 (22)	18 (9)	Chi-square (χ^2 = 8.06)	0.005
PTX, n (%)	27 (27)	82 (41)	Chi-square (χ^2 = 5.36)	0.021
Time from diagnosis to PTX, months, median (IQR)	14.0 (8.0-22.0)	11.0 (7.0-18.0)	Mann-Whitney U (Z = -1.89)	0.059
Any anti-osteoporosis medication, n (%)	39 (39)	54 (27)	Chi-square (χ^2 = 4.13)	0.042
Bisphosphonates, n (%)	28 (28)	40 (20)	Chi-square (χ^2 = 2.27)	0.132
Denosumab, n (%)	6 (6)	6 (3)	Chi-square (χ^2 = 1.33)	0.249
Traditional Chinese medicine bone formulae, n (%)	5 (5)	8 (4)	Chi-square (χ^2 = 0.10)	0.747
Vitamin D supplementation, n (%)	44 (44)	98 (49)	Chi-square (χ^2 = 0.64)	0.424

Notes: IQR, interquartile range; BMI, body mass index; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PTX, parathyroidectomy.

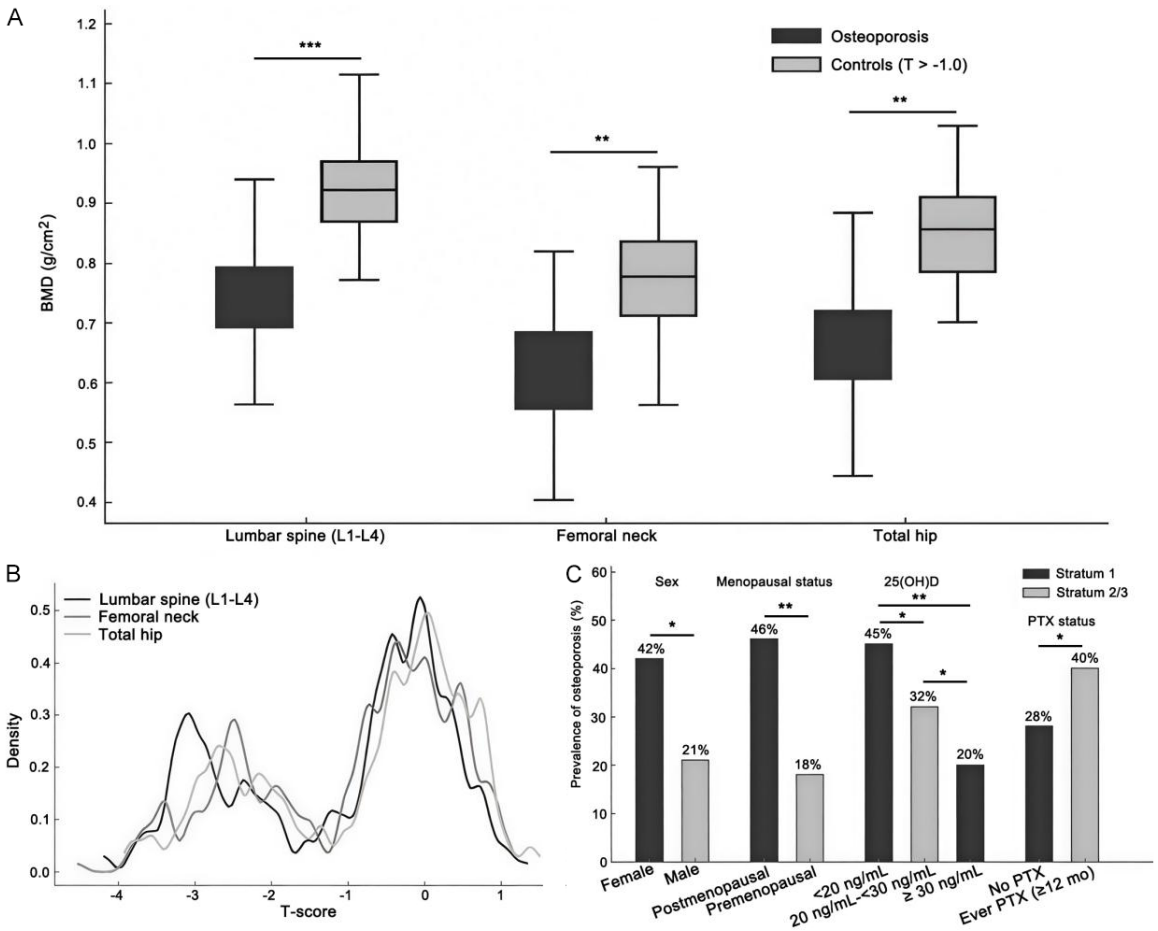

Figure 2. Distribution of bone mineral density and osteoporosis burden in primary hyperparathyroidism. A. Box plots display bone mineral density (BMD, g/cm^2, IOR) at the lumbar spine (L1-L4), femoral neck, and total hip in patients with osteoporosis (black) and normal bone mass controls (grey). The line in the boxes is median value; whiskers indicate 1.5 × IQR. $^{**}P < 0.01$, $^{***}P < 0.001$. B. These curves show the distribution of T-scores across skeletal sites and different densities, and lumbar spine line demonstrates a leftward shift compared to the total hip line. C. Bar charts, the prevalence of osteoporosis impacted by different indicators including sex, menopausal status, serum 25-hydroxyvitamin D categories (< 20, 20- < 30, ≥ 30 ng/mL), and parathyroidectomy (PTX) status (ever PTX ≥ 12 months before index DXA vs no PTX). $^{*}P < 0.05$, $^{**}P < 0.01$.

to parathyroidectomy status: 40% in patients without surgery versus 28% in those who had undergone surgery at least 12 months before the index DXA (**Figure 2C**). Collectively, these distributions quantitatively describe site-specific BMD patterns and the burden of osteoporosis in key subgroups and served as the basis for defining strata in subsequent risk-factor analyses (**Figure 2A-C**).

Primary outcome

In the multivariable logistic regression analysis performed after propensity-score matching, several independent determinants of osteoporosis were identified (**Tables 2**, **3**). Increasing age and postmenopausal status were associated with greater odds of osteoporosis, with an aOR of 1.28 (95% CI 1.10-1.50) per 10-year increment and 1.44 (1.03-2.02) for postmenopausal versus premenopausal women. Higher body mass index was inversely related to osteoporosis risk (aOR 0.93, 0.89-0.97 per 1 kg/m^2), whereas higher renal function was modestly associated with lower risk (aOR 0.90, 0.82-0.99 per 10 mL/min/1.73 m^2 increase in eGFR). Each 0.25 mmol/L increase in albumin-corrected calcium was associated with a 30% higher odds of osteoporosis (aOR 1.30, 1.12-1.51). Compared with patients in the lowest tertile of PTH, those in the highest tertile had an approximately two-fold higher risk (aOR

Table 2. Multivariable logistic regression results for osteoporosis

Variable (coding)	Adjusted OR (95% CI)	*P* value
Age (per 10 years)	1.28 (1.10-1.50)	0.002
Female sex (vs male)	1.35 (0.84-2.19)	0.209
Postmenopausal (yes vs no)	1.44 (1.03-2.02)	0.032
BMI (per 1 kg/m^2)	0.93 (0.89-0.97)	0.001
eGFR (per 10 mL/min/1.73 m^2)	0.90 (0.82-0.99)	0.028
Albumin-corrected calcium (per 0.25 mmol/L)	1.30 (1.12-1.51)	0.001
Parathyroid hormone (PTH)		
Q2 vs Q1	1.35 (0.86-2.12)	0.191
Q3 vs Q1	1.95 (1.24-3.06)	0.004
25-hydroxyvitamin D		
< 20 ng/mL vs ≥ 30 ng/mL	2.05 (1.34-3.14)	0.001
20- < 30 ng/mL vs ≥ 30 ng/mL	1.34 (0.89-2.02)	0.160
Parathyroidectomy ≥ 12 months before index DXA (yes vs no)	0.63 (0.41-0.96)	0.031
Current/ever smoking (yes vs no)	1.12 (0.64-1.96)	0.689
Alcohol use (yes vs no)	1.05 (0.58-1.89)	0.867
Calendar year of index DXA (per 1 year)	0.98 (0.93-1.03)	0.450

Notes: OR, odds ratios; BMI, body mass index; eGFR, estimated glomerular filtration rate; PTH, Parathyroid hormone; DXA, dual-energy X-ray absorptiometry.

Table 3. Multivariable logistic regression analysis of risk factors for clinical fragility fractures in PHPT

Variables (coding)	n (%) in analytic set	Adjusted OR (95% CI)	*P* value
Age (per 10 years)	-	1.45 (1.18-1.79)	< 0.001
Female sex (vs male)	193 (69.9)	1.34 (0.82-2.18)	0.241
Postmenopausal (yes vs no)	160 (58.0)	1.52 (1.04-2.24)	0.031
BMI (per 1 kg/m^2)	-	0.94 (0.90-0.99)	0.012
Baseline BMD T-score (per 1.0 unit lower)	-	1.62 (1.25-2.10)	< 0.001
eGFR (per 10 mL/min/1.73 m^2)	-	0.96 (0.88-1.04)	0.292
Albumin-corrected calcium (per 0.25 mmol/L)	-	1.18 (1.02-1.37)	0.028
Parathyroid hormone (PTH) tertiles			
Q2 vs Q1	92 (33.3)	1.22 (0.77-1.95)	0.399
Q3 vs Q1	92 (33.3)	1.70 (1.06-2.73)	0.028
25(OH)D			
< 20 ng/mL vs ≥ 30 ng/mL	155 (56.2)	1.52 (1.01-2.29)	0.044
20- < 30 ng/mL vs ≥ 30 ng/mL	83 (30.1)	1.21 (0.79-1.87)	0.374
Parathyroidectomy before index event (≥ 6 months vs none)	68 (24.6)	0.58 (0.36-0.92)	0.020
Prior low-energy fracture (yes vs no)	45 (16.3)	2.12 (1.23-3.67)	0.007

Notes: PHPT, primary hyperparathyroidism; OR, odds ratios; BMI, body mass index; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; PTH, Parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

1.95, 1.24-3.06), while those in the intermediate tertile showed a nonsignificant increase (aOR 1.35, 0.86-2.12).

Serum 25-hydroxyvitamin D concentration was also a strong determinant of osteoporosis. Patients with vitamin D deficiency (< 20 ng/mL) had more than double the odds of osteoporosis compared with those with sufficient levels (≥ 30 ng/mL) (aOR 2.05, 1.34-3.14), whereas those with insufficiency (20- < 30 ng/mL) had a smaller and nonsignificant elevation (aOR 1.34, 0.89-2.02). Undergoing parathyroidectomy at least 12 months before the index DXA was independently associated with a reduced risk (aOR 0.63, 0.41-0.96). Smoking, alcohol

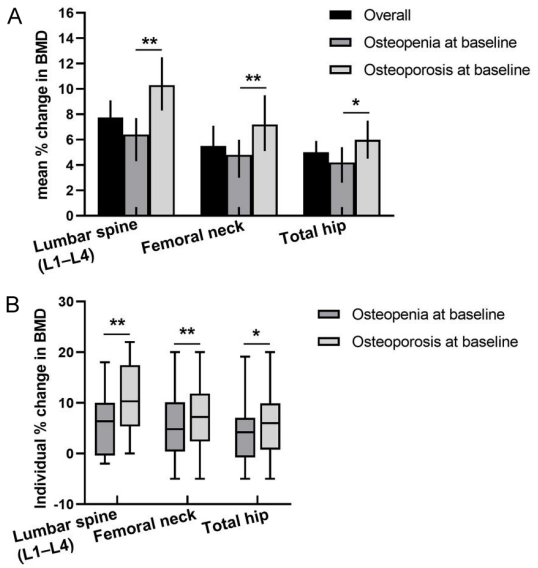

Figure 3. BMD changes after PTX. A. Mean percentage change (95% CI) at lumbar spine, femoral neck, and total hip 12-24 months post-PTX for overall cohort and by baseline bone status (osteopenia/osteoporosis). $^{*}P < 0.05$, $^{**}P < 0.01$. B. Box plots of individual percentage changes stratified by baseline osteopenia/osteoporosis. $^{*}P < 0.05$, $^{**}P < 0.01$.

use, and calendar year of DXA were not significantly associated with osteoporosis (all P > 0.05) (**Table 2**).

Secondary outcome

After propensity-matching, 276 patients were included for the nested case-control analysis. Among them, 92 individuals experienced at least one clinical fragility fracture during the follow-up period. The most common fracture sites were vertebral (46%), forearm (28%), and proximal femur (15%) sites. The independent risk factors for fracture were identified by multivariable logistic regression (**Table 3**). Specifically, age (1.45 times for per ten-year increase, 95% CI 1.18-1.79), postmenopausal status (aOR 1.52, 1.04-2.24), BMI (aOR 0.94, 0.90-0.99 per 1 kg/m^2), baseline BMD T-score (per unit decrease in the score, 62% higher the risk, aOR 1.62, 1.25-2.10), and albumin-corrected calcium (aOR 1.18, 1.02-1.37) were all risk factors for fracture (Supplementary Table 3). In addition, female sex alone did not independently predict fractures after adjustment (P = 0.24), whereas eGFR was not significantly associated (P = 0.29).

The levels of PTH concentration were also associated with fracture risk. Patients with the highest tertile level in PTH exhibited greater fracture risk compared with those in the lowest tertile (aOR 1.70, 1.06-2.73), while intermediate levels were not significantly related. Vitamin D deficiency (< 20 ng/mL) was negatively related with fracture risk (aOR 1.52, 1.01-2.29), whereas higher deficiency (20- < 30 ng/mL) showed a weaker and nonsignificant association (aOR 1.21, 0.79-1.87). Having received parathyroidectomy ≥ 6 months prior was independently a protective factor, lowering the odds of 42% in fracture (aOR 0.58, 0.36-0.92). History of prior low-energy fracture was a strong predictor of subsequent events (aOR 2.12, 1.23-3.67). The model after comprehensive and reasonable adjustment demonstrated good discriminative capability (AUC = 0.82) and good calibration (Hosmer-Lemeshow P = 0.48), showing robust internal validity (**Table 3**).

Response to parathyroidectomy

After parathyroidectomy, 146 patients received paired DXA scans 12 to 24 months, and results showed that BMD increased across all skeletal sites. Mean percentage changes were 7.7% at the lumbar spine, 5.6% at the femoral neck, and 5.0% at the total hip, and the confidence intervals did not overlap, indicating statistically significant gains across sites (**Figure 3A**; Supplementary Table 4). From the distribution plot, we could confirm that most individuals experienced positive changes at each site, with the spine undergoing wider dispersion than the hip (**Figure 3B**). Women and men both have comparable improvements, whereas patients < 60 years showed larger gains, particularly at the spine and femoral neck than those aged 60 years or above (Supplementary Table 4).

The extent of recovery after operation was strongly associated with baseline bone status, vitamin D level, and parathyroid hormone. Patients with baseline osteoporosis exhibited greater gains than those with osteopenia, with mean increases of 10.3% at the spine, 7.2% at the femoral neck, and 6.0% at the total hip versus 6.4%, 4.8%, and 4.2%, respectively (**Figure 3A**; Supplementary Table 4). A graded pattern was observed across vitamin D categories, with larger improvements in patients with 25-hydroxyvitamin D ≥ 30 ng/mL compared with that < 20 ng/mL (all *P* < 0.05). Higher parathyroid hormone tertiles before the

Table 4. Subgroup effects and interaction tests for clinical fragility fractures in PHPT

Variables (exposure effect shown)	n (%)	OR (95% CI)	*P* value
PTX ≥ 6 months vs none - Age < 60 years	120 (43.5)	0.52 (0.30-0.90)	0.02
PTX ≥ 6 months vs none - Age ≥ 60 years	156 (56.5)	0.62 (0.38-0.99)	0.046
PTX ≥ 6 months vs none - 25(OH)D ≥ 30 ng/mL	74 (26.8)	0.48 (0.25-0.92)	0.027
PTX ≥ 6 months vs none - 25(OH)D < 20 ng/mL	155 (56.2)	0.74 (0.44-1.25)	0.259
PTH Q3 vs Q1 - Age < 60 years	120 (43.5)	1.58 (0.93-2.69)	0.09
PTH Q3 vs Q1 - Age ≥ 60 years	156 (56.5)	1.82 (1.06-3.12)	0.029
PTH Q3 vs Q1 - 25(OH)D < 20 ng/mL	155 (56.2)	1.94 (1.13-3.34)	0.016
PTH Q3 vs Q1 - 25(OH)D ≥ 30 ng/mL	74 (26.8)	1.42 (0.73-2.76)	0.304
25(OH)D < 20 vs ≥ 30 ng/mL - Age < 60 years	120 (43.5)	1.38 (0.84-2.28)	0.205
25(OH)D < 20 vs ≥ 30 ng/mL - Age ≥ 60 years	156 (56.5)	1.68 (1.03-2.75)	0.038
Baseline BMD T-score (per 1.0 lower) - Women	193 (69.9)	1.66 (1.24-2.22)	0.001
Baseline BMD T-score (per 1.0 lower) - Men	83 (30.1)	1.54 (1.02-2.33)	0.04
BMI (per 1 kg/m^2) - Women	193 (69.9)	0.92 (0.87-0.98)	0.006
BMI (per 1 kg/m^2) - Men	83 (30.1)	0.96 (0.88-1.05)	0.372
PTX ≥ 6 months vs none - Baseline osteoporosis	130 (47.1)	0.56 (0.33-0.95)	0.031
PTX ≥ 6 months vs none - Baseline osteopenia/normal	146 (52.9)	0.61 (0.37-1.03)	0.064
PTX ≥ 6 months vs none - Age < 60 years	120 (43.5)	0.52 (0.30-0.90)	0.02

Notes: PHPT, primary hyperparathyroidism; PTX, parathyroidectomy; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; OR, odds ratios; BMI, body mass index.

operation were associated with greater BMD gains, with a significant linear relationship between BMD and this hormone (all $P < 0.05$). Significant skeletal post-operative recovery within 12 to 24 months and the quantification of subgroup differences could provide some insights for subsequent sensitivity analyses and treatment implications (**Figure 3A**, **3B**; Supplementary Table 4).

Sensitivity and subgroup analyses

Sensitivity analyses for the primary outcome demonstrated robustness across multiple alternative specifications (Supplementary Table 5). When the control group was broadened to include patients with osteopenia, the associations of age, BMI, corrected calcium, PTH, and vitamin D deficiency with osteoporosis remained directionally consistent, albeit with variations in effect magnitude; for instance, the adjusted odds ratio (aOR) for the highest versus lowest PTH tertile was 1.80 (95% CI 1.15-2.85), and that for vitamin D < 20 ng/mL versus ≥ 30 ng/mL was 1.92 (1.25-2.95). Altering the parathyroidectomy exposure window to ≥ 18 months or applying tighter follow-up alignment (≤ 6 months) yielded similar protective associations to the main model, with aORs of 0.66 (0.43-1.02) and 0.64 (0.42-0.98), respectively. Model discrimination remained stable across scenarios, with the area under the curve (AUC) ranging from 0.78 to 0.80 (Supplementary Table 5).

For the secondary outcome of fragility fractures, results were equally stable (Supplementary Table 6). Excluding early events, requiring a ≥ 12-month surgical window, restricting the analysis to surgery-eligible patients, or limiting to non-vertebral fractures did not materially alter the direction of associations for baseline BMD T-score, BMI, corrected calcium, PTH, vitamin D, or prior parathyroidectomy. The protective effect of surgery remained consistent across these sensitivity analyses: the aOR was 0.57 (0.35-0.93) after excluding early events, 0.61 (0.37-1.00) for a ≥ 12-month window, 0.60 (0.37-0.98) for tighter follow-up alignment, 0.55 (0.33-0.91) when restricted to surgery-eligible patients, and 0.62 (0.37-1.05) for non-vertebral fractures. The c-statistics across these sensitivity analyses ranged from 0.80 to 0.83 (Supplementary Table 6).

Prespecified subgroup analyses indicated limited but clinically coherent heterogeneity (**Table 4**). The association of prior parathyroidectomy with reduced fracture risk appeared stronger in patients with sufficient vitamin D (≥ 30 ng/mL;

aOR 0.48, 0.25-0.92) than in those with vitamin D deficiency (< 20 ng/mL; aOR 0.74, 0.44-1.25), with evidence of interaction by vitamin D status, and trended stronger in patients younger than 60 years (aOR 0.52, 0.30-0.90) compared with those aged 60 years or older (aOR 0.62, 0.38-0.99). The effect of high PTH (tertile 3 versus tertile 1) on fracture was more pronounced in older patients (aOR 1.82, 1.06-3.12) and in those with vitamin D deficiency (aOR 1.94, 1.13-3.34). Lower baseline BMD T-score predicted fractures in both women and men, with aORs 1.66 (1.24-2.22) and 1.54 (1.02-2.33), respectively, whereas the inverse association of BMI with fractures was evident in women (aOR 0.92, 0.87-0.98) but not in men (aOR 0.96, 0.88-1.05) (**Table 4**). Collectively, these analyses support the robustness of the primary findings and suggest that surgical and metabolic factors may differentially influence fracture risk across vitamin D and age strata (Supplementary Tables 5, 6; **Table 4**).

Proposed risk stratification system for skeletal complications in Chinese PHPT patients

To translate the identified determinants into a clinically actionable framework tailored to Chinese PHPT patients, we developed a preliminary risk stratification scoring system based on the magnitude of aORs from our multivariable models. Points were assigned proportionally to the strength of each independent predictor: postmenopausal status (2 points), age ≥ 60 years (2 points), BMI < 22 kg/m^2 (1 point), albumin-corrected calcium ≥ 2.8 mmol/L (1 point), PTH in the highest tertile (2 points), and 25(OH)D < 20 ng/mL (2 points), yielding a total score ranging from 0 to 10 (Supplementary Table 7). Based on the score distribution in our cohort, patients were categorized into three risk tiers: low risk (0-2 points), moderate risk (3-5 points), and high risk (≥ 6 points). When applied to our study population, the prevalence of osteoporosis showed a clear stepwise increase across risk tiers: 14.3% in the low-risk group, 38.6% in the moderate-risk group, and 68.2% in the high-risk group (P for trend < 0.001); similarly, the incidence of clinical fragility fractures rose from 8.9% to 21.4% and 46.7%, respectively (P for trend < 0.001), demonstrating good internal gradient validity. This stratification provides clinicians with an intuitive, office-based tool to identify high-risk individuals who may derive the greatest benefit from timely parathyroidectomy referral, intensive vitamin D repletion, and targeted anti-osteoporosis therapy, while low-risk patients could be managed with routine monitoring and lifestyle optimization.

Discussion

This real-world cohort study clarifies the clinical and biochemical determinants of skeletal fragility in primary hyperparathyroidism and quantifies the extent of postoperative recovery [17]. Across complementary analytical approaches, we observed that older age, postmenopausal status, lower body mass index, higher albumin-corrected calcium, higher parathyroid hormone levels, and vitamin D deficiency were independently associated with osteoporosis at baseline, and that largely overlapping factors also predicted the occurrence of clinical fragility fractures [19-21]. The protective association of prior parathyroidectomy was consistent for both outcomes, while paired densitometry demonstrated substantial gains in bone mineral density within 12 to 24 months after surgery-greatest at the lumbar spine and also evident at the femoral neck and total hip [22].

Chronic exposure to excess parathyroid hormone accelerates bone remodeling, increases resorption, and promotes cortical thinning with associated porosity, thereby compromising bone strength [23]. Vitamin D deficiency may further elevate fall risk through impaired mineralization and neuromuscular weakness. In our model, albumin-corrected calcium emerged as an additional risk factor, reflecting metabolic activity and consistent with a marker of disease severity [24]. The inverse association between BMI and skeletal outcomes likely reflects both lower bone mass and reduced shock attenuation. Lumbar spine BMD showed prominent gains after surgery, which aligns with our expectation that trabecular-rich sites recover more rapidly under high-turnover conditions, whereas hip sites exhibit a slower response. Meanwhile, degenerative changes at the lumbar spine may confound densitometric measurements, underscoring the importance of site-specific reporting and consistent quality control.

In primary hyperparathyroidism, biochemical activity and low bone mineral density are consistently associated with fracture risk, and our

findings corroborate the conclusions of prior cohort studies [25]. The present study extends the existing literature in several important respects. First, it evaluates structural outcomes and biochemical indicators within the same underlying population using harmonized definitions before and after surgery, thereby enhancing the comparability between study groups. Second, by prespecifying exposure windows, the study estimates the association between parathyroidectomy and both bone mineral density and fractures while limiting immortal-time bias and indication bias inherent to retrospective data [17]. Third, it provides clinical evidence grounded in the Chinese tertiary care setting. In China, vitamin D deficiency is highly prevalent, average body mass index is generally lower, and both access to and timing of surgery, as well as patterns of antiresorptive therapy, differ substantially from those observed in Western populations [26]. These contextual features collectively support the external validity and clinical translatability of our findings.

Clinically, a pragmatic risk stratification model that integrates biochemical activity with modifiable factors can be derived from our data. Patients who are older, vitamin D deficient, or present with higher parathyroid hormone or corrected calcium levels, along with lower body mass index, appear to carry a greater skeletal risk and may derive enhanced marginal benefit from timely surgical referral, combined with optimization of vitamin D status and targeted bone-protective therapy [9, 27]. Randomized controlled trials have demonstrated that vitamin D supplementation-either as daily cholecalciferol 2,800 IU or weekly 14,000 IU vitamin D_3-effectively increases 25-hydroxyvitamin D levels, reduces parathyroid hormone by approximately 17%, and improves lumbar spine BMD by 2.5%, without inducing hypercalcemia or hypercalciuria [28-30]. Furthermore, a meta-analysis encompassing 2,750 patients reported that preoperative vitamin D supplementation significantly reduced the risk of postoperative total hypocalcemia (RR = 0.35) and symptomatic hypocalcemia (RR = 0.53) [31]. In summary, based on our findings and the evidence, we recommend a target serum 25-hydroxyvitamin D level of ≥ 75 nmol/L (30 ng/mL) for PHPT patients. An appropriate supplementation strategy may include weekly 14,000 IU vitamin D_3, or an initial loading phase with weekly 50,000 IU vitamin D_2 followed by maintenance at 1,000-1,600 IU daily, with regular monitoring. This approach not only independently reduces the risk of skeletal complications but also maximizes the skeletal protective benefits of surgical treatment.

Several methodological features substantiate the internal validity of our findings. We coupled propensity score matching for the primary analysis with multivariable logistic regression and employed conditional logistic regression in the risk-set matched fracture sample. Surgical exposure windows were prespecified to minimize time-related bias. Model discrimination and calibration were satisfactory, and effect estimates remained robust across a range of alternative specifications and restriction analyses. Nevertheless, several limitations of this work should be acknowledged. The proposed risk stratification scoring system was derived from a single-center retrospective cohort and has not yet been externally validated; its generalizability to other populations or healthcare settings awaits confirmation in future prospective, multi-center studies. Data on the timing and cumulative dose of medication exposure were not fully captured. Variability in densitometry equipment and reference databases may introduce challenges in cross-study comparability, and although covariates and matching criteria were prespecified, residual confounding cannot be excluded. Moreover, the number of events limited the scope of interaction testing.

Future multi-center prospective studies with extended follow-up are warranted to assess fracture incidence and recurrences. The risk model developed herein requires external validation and recalibration, and the integration of bone quality metrics-such as trabecular bone score or high-resolution peripheral quantitative computed tomography-should be considered. Quasi-experimental designs may further clarify the causal effects of surgical timing and routine care pathways. By quantifying postoperative recovery indicators, this study delineates clinically actionable determinants of skeletal fragility in primary hyperparathyroidism and supports an integrated approach to metabolic and skeletal management.

This study has several limitations. First, its single-center retrospective design may have introduced selection bias and limited the generaliz-

ability of the findings. Second, asymptomatic vertebral fractures may have been underdiagnosed due to the lack of systematic screening in some patients. Third, incomplete information regarding medication timing and potential variations in densitometric measurements may have introduced additional sources of bias. Furthermore, residual confounding from unmeasured clinical and lifestyle-related factors cannot be completely excluded. Future research should prioritize multi-center prospective cohorts, external validation of the proposed risk model, incorporation of additional bone quality metrics, longer follow-up periods, and the application of quasi-experimental designs to further clarify causal relationships. From a clinical and healthcare system perspective, efforts should be directed toward developing integrated metabolic-skeletal care pathways, establishing clear surgical decision-making criteria, implementing routine vitamin D assessment, and strengthening DXA quality assurance. Collectively, these findings support a risk-stratified approach to patient management and provide evidence that may contribute to future refinement of clinical guidelines.

Conclusion

Older age, postmenopausal status, lower BMI, elevated parathyroid hormone and albumin-corrected calcium levels, and vitamin D deficiency were independently associated with osteoporosis and fragility fractures, whereas prior parathyroidectomy was associated with a lower risk of both outcomes and meaningful bone mineral density gains within 12 to 24 months.

Disclosure of conflict of interest

None.

Address correspondence to: Yarong Yang, Department of Nuclear Medicine, Wuhan Fourth Hospital, No. 76, Jiefang Avenue, Wuhan 430033, Hubei, China. Tel: +86-13307161632; E-mail: zengmei10010@163.com

References

[1] Silva BC, Cusano NE and Bilezikian JP. Primary hyperparathyroidism. Best Pract Res Clin Endocrinol Metab 2018; 32: 593-607.

[2] Palermo A, Tabacco G, Makras P, Zavatta G, Trimboli P, Castellano E, Yavropoulou MP, Naciu AM and Anastasilakis AD. Primary hyperparathyroidism: from guidelines to outpatient clinic. Rev Endocr Metab Disord 2024; 25: 875-896.

[3] Marini F, Giusti F and Brandi ML. Congenital primary hyperparathyroidism. Best Pract Res Clin Endocrinol Metab 2025; 39: 101982.

[4] Walker MD, Nishiyama KK, Zhou B, Cong E, Wang J, Lee JA, Kepley A, Zhang C, Guo XE and Silverberg SJ. Effect of low vitamin D on volumetric bone mineral density, bone microarchitecture, and stiffness in primary hyperparathyroidism. J Clin Endocrinol Metab 2016; 101: 905-913.

[5] Wang W, Nie M, Jiang Y, Li M, Meng X, Xing X, Wang O and Xia W. Impaired geometry, volumetric density, and microstructure of cortical and trabecular bone assessed by HR-pQCT in both sporadic and MEN1-related primary hyperparathyroidism. Osteoporos Int 2020; 31: 165-173.

[6] Jassam N, Thomas A, Hayden K, Dearman R and Barth JH. The impact of the analytical performance specifications of calcium and albumin on adjusted calcium. Ann Clin Biochem 2020; 57: 382-388.

[7] McCormick RK. Osteoporosis: integrating biomarkers and other diagnostic correlates into the management of bone fragility. Altern Med Rev 2007; 12: 113-145.

[8] Morshed S, Corrales L, Genant H and Miclau T 3rd. Outcome assessment in clinical trials of fracture-healing. J Bone Joint Surg Am 2008; 90 Suppl 1: 62-67.

[9] Seib CD, Meng T, Suh I, Harris AHS, Covinsky KE, Shoback DM, Trickey AW, Kebebew E and Tamura MK. Risk of fracture among older adults with primary hyperparathyroidism receiving parathyroidectomy vs nonoperative management. JAMA Intern Med 2022; 182: 10-18.

[10] Park SH, Ahn S, Hong N, Park JH, Hwang SS and Lee KH. Quality of reporting noninferiority/similarity in research studies of diagnostic imaging. Radiology 2014; 270: 241-247.

[11] Grineski SE, Collins TW and Morales DX. Asian Americans and disproportionate exposure to carcinogenic hazardous air pollutants: a national study. Soc Sci Med 2017; 185: 71-80.

[12] Chen X, Shen L, Gao C, Weng R, Fan Y, Xu S, Zhang Z and Hu W. Vitamin D status and its associations with bone mineral density, bone turnover markers, and parathyroid hormone in Chinese postmenopausal women with osteopenia and osteoporosis. Front Nutr 2024; 10: 1307896.

[13] Liu X, Zhu Z and Wang X. Analysis of medication treatment for women with osteoporosis: a real-world retrospective study from Chinese

tertiary grade A hospital. Bone Rep 2024; 21: 101778.
[14] Zhu X, Chen L, Pan L, Zeng Y, Fu Q, Liu Y, Peng Y, Wang Y and You L. Risk factors of primary and recurrent fractures in postmenopausal osteoporotic Chinese patients: a retrospective analysis study. BMC Womens Health 2022; 22: 465.
[15] Hauser B, Alonso N and Riches PL. Review of current real-world experience with teriparatide as treatment of osteoporosis in different patient groups. J Clin Med 2021; 10: 1403.
[16] Guan G, Du Y, Tang W, Chen M, Yu W, Li H and Cheng Q. Impacts of prior anti-osteoporosis treatments on sequential denosumab responses in BMD changes among postmenopausal osteoporosis women in East China: real-world data analysis. Clin Interv Aging 2025; 20: 573-586.
[17] Roumpou A, Palermo A, Tournis S, Hasenmajer V, Pasieka JL, Kaltsas G, Isidori A and Kassi E. Bone in parathyroid diseases revisited: evidence from epidemiological, surgical and new drug outcomes. Endocr Rev 2025; 46: 576-620.
[18] Zhao W, Chen S, Tang C and Zhang C. The efficiency of antiosteoporosis medicine after intertrochanteric fracture surgery: a retrospective study of refracture rate, function recovery, complications, and mortality in the chinese elderly population. Surg J (N Y) 2024; 10: e11-e19.
[19] Chandran M and Tse Tan SY. Disorders of bone and mineral metabolism in pregnancy and lactation: a case based clinical review. Osteoporos Sarcopenia 2025; 11: 1-8.
[20] Cardoso LM, Rolighed L, Amrein K, Pilz S, Underbjerg L, Pretorius M, Cetani F, Zahn A, Almquist M, Makay O, Marcocci C, Rejnmark L, Siggelkow H, Tsourdi E, Kamenický P and Bollerslev J. Advances in the clinical management of parathyroid disorders: report from the 2024 workshop by the ESE educational program on parathyroid disorders. Eur J Endocrinol 2025; 193: R65-R88.
[21] Lee S, Hong N, Kim KJ, Park CH, Lee J and Rhee Y. Bone density after teriparatide discontinuation with or without antiresorptive therapy in pregnancy- and lactation-associated osteoporosis. Calcif Tissue Int 2021; 109: 544-553.
[22] Pretorius M, Lundstam K, Heck A, Fagerland MW, Godang K, Mollerup C, Fougner SL, Pernow Y, Aas T, Hessman O, Rosén T, Nordenström J, Jansson S, Hellström M and Bollerslev J. Mortality and morbidity in mild primary hyperparathyroidism: results from a 10-year prospective randomized controlled trial of parathyroidectomy versus observation. Ann Intern Med 2022; 175: 812-819.
[23] di Filippo L, Bilezikian JP, Canalis E, Terenzi U and Giustina A. New insights into the vitamin D/PTH axis in endocrine-driven metabolic bone diseases. Endocrine 2024; 85: 1007-1019.
[24] Dieli-Conwright CM, Mortimer JE, Schroeder ET, Courneya K, Demark-Wahnefried W, Buchanan TA, Tripathy D and Bernstein L. Randomized controlled trial to evaluate the effects of combined progressive exercise on metabolic syndrome in breast cancer survivors: rationale, design, and methods. BMC Cancer 2014; 14: 238.
[25] Joyce NC, Hache LP and Clemens PR. Bone health and associated metabolic complications in neuromuscular diseases. Phys Med Rehabil Clin N Am 2012; 23: 773-799.
[26] Silva BC and Bilezikian JP. Skeletal abnormalities in hypoparathyroidism and in primary hyperparathyroidism. Rev Endocr Metab Disord 2021; 22: 789-802.
[27] Gheorghe AM, Nistor C, Ranetti AE, Ciuche A, Ciobica ML, Stanciu M, Tanasescu D, Popa FL and Carsote M. Osteoporosis and normocalcemic primary hyperparathyroidism (conservatively or surgically managed). J Clin Med 2024; 13: 6325.
[28] Rolighed L, Rejnmark L, Sikjaer T, Heickendorff L, Vestergaard P, Mosekilde L and Christiansen P. Vitamin D treatment in primary hyperparathyroidism: a randomized placebo controlled trial. J Clin Endocrinol Metab 2014; 99: 1072-1080.
[29] Pallone SG, Ohe MN, Dos Santos LM, Nacaguma IO, Kunii IS, da Silva REC, Maeda SS, Brandão CMA, Vieira JGH and Lazaretti-Castro M. Vitamin D supplementation in primary hyperparathyroidism: effects on 1,25(OH) (2) vitamin D and FGF23 levels. J Endocrinol Invest 2025; 48: 91-98.
[30] Zhu CY, Sturgeon C and Yeh MW. Diagnosis and management of primary hyperparathyroidism. JAMA 2020; 323: 1186-1187.
[31] Gynn M, Dana HM and Butskiy O. Vitamin D pretreatment to prevent the risk of postoperative hypocalcemic complications after parathyroidectomy in primary hyperparathyroidism: a systematic review and meta-analysis. Head Neck 2026; 48: 1865-1875.

Supplementary Table 1. Standardized mean differences (SMD) before and after propensity score matching

Covariate	Before matching, |SMD|	After PSM, |SMD|
Demographics		
Age, years	0.52	0.03
Female, n (%)	0.26	0.02
Calendar year of index DXA	0.05	0.01
Anthropometric and metabolic parameters		
Body mass index, kg/m^2	0.38	0.06
Postmenopausal (women)	0.33	0.05
Renal and biochemical indices		
eGFR, mL/min/1.73 m^2	0.28	0.04
25-hydroxyvitamin D, ng/mL	0.45	0.07
Lifestyle and comorbidities		
Current/ever smoking, n (%)	0.09	0.02
Alcohol use, n (%)	0.07	0.03
Diabetes mellitus, n (%)	0.09	0.04
Hypertension, n (%)	0.10	0.05

Notes: SMD, standardized mean difference; DXA, dual-energy X-ray absorptiometry; BMI, body mass index; eGFR, estimated glomerular filtration rate; PSM, propensity score matching; PTX, parathyroidectomy.

Supplementary Table 2. VIFs for covariates in the multivariable logistic regression model for osteoporosis (primary outcome)

Covariate	VIF
Age (per 10 years)	1.62
Female sex (vs male)	1.18
Postmenopausal status (yes vs no)	1.44
BMI (per 1 kg/m^2)	1.22
eGFR (per 10 mL/min/1.73 m^2)	1.35
Albumin-corrected calcium (per 0.25 mmol/L)	1.68
PTH Q2 vs Q1	1.82
PTH Q3 vs Q1	1.89
25(OH)D < 20 vs ≥ 30 ng/mL	1.56
25(OH)D 20- < 30 vs ≥ 30 ng/mL	1.50
Parathyroidectomy ≥ 12 months (yes vs no)	1.24
Current/ever smoking (yes vs no)	1.10
Alcohol use (yes vs no)	1.08
Calendar year of index DXA (per 1 year)	1.06

Notes: VIFs, Variance inflation factors; BMI, body mass index; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

Supplementary Table 3. VIFs for covariates in the conditional logistic regression model for clinical fragility fractures (secondary outcome)

Covariate	VIF
Age (per 10 years)	1.75
Female sex (vs male)	1.20
Postmenopausal status (yes vs no)	1.52
BMI (per 1 kg/m^2)	1.28
Baseline BMD T-score (per 1.0 unit lower)	1.45
eGFR (per 10 mL/min/1.73 m^2)	1.31
Albumin-corrected calcium (per 0.25 mmol/L)	1.72
PTH Q2 vs Q1	1.88
PTH Q3 vs Q1	2.11
25(OH)D < 20 vs ≥ 30 ng/mL	1.62
25(OH)D 20- < 30 vs ≥ 30 ng/mL	1.55
Parathyroidectomy before event (≥ 6 months vs none)	1.26
Prior low-energy fracture (yes vs no)	1.09

Notes: VIFs, Variance inflation factors; BMI, body mass index; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

Supplementary Table 4. Postoperative percentage change in bone mineral density (BMD) 12-24 months after parathyroidectomy (PTX), by baseline characteristics (PTX cohort n = 146)

Subgroup (n, %)	Lumbar spine (L1-L4), mean % change (95% CI)	Femoral neck, mean % change (95% CI)	Total hip, mean % change (95% CI)
Overall (146, 100%)	7.7 (6.4-9.0)	5.6 (4.2-7.0)	5.0 (3.8-6.3)
Baseline bone status			
Osteopenia (80, 54.8%)	6.4 (4.9-7.9)	4.8 (3.3-6.3)	4.2 (2.7-5.6)
Osteoporosis (66, 45.2%)	10.3 (8.4-12.2)	7.2 (5.3-9.1)	6.0 (4.5-7.6)
P value	0.008	0.006	0.015
Sex			
Women (100, 68.5%)	7.9 (6.3-9.5)	5.7 (4.1-7.3)	5.2 (3.7-6.7)
Men (46, 31.5%)	7.3 (5.2-9.4)	5.4 (3.3-7.5)	4.7 (2.8-6.7)
P value	0.624	0.698	0.513
Age			
< 60 years (64, 43.8%)	8.4 (6.6-10.2)	6.1 (4.3-7.9)	5.4 (3.9-6.9)
≥ 60 years (82, 56.2%)	6.9 (5.3-8.6)	5.1 (3.4-6.8)	4.7 (3.3-6.2)
P value	0.09	0.111	0.154
25-hydroxyvitamin D			
< 20 ng/mL (55, 37.7%)	6.5 (4.8-8.3)	4.5 (2.8-6.1)	4.1 (2.7-5.6)
20- < 30 ng/mL (52, 35.6%)	7.6 (5.8-9.4)	5.6 (3.8-7.5)	5.0 (3.4-6.6)
≥ 30 ng/mL (39, 26.7%)	9.0 (6.8-11.3)	6.8 (4.6-9.1)	6.0 (4.2-7.8)
P value	0.043	0.025	0.047
PTH tertiles			
Q1 (lowest, 48, 32.9%)	6.9 (5.1-8.7)	4.9 (3.1-6.7)	4.3 (2.9-5.7)
Q2 (middle, 49, 33.6%)	7.6 (5.8-9.4)	5.6 (3.8-7.5)	5.1 (3.6-6.6)
Q3 (highest, 49, 33.6%)	8.8 (6.9-10.7)	6.4 (4.5-8.3)	5.8 (4.1-7.6)
P value	0.037	0.041	0.049

Notes: BMD, bone mineral density; PTH, parathyroid hormone; PTX, parathyroidectomy.

Supplementary Table 5. Sensitivity analyses for the primary outcome (osteoporosis) in PHPT (multivariable logistic regression; cases n = 100, controls n = 200)

Scenario	Age (per 10 yr) OR (95% CI)	BMI (per 1 kg/m^2) OR (95% CI)	Corrected Ca (per 0.25 mmol/L) OR (95% CI)	PTH Q3 vs Q1 OR (95% CI)	25(OH)D < 20 vs ≥ 30 ng/mL OR (95% CI)	PTX ≥ 12 mo vs none OR (95% CI)	AUC
Main analysis	1.28 (1.10-1.50)	0.93 (0.89-0.97)	1.30 (1.12-1.51)	1.95 (1.24-3.06)	2.05 (1.34-3.14)	0.63 (0.41-0.96)	0.79
Controls broadened to include osteopenia	1.25 (1.07-1.47)	0.94 (0.90-0.98)	1.26 (1.08-1.48)	1.80 (1.15-2.85)	1.92 (1.25-2.95)	0.68 (0.45-1.02)	0.78
PTX exposure window ≥ 18 months	1.27 (1.09-1.49)	0.93 (0.89-0.97)	1.29 (1.11-1.50)	1.92 (1.22-3.02)	2.00 (1.31-3.07)	0.66 (0.43-1.02)	0.79
Follow-up length matched within ≤ 6 months	1.26 (1.08-1.48)	0.93 (0.89-0.97)	1.28 (1.11-1.49)	1.88 (1.20-2.96)	2.01 (1.32-3.07)	0.64 (0.42-0.98)	0.79
Restricted to surgery-eligible patients	1.29 (1.10-1.52)	0.92 (0.88-0.96)	1.31 (1.12-1.54)	2.02 (1.27-3.22)	2.12 (1.37-3.29)	0.58 (0.37-0.92)	0.80
Vitamin D sufficiency threshold set at ≥ 40 ng/mL (reference)	1.26 (1.08-1.47)	0.93 (0.89-0.97)	1.27 (1.10-1.48)	1.88 (1.19-2.98)	2.18 (1.30-3.64)	0.65 (0.42-1.01)	0.79

Notes: PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; PTX, parathyroidectomy; AUC, area under the curve.

Supplementary Table 6. Sensitivity analyses for the secondary outcome (clinical fragility fractures) in PHPT (conditional logistic regression; cases n = 92, controls n = 184)

Scenario	Age (per 10 yr) OR (95% CI)	BMI (per 1 kg/m^2) OR (95% CI)	Baseline BMD T-score (per 1.0 lower) OR (95% CI)	Corrected Ca (per 0.25 mmol/L) OR (95% CI)	PTH Q3 vs Q1 OR (95% CI)	25(OH)D < 20 vs ≥ 30 ng/mL OR (95% CI)	PTX before event OR (95% CI)	AUC
Main analysis	1.45 (1.18-1.79)	0.94 (0.90-0.99)	1.62 (1.25-2.10)	1.18 (1.02-1.37)	1.70 (1.06-2.73)	1.52 (1.01-2.29)	0.58 (0.36-0.92)	0.82
Excluding fractures within 6 months of diagnosis	1.43 (1.16-1.78)	0.94 (0.90-0.99)	1.59 (1.23-2.07)	1.17 (1.01-1.36)	1.66 (1.02-2.70)	1.49 (0.98-2.27)	0.57 (0.35-0.93)	0.82
PTX window ≥ 12 months before event	1.44 (1.17-1.78)	0.94 (0.90-0.99)	1.60 (1.24-2.08)	1.17 (1.01-1.36)	1.68 (1.04-2.72)	1.51 (1.00-2.28)	0.61 (0.37-1.00)	0.82
Follow-up length matched within ≤ 6 months	1.46 (1.18-1.81)	0.94 (0.90-0.99)	1.63 (1.26-2.12)	1.18 (1.02-1.38)	1.72 (1.07-2.77)	1.53 (1.01-2.31)	0.60 (0.37-0.98)	0.82
Restricted to surgery-eligible patients	1.47 (1.18-1.82)	0.93 (0.89-0.98)	1.66 (1.27-2.16)	1.19 (1.03-1.39)	1.74 (1.07-2.84)	1.55 (1.01-2.37)	0.55 (0.33-0.91)	0.83
Non-vertebral fractures only	1.38 (1.10-1.74)	0.95 (0.90-1.00)	1.48 (1.12-1.96)	1.15 (0.99-1.35)	1.58 (0.95-2.62)	1.41 (0.91-2.18)	0.62 (0.37-1.05)	0.80

Notes: BMI, body mass index; BMD, bone mineral density; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; PTX, parathyroidectomy; AUC, area under the curve.

Supplementary Table 7. Proposed risk stratification scoring system for osteoporosis and fragility fractures in Chinese patients with primary hyperparathyroidism

Risk factor	Category	Points assigned
Age	≥ 60 years	2
	< 60 years	0
Menopausal status	Postmenopausal	2
	Premenopausal/Male	0
Body mass index	< 22 kg/m^2	1
	≥ 22 kg/m^2	0
Albumin-corrected calcium	≥ 2.8 mmol/L	1
	< 2.8 mmol/L	0
PTH	Highest tertile (Q3)	2
	Middle tertile (Q2)	1
	Lowest tertile (Q1)	0
25-hydroxyvitamin D	< 20 ng/mL (deficiency)	2
	≥ 20 ng/mL	0
Total score	-	0-10

Notes: PHPT, primary hyperparathyroidism; PTH, Parathyroid hormone.