



A diagnostic predictive model for secondary osteoporosis in patients with fragility fracture: a retrospective cohort study in a tertiary care hospital

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Abstract

Summary Identifying secondary causes among osteoporotic patients is crucial. However, there is no simple tool for screening secondary osteoporosis. A predictive model for screening secondary osteoporosis was constructed using simple clinical and biochemical parameters. This predictive model may provide clinicians with guidance to perform further investigations for specific causes of osteoporosis.

Purpose Establishing whether a fragility fracture is secondary to a specific cause of osteoporosis is crucial for treatment outcomes. Therefore, this study aimed to develop a simple screening tool for secondary osteoporosis in the elderly initially presented with fragility fractures.

Methods A retrospective cohort study including 456 patients with fragility hip and vertebral fractures that occurred between January 2017 and July 2022 was conducted. Demographic, clinical, biochemical, and final diagnostic data were retrieved. Potential predictors for secondary osteoporosis were determined by multivariable logistic regression analysis, and a predictive model for secondary osteoporosis was subsequently developed using identified potential predictors.

Results This study included 343 females and 113 males with a mean age of 76.9 ± 11.0 years. One hundred and twenty-one patients (26.5%) were diagnosed with secondary osteoporosis. Vitamin D deficiency (71.9%) was the most common cause of secondary osteoporosis, followed by glucocorticoid-induced osteoporosis (23.9%) and primary hyperparathyroidism (9.9%). The potential predictors for secondary osteoporosis included in the predictive model were age, body mass index (BMI), corrected calcium, phosphate, thyroid stimulating hormone, and a 10-year probability of hip fractures calculated by BMI-based FRAX®. With a cut-off level of 0.22, the proposed predictive model has an AuROC of 0.75 (95% CI 0.69 to 0.81) with a sensitivity of 77%, a specificity of 66%, and an accuracy of 68.9%.

Conclusion A predictive model for screening secondary osteoporosis was constructed using simple clinical and biochemical parameters. This newly developed predictive model may provide clinicians with guidance to perform further advanced investigations for secondary causes of osteoporosis.

Keywords Secondary osteoporosis · Fragility fracture · Elderly · Predictive model · Vitamin D deficiency

Introduction

Osteoporosis is a concerning disease worldwide because of its increasing prevalence along with the trend of an aging society, as well as its impact on the independence of individuals who experience osteoporosis-related fractures. Even though primary osteoporosis is the most common type of osteoporosis, specific contributing factors for osteoporosis were identified in 20–30%, 40–50%, and 50–80% in postmenopausal women, premenopausal women, and men, respectively [1–3]. Undiagnosed secondary osteoporosis usually does not respond as well to osteoporotic therapy as

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primary osteoporosis [4]. As a result, the correct diagnosis of secondary osteoporosis before starting pharmacologic treatment for osteoporosis is critical for the treatment's success.

Multiple clinical practice guidelines, both international and regional, recommend a thorough clinical evaluation and laboratory panel for all osteoporotic cases to determine secondary causes of osteoporosis [5–10]. In addition, the specific contributing factors for osteoporosis should be explored in medication-compliance patients who poorly respond to treatment, even those who previously had a negative screening panel for secondary osteoporosis [11, 12]. Almost all clinical practice guidelines recommend basic laboratory investigations, including complete blood count, blood chemistry, liver function tests, and serum 25-hydroxy vitamin D (25(OH)D) in all cases of osteoporosis. Additional investigations, including thyroid function tests and parathyroid hormone levels, should be evaluated upon specific clues identified by either clinical evaluation or a basic laboratory investigation [5, 6, 8–10]. Several studies have shown that different screening panels for secondary osteoporosis are beneficial [13–15]. Nevertheless, to date, there is no simple tool for screening secondary osteoporosis.

Fragility fracture is the most devastating skeletal outcome of osteoporosis. Patients with previous fragility fractures are at the highest risk for recurrent fractures. Therefore, it is essential to establish a diagnosis of osteoporosis and specify its type for pursuing a proper treatment algorithm. However, many patients have missed opportunities for appropriate investigation and treatment [16–19]. Therefore, it would be beneficial in the clinic if there were a simple screening tool for secondary osteoporosis to guide physicians in their decision to further investigate the specific cause of osteoporosis. This study aimed to identify specific contributing factors to osteoporosis in the patients who first presented with fragility fractures as well as to develop a predictive model for secondary osteoporosis.

Methods

Study subjects and design

A retrospective cohort study of patients diagnosed with fragility fracture between January 2017 to July 2022 was conducted. We included patients first documented with fragility fractures, including hip and vertebral fragility fractures, aged more than 18 years based on the relevant International Classification of Diseases 10th revision (ICD-10) code: M4840, M4845-4846, M4849-4850, M4854-4856, M4859, M8000-8029, M8040-8059, S2200, S2210, S3200, S7200, S7220, S7230, S7290, S8280, and S8290 (Online Resource 1). Our implemented inclusion is primarily based on ICD10, which

includes hip and vertebral fractures diagnosed without a specific cause, allowing us to encompass a wide range of cases. The exclusion criteria were: (1) fracture associated with the preexisting pathological bone lesion or high energy trauma, which is unrelated to falling from a standing height or less, such as a vehicle accident or falling from a stair [8], (2) patients who were already diagnosed with osteoporosis, (3) patients who had been prescribed anti-resorptive or anabolic agents, and (4) patients who received an incomplete evaluation for the secondary osteoporosis according to current guidelines [6, 8–10]. The study was approved by the Institutional Board Review of the Faculty of Medicine Chiang Mai University (MED-2564-08627). The study flow is shown in Fig. 1. The study size was calculated based on a pilot study of 20 patients giving a total number of 455 patients to reach the power of 80%.

Measurement and definition

Demographic characteristics and laboratory tests were collected during the admission. Bone mineral density (BMD) was collected if the patient underwent to perform BMD after the fracture and before anti-resorptive or anabolic agent initiation. BMD was performed with the exclusion of the fracture area and determined based on the lowest value. The BMD T-score and Z-score were measured by dual-energy X-ray absorptiometry (DXA) (Discovery™ QDR series, Hologic®, Marlborough, MA, USA). The patient's fracture risk was calculated using the fracture risk assessment tool (FRAX®) based on body mass index (BMI) according to Thailand's database [6, 20]. We calculated FRAX® without a previous fracture history and used data from the first day of admission to determine the baseline pre-injury fracture risk. According to previous literature, the 10-year probability of major osteoporotic fractures (FRAX-M) and hip fractures (FRAX-H) calculated by FRAX® in type 2 diabetes (T2DM) patients should be adjusted [21]. As a result, in patients with T2DM, we adjusted the FRAX-M and FRAX-H by adding

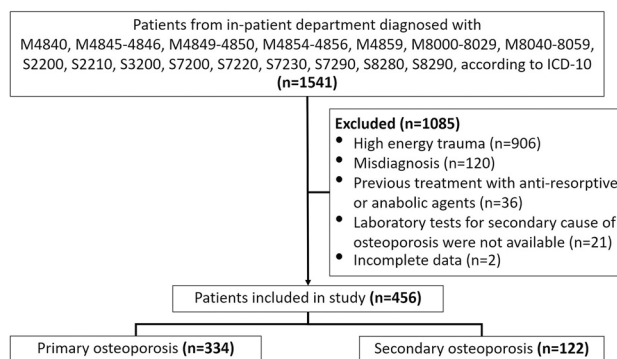


Fig. 1 Flow diagram of individuals with fragility fractures included in study

10 years of age or substituting rheumatoid arthritis. The higher value was subsequently used for further analysis. For patients with prednisolone use, we adjusted the FRAX-M and FRAX-H based on the current dose of prednisolone [6, 20].

Secondary osteoporosis is defined as low bone mass with microarchitectural alterations in bone leading to fragility fractures in the presence of an underlying disease or medication [4]. Therefore, in this study, we defined secondary osteoporosis as osteoporosis with at least one identified contributing factor for osteoporosis according to the clinical evidence recorded in the electronic medical record after the episode of fragility fracture. Every patient included in this study has neither a previous fracture nor documentation of any contributing factors for osteoporosis prior to the episode of fracture. The specific contributing factors for osteoporosis included the following documented factors as causes of secondary osteoporosis: hypercortisolism, hyperparathyroidism, hypogonadism, hypophosphatemia, vitamin D deficiency, drugs induced osteoporosis, myeloma, and early menopause [22]. Vitamin D deficiency was defined by serum 25(OH)D level of less than 20 ng/mL [23, 24]. The 25(OH)D level was measured by electrochemiluminescence immunoassay (ECLIA) (Eleclys® 2010/1010, Modular E 170, cobas e411, Roche Diagnostics International Ltd, Rotkreuz, Switzerland) with a detectable dose ranging from 3 to 70 ng/mL. The coefficient of variation (CV) of intra- and inter-assay was below 5.4% and 5.7%, respectively. The 25(OH)D level was assessed using standardized laboratory procedures. Hypercortisolism was diagnosed based on increased 24-h urinary free cortisol and non-suppressed serum cortisol level by overnight 1 mg dexamethasone suppression test (DST) or low-dose 2-day dexamethasone test (LDDT) [25]. Hyperparathyroidism included primary, secondary, and tertiary hyperparathyroidism. Classic primary hyperparathyroidism (PHPT) was defined by the elevation of serum calcium and non-suppressed parathyroid hormone level with a cut-off level of 10.5 mg/dL and 15 pg/dL, respectively. Normocalcemic PHPT (NPHPT), a well-recognized variant of PHPT, was defined by normal total serum calcium levels without any known etiologies for a secondary elevation of the PTH [26]. According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, secondary (SHPT) and tertiary hyperparathyroidism (THPT) was defined as the PTH level above nine times the upper normal limit [27]. Drug-induced osteoporosis was defined as osteoporotic patients who received glucocorticoid, aromatase inhibitors, ovarian suppressing agents, androgen deprivation therapy, thiazolidinediones, psychotropic and anticonvulsant therapy, selective serotonin reuptake inhibitors, anticonvulsants, drugs targeting the immune system, calcineurin inhibitor, and anti-retroviral therapy without others cause of osteoporosis [28]. Additionally, early menopause was defined as women who

experienced menopause before the age of 45 [29]. If the final diagnosis were inconclusive, a consensus on the diagnosis was made by two endocrinologists who had independently performed a chart review.

Statistical methods

All statistical analyses were performed using STATA (version 16.0, StataCorp LLC., College Station, TX, USA). Continuous data were presented by the mean and standard deviation (SD) for normally distributed data. For non-normally distributed data, median and interquartile ranges (IQR) were used. Continuous data were analyzed using an independent *t*-test and the Mann-Whitney *U* test as appropriate. Categorical data were presented by frequency and percentage, which were compared using Fisher's exact probability test. A comparison of three or more groups was performed using analysis of variance (ANOVA) with Bonferroni correction. Statistically significant was defined as a *p*-value less than 0.05.

A diagnostic screening tool was developed according to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statements [30]. Candidate predictors were selected according to clinical relevance and statistical significance via multivariable logistic regression modeling with a stepwise backward elimination approach. In addition, all continuous parameters were included in the model without categorization to avoid unnecessary information loss. We employed the multivariable fractional polynomials (MFP) function to identify each continuous variable Field's most appropriate functional form [31]. As a result, a non-linear model could be generated to reflect the true association between the dependent and independent variables. The developed model's performance was evaluated using the area under the receiver operating characteristics (AuROC) curve. The model's calibration, an agreement between the predicted and observed risk, was presented via calibration plot. Internal validation was performed using the bootstrap resampling method to identify the model's optimism. Overfitting was tested using calibration slope, calibration-in-the-large (CITL) value, and the shrinkage factor.

Results

Specific contributing factors were identified in one-quarter of apparent healthy elderly presenting with fragility fractures

A total of 456 patients were eligible to enter the study (Fig. 1). Most of the study population was female (75.2%), with a mean age of 76.9 ± 11.0 years. Most of the fragility

fractures were hip fractures (77.8%), followed by vertebral fractures (22.2%). In general, our enrolled patients had low BMD in the osteoporotic range and had a high risk of hip fractures as defined by the 10-year probability of hip fracture calculated by FRAX® (FRAX-H) of greater than 3%. One hundred and twenty-one (26.5%) patients were diagnosed with secondary osteoporosis. Patients with secondary osteoporosis were younger (73.2 ± 12.0 years vs. 78.3 ± 10.3 years, $p < 0.001$) and had a higher BMI (22.2 ± 3.7 kg/m² vs. 21.3 ± 4.5 kg/m², $p = 0.024$). Patients with secondary osteoporosis had a significantly higher prevalence of rheumatoid arthritis and systemic lupus erythematosus, as well as a higher usage rate of prednisolone. Although the prevalence of diabetes mellitus was comparable in both groups, patients with secondary osteoporosis tended to receive pioglitazone and sodium-glucose transporter 2 (SGLT2) inhibitors more frequently than primary osteoporosis. In terms of the basic laboratory profile, only serum phosphate (3.4 ± 1.2 mg/dL vs. 3.2 ± 0.6 mg/dL, $p = 0.033$) and TSH (7.15 ± 30.4 μ IU/mL vs. 2.54 ± 2.2 μ IU/mL, $p = 0.013$) were significantly higher in those with secondary osteoporosis (Table 1). Among those with secondary osteoporosis, there were no clues of a specific disease detected by clinical evaluation and basic laboratory investigation.

Vitamin D deficiency leading contributing factor to fragility fractures in the elderly population

Vitamin D deficiency was the most common cause of secondary osteoporosis (87 patients, 71.9%). Other less common etiologies were glucocorticoid-induced osteoporosis (GIO) (29 patients, 23.9%), followed by PHPT (12 patients, 9.9%), SHPT (5 patients, 4.1%), and multiple myeloma (4 patients, 3.3%) (Online Resource: Table 1). There were 21 patients with more than one diagnosis, including eleven patients with vitamin D deficiency plus GIO, eight with vitamin D deficiency plus PHPT, one with vitamin D deficiency plus SHPT associated with chronic renal failure, and one with vitamin D deficiency plus multiple myeloma. The mean duration of prednisolone usage in GIO was 2.76 ± 2.83 years before the fracture, with a mean dosage of 8.53 ± 11.1 mg per day and a mean accumulative dosage of 2.81 ± 2.9 g per year. The patient characteristics of each identified secondary cause are shown in Online Resource: Table 1. Hip fractures were predominant in patients with vitamin D deficiency, PHPT, and SHPT. Low BMD within the osteoporosis range was demonstrated in patients with any identified secondary causes; however, patients with hyperparathyroidism tended to have a lower BMD compared to those with other causes.

Among 329 patients tested for serum 25(OH)D levels, 87 (26.1%) patients were diagnosed with vitamin D deficiency. One hundred and twenty-nine (39.5%) patients were diagnosed with vitamin D insufficiency, as defined by serum

25(OH)D levels ranging from 20 to 29.9 ng/mL. The characteristics of the three groups of patients according to their vitamin D levels were demonstrated in Table 2. The levels of serum 25(OH)D levels were significantly different among the three groups (13.83 ± 3.97 ng/mL vs. 25.53 ± 2.8 ng/mL vs. 38.03 ± 8.4 ng/mL, $p < 0.001$). Since SHPT is related to vitamin D deficiency, PTH levels tended to be higher in the group with vitamin D deficiency compared to the other two groups. All parameters were comparable among the three groups, except BMI and the FRAX-M. The pairwise comparison with Bonferroni adjustment revealed that BMI significantly differed between groups with vitamin D deficiency and vitamin D adequacy (22.5 ± 3.8 kg/m² vs. 21.1 ± 3.5 kg/m², $p = 0.019$) while the FRAX-M significantly differed in both the vitamin D deficiency group compared to the vitamin insufficiency group ($9.2 \pm 4.6\%$ vs. $7.6 \pm 3.9\%$, $p = 0.016$) and the vitamin D deficiency group compared to the vitamin D adequacy group ($9.2 \pm 4.6\%$ vs. $7.6 \pm 3.7\%$, $p = 0.020$). Twenty-eight patients in the vitamin D deficiency group had severe vitamin D deficiency (mean 25(OH)D 9.1 ± 1.9 ng/mL), as defined by serum 25(OH)D level of lower than 12 ng/mL [32]. The PTH levels were comparable between patients with severe and non-severe vitamin D deficiency (97.3 ± 157.8 ng/mL vs. 112.7 ± 349.5 ng/mL, $p = 1.000$). Even though osteomalacia frequently occurs in severe vitamin D deficiency, no bone pain and muscle weakness were reported in those with severe vitamin deficiency, and the levels of serum calcium, serum phosphate, and ALP were normal in all those patients in the study, suggesting a clinical diagnosis of osteoporosis but not osteomalacia.

Predictive model as a diagnostic screening tool for secondary osteoporosis in elderly

All potential predictors for secondary osteoporosis were included in multivariable logistic regression modeling with the multivariable fractional polynomial (MFP) algorithm to develop a diagnostic screening tool (Online Resource: Table 2). After applying the stepwise backward elimination method, the patient's age, BMI, corrected calcium level, phosphate level, TSH level, and FRAX-H were shown as predictive factors for secondary osteoporosis. The patient's age negatively correlated with the risk of developing secondary osteoporosis. In contrast, the BMI, FRAX-H, phosphate level, TSH level, and serum calcium level that was outside the range of 9 to 10 mg/dL positively correlated with the risk of developing secondary osteoporosis. No multicollinearity was identified among predictors. The predicted probability of secondary osteoporosis was calculated according to each included predictor's covariate transformations and regression coefficient (Table 3). The model's performance was acceptable, with an AuROC of 0.75 (95% CI 0.69 to 0.81) (Fig. 2). All six factors contributed to the power of the

Table 1 Demographics of patients diagnosed with secondary and primary osteoporosis

Demographic	Total (n = 456)	2° osteoporosis (n = 121)	1° osteoporosis (n = 335)	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	76.9 ± 11.0	73.2 ± 12.0	78.3 ± 10.3	<0.001
Female (n, %)	343 (75.2)	98 (80.9)	245 (73.1)	0.110
BMI ¹ (kg/m ²)	21.5 ± 3.5	22.2 ± 3.7	21.3 ± 4.5	0.024
Fracture (n, %)				
Hip	355 (77.8)	92 (76)	263 (78.5)	0.610
Vertebral	101 (22.2)	29 (23.9)	72 (21.5)	
Comorbidities (n, %)				
RA ²	11 (2.4)	10 (8.3)	1 (0.3)	<0.001
SLE ³	6 (1.32)	6 (4.96)	0 (0)	<0.001
CKD ⁶ stage 4 and 5	67 (14.6)	19 (15.7)	48 (14.3)	0.765
T2DM ⁷	91 (19.9)	27 (22.3)	64 (19.1)	0.507
Medication (n, %)				
Insulin	23 (5)	8 (6.6)	15 (4.5)	0.342
Sulfonylurea	21 (4.6)	7 (5.8)	14 (4.2)	0.456
Pioglitazone	6 (1.3)	4 (3.3)	2 (0.6)	0.045
SGLT2i ⁹	8 (1.8)	5 (4.1)	3 (0.9)	0.034
Prednisolone	29 (6.4)	29 (23.9)	0 (0)	<0.001
BMD				
T-score, n = 185	-2.7 ± 0.9	-2.8 ± 1.0	-2.6 ± 0.9	0.375
Z-score, n = 175	-0.71 ± 0.9	-0.93 ± 1.0	-0.61 ± 0.9	0.059
T-Z difference, n = 175	2.04 ± 0.7	1.95 ± 0.7	2.1 ± 0.7	0.283
10-year probability of fractures				
Hip (FRAX-H)	4.5 ± 3.1	4.6 ± 3.8	4.5 ± 2.8	0.667
Major (FRAX-M)	8.3 ± 4.4	8.77 ± 4.9	8.13 ± 4.1	0.168
Hematology				
Hb ¹¹ (g/dL)	11.3 ± 1.9	11.1 ± 2.0	11.4 ± 1.8	0.226
WBC ¹² (10 ³ /μL)	9.4 ± 3.5	9.14 ± 3.6	9.5 ± 3.4	0.381
Platelet (10 ³ /μL)	238.8 ± 92.5	243.7 ± 92.9	237 ± 92.4	0.489
Blood chemistry				
Cr ¹⁷ (mg/dL)	1.44 ± 2.0	1.6 ± 2.5	1.38 ± 1.8	0.311
eGFR ¹⁸	65.15 ± 28.2	68.2 ± 30.2	64.1 ± 27.4	0.165
Corrected Ca ²⁴ (mg/dL)	9.2 ± 0.6	9.2 ± 0.8	9.2 ± 0.5	0.795
Mg ²⁵ (mg/dL)	1.67 ± 0.3	1.69 ± 0.3	1.66 ± 0.3	0.430
PO ₄ ²⁶ (mg/dL)	3.26 ± 0.8	3.4 ± 1.2	3.2 ± 0.6	0.033
AST ²⁷ (U/L)	29.8 ± 27.5	29.9 ± 30.5	29.8 ± 26.4	0.954
ALT ²⁸ (U/L)	20.5 ± 15.9	21.1 ± 20.4	20.2 ± 14.0	0.602
ALP ²⁹ (U/L)	91.4 ± 46.0	97.4 ± 46.5	89.2 ± 45.7	0.096
ESR ³⁰ (mm/h), n = 50	45.2 ± 26.5	41.6 ± 22.9	47.7 ± 28.8	0.421
FBS ³¹ (mg/dL), n = 332	100.6 ± 23.3	102.4 ± 23.5	99.9 ± 23.6	0.407
TSH ³² (μU/mL), n = 365	3.68 ± 15.3	7.15 ± 30.4	2.54 ± 2.2	0.013
25(OH)D (ng/mL), n = 329	26.8 ± 25.6	18.3 ± 10.4	31.1 ± 8.4	<0.001
PTH ³³ (pg/mL), n = 309	88.7 ± 246.2	151.5 ± 403.8	58.3 ± 92.4	0.002

¹BMI body mass index, ²RA rheumatoid arthritis, ³SLE systemic lupus erythematosus, ⁴COPD chronic obstructive pulmonary disease, ⁵VTE venous thromboembolism, ⁶CKD chronic kidney disease, ⁷T2DM type 2 diabetes, ⁸DLP dyslipidemia, ⁹SGLT2i sodium-glucose cotransporter-2 inhibitors, ¹⁰DPP4i dipeptidyl peptidase-4 inhibitors, ¹¹SSRI selective serotonin reuptake inhibitors, ¹¹Hb hemoglobin, ¹²WBC white blood cell count, ¹³PMN polymorphonuclear cell, ¹⁴ANC absolute neutrophil count, ¹⁵ALC absolute lymphocyte count, ¹⁶BUN blood urea nitrogen, ¹⁷Cr creatinine, ¹⁸eGFR estimated glomerular filtration rate (mL/min/1.73m²), ¹⁹Na serum sodium, ²⁰K serum potassium, ²¹Cl serum chloride, ²²HCO₃ serum bicarbonate, ²³Ca serum calcium, ²⁴Corrected Ca corrected calcium is calculated as following formula [corrected calcium = measured calcium + 0.8 (4-serum albumin)], ²⁵Mg serum magnesium, ²⁶PO₄ serum phosphate, ²⁷AST aspartate aminotransferase, ²⁸ALT alanine transaminase, ²⁹ALP alkaline phosphatase, ³⁰ESR erythrocyte sedimentation rate, ³¹FBS fasting-blood sugar, ³²TSH thyroid stimulating hormone, ³³PTH parathyroid hormone

Table 2 Demographics of patients classified by different 25(OH)D levels

Demographic	Vitamin D deficiency 25(OH) D < 20 ng/mL (n = 87)	Vitamin D insufficiency 25(OH) D 20-29.9 ng/mL (n = 129)	Vitamin D adequacy 25(OH) D ≥ 30 ng/mL (n = 113)	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	
25(OH)D level	13.83 ± 3.97	25.53 ± 2.8	38.03 ± 8.4	<0.001*
Age (years)	74.9 ± 10.5	76.8 ± 11.1	76.7 ± 11.2	0.397
Female (n, %)	72 (83.7%)	91 (70.0%)	81 (71.7%)	0.055
BMI ¹ (kg/m ²)	22.5 ± 3.8	21.8 ± 3.4	21.1 ± 3.5	0.024**
Fracture (n, %)				0.574
Hip	69 (79.1%)	98 (76.2%)	82 (72.6%)	
Vertebral	18 (20.9%)	31 (23.4%)	31 (27.4%)	
Comorbidities (n, %)				
RA ²	2 (2.3%)	1 (0.8%)	4 (3.5%)	0.345
SLE ³	2 (2.3%)	0 (0.0%)	3 (2.7%)	0.124
Liver disease	0 (0.0%)	4 (3.1%)	3 (2.7%)	0.270
CKD ⁶ stage 4 and 5	12 (13.8%)	13 (10.8%)	16 (14.2%)	0.706
T2DM ⁷	21 (24.1%)	24 (18.5%)	18 (15.9%)	0.305
BMD				
T-score	-2.8 ± 1.9	-2.7 ± 0.8	-2.6 ± 0.9	0.789
Z-score	-0.8 ± 1.0	-0.7 ± 1.0	-0.6 ± 0.9	0.572
T-Z difference	-1.9 ± 1.0	-1.9 ± 1.0	-2.0 ± 0.7	0.937
10-year probability of fractures				
Hip (FRAX-H)	4.8 ± 3.4	4.1 ± 2.9	4.3 ± 3.1	0.248
Major (FRAX-M)	9.2 ± 4.6	7.6 ± 3.9	7.6 ± 3.7	0.009***
Hematology				
Hb ⁹ (g/dL)	11.4±2.0	11.6±1.8	11.4±1.9	0.525
WBC ¹⁰ (10 ³ /μL)	9.3±3.8	9.7±3.7	9.4±3.5	0.667
Platelet (10 ³ /μL)	247.9 ± 92.2	232.8 ± 86.5	233.6 ± 88.0	0.416
Blood chemistry				
Cr ¹⁵ (mg/dL)	1.5 ± 2.5	1.2 ± 1.2	1.3 ± 1.2	0.459
eGFR ¹⁶	68.6 ± 27.6	69.3 ± 26.3	64.4 ± 28.1	0.349
Corrected Ca ²² (mg/dL)	9.2 ± 0.7	9.3 ± 0.6	9.2 ± 0.6	0.358
Mg ²³ (mg/dL)	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.2	0.673
PO ₄ ²⁴ (mg/dL)	3.4 ± 1.3	3.1 ± 0.6	3.2 ± 0.7	0.105
Albumin (g/dL)	3.7 ± 0.6	3.8 ± 0.5	3.7 ± 0.5	0.780
AST ²⁵ (U/L)	28.6 ± 19.1	27.9 ± 19.9	28.1 ± 18.6	0.964
ALT ²⁶ (U/L)	20.2 ± 15.4	20.9 ± 13.1	19.0 ± 12.3	0.562
ALP ²⁷ (U/L)	91.7 ± 34.2	89.8 ± 49.5	93.9 ± 52.7	0.798
PTH ²⁸ (pg/mL)	108.0 ± 302.7	49.2 ± 68.7	59.5 ± 109.0	0.066

¹BMI body mass index, ²RA rheumatoid arthritis, ³SLE systemic lupus erythematosus, ⁴COPD chronic obstructive pulmonary disease, ⁵VTE venous thromboembolism, ⁶CKD chronic kidney disease, ⁷T2DM type 2 diabetes, ⁸DLP dyslipidemia, ⁹Hb hemoglobin, ¹⁰WBC white blood cell count, ¹¹PMN polymorphonuclear cell, ¹²ANC absolute neutrophil count, ¹³ALC absolute lymphocyte count, ¹⁴BUN blood urea nitrogen, ¹⁵Cr creatinine, ¹⁶eGFR estimated glomerular filtration rate (mL/min/1.73m²), ¹⁷Na serum sodium, ¹⁸K serum potassium, ¹⁹Cl serum chloride, ²⁰HCO₃ serum bicarbonate, ²¹Ca serum calcium, ²²Corrected Ca corrected calcium is calculated as following formula [corrected calcium = measured calcium + 0.8 (4-serum albumin)], ²³Mg serum magnesium, ²⁴PO₄ serum phosphate, ²⁵AST aspartate aminotransferase, ²⁶ALT alanine transaminase, ²⁷ALP alkaline phosphatase, ²⁸PTH parathyroid hormone

*Significant difference between 25(OH)D < 20 ng/mL and 25(OH)D 20-30 ng/mL ($p = <0.001$), 25(OH)D < 20 ng/mL and 25(OH)D > 30 ng/mL ($p = <0.001$), 25(OH)D 20-30 ng/mL and 25(OH)D > 30 ng/mL ($p = <0.001$)

**Significant difference between 25(OH)D < 20 ng/mL and 25(OH)D > 30 ng/mL ($p = 0.019$)

***Significant difference between 25(OH)D < 20 ng/mL and 25(OH)D 20-30 ng/mL ($p = 0.016$), 25(OH)D < 20 ng/mL and 25(OH)D > 30 ng/mL ($p = 0.020$)

Table 3 Final multivariable fractional polynomial (MFP) logistic regression model after backward elimination

Predictors	Covariate transformation		β	95% CI		P-value
	df	Formula		LB ⁶	UB ⁷	
Intercept			-1.52	-1.85	-1.19	
Age (years)	1	Age-76.96	-0.08	-0.11	-0.05	<0.001
BMI ¹ (kg/m ²)	1	BMI-21.48	0.12	0.04	0.19	0.004
Corrected Ca ²	4	Ca ² -84.82	-0.57	-0.87	-0.26	<0.001
		Ca ³ -781.16	0.04	0.02	0.06	<0.001
PO ₄ ³ (mg/dL)	1	PO ₄ -3.29	0.36	0.07	0.65	0.015
TSH ⁴ (μ IU/mL)	1	TSH-3.68	0.06	-0.02	0.14	0.139
FRAX-H ⁵ (%)	1	FRAX-4.65	0.21	0.11	0.31	<0.001

¹BMI body mass index, ²Corrected Ca corrected calcium is calculated as following formula [corrected calcium = measured calcium + 0.8 (4-serum albumin)], ³PO₄ serum phosphate, ⁴TSH thyroid stimulating hormone, ⁵FRAX-H 10-year probability of hip fracture as calculated by BMI-based FRAX®, ⁶LB lower bound, ⁷UB upper bound

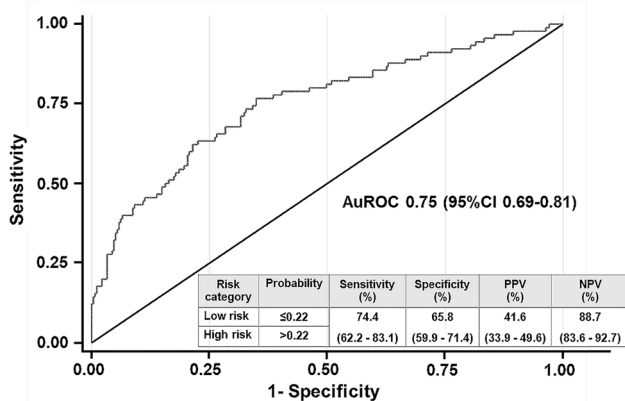


Fig. 2 Area under receiver operating characteristic (AuROC) curve of secondary osteoporosis predicted by predictive model (gray line) and 50% chance prediction (diagonal line). Risk categories of secondary osteoporosis diagnosis with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and their 95% confidence intervals were shown

constructed predictive model. The calibration plot illustrated an agreement between observed and predicted probabilities (Online Resource: Fig. 1). In addition, the developed model demonstrated good internal validity with minimal optimism (0.02, 95% CI -0.08 to 0.09) and overfitting (E:O ratio = 1.00, CITL ≤ 0.01, calibration slope = 1.00).

A risk category was created to provide an appropriate recommendation regarding a patient's risk (e.g., high and low risk). An optimum probability cut-off level was identified using the Youden index. As a result, a cut-off level of 0.22 demonstrated a maximum sensitivity of 74.4%, a specificity of 65.8%, a positive predictive value (PPV) of 41.6%, and a negative predictive value (NPV) of 88.7% (Fig. 2). The diagnostic indices of other cut-off values were demonstrated in Online Resource: Table 3. For practical use, the developed model was transformed into a web-applicable diagnostic

screening tool, which is available at: <https://www.calconic.com/calculator-widgets/secondary-osteoporosis-screening-tool/62f7c112d5da86001f8e3a25?layouts=true> (Online Resource: Fig. 2).

Discussion

This study reported epidemiological information on secondary osteoporosis in the elderly who presented with fragility fractures. We also identified that the patient's age, BMI, corrected calcium level, phosphate level, TSH, and 10-year probability of hip fractures calculated by BMI-based FRAX® were contributing factors for secondary osteoporosis. In addition, a diagnostic screening tool derived from the discovered risk factors demonstrated good diagnostic performance for secondary osteoporosis.

This study showed that 26.5% of apparently healthy elderly people who had no clinical clues for secondary osteoporosis but presented with fragility fractures had at least one specific contributing factor for osteoporosis. Since our study involved mainly postmenopausal women (75%), the prevalence of secondary osteoporosis in this study is consistent with the previously reported prevalence of 30% in postmenopausal women [3]. Even though GIO was previously shown as the most common cause of secondary osteoporosis, vitamin D deficiency was the most common etiology related to osteoporosis found in this current study. The prevalence of vitamin D deficiency in our enrolled patients was in the same range as shown in the previous reports done on postmenopausal Thais [33, 34]. Chailurkit and colleagues [33] reported a prevalence of vitamin D deficiency of 31.6% in postmenopausal women (mean age 67.5 ± 6.0 years). Furthermore, their findings demonstrated that osteoporotic patients, defined by the femoral neck BMD,

had significantly lower 25(OH)D levels compared to those without osteoporosis.

In our study, one-third of patients diagnosed with vitamin D deficiency had serum 25(OH)D of lower than 12 ng/mL, indicating severe vitamin D deficiency [32]. According to a bone histomorphometric study of iliac crest biopsy, Priemel and colleagues [35] demonstrated mineralization defect in patients with serum 25(OH)D lower than 30 ng/mL but the highest prevalence was illustrated in patients with 25(OH)D lower than 12 ng/mL. However, the mineralization defect was not present in all patients with serum 25(OH)D levels less than 12 ng/mL. SHPT and chronic calcium deficiency would result in hyperphosphaturia and hypophosphatemia, resulting in bone mineralization defects [32]. Therefore, hypocalcemia and hypophosphatemia are indispensable for the occurrence of osteomalacia in cases of vitamin D deficiency. In this study, SPHT secondary was demonstrated in patients with vitamin D deficiency, but the PTH level did not positively correlate with the severity of the vitamin D deficiency. In addition, no patients with severe vitamin D deficiency revealed clinical features and biochemical abnormalities suggesting osteomalacia, including bone pain, muscle weakness, hypocalcemia, hypophosphatemia, and hyperphosphatasia. Accordingly, we are certain that patients with severe vitamin D deficiency had a clinical diagnosis of osteoporosis without osteomalacia in the present study.

Identifying secondary causes among osteoporotic patients is crucial since secondary osteoporosis usually does not respond well to the primary osteoporosis treatment protocol [4]. Secondary osteoporosis could be found in a significant number of patients who had primary osteoporosis by first clinical impression. Therefore, screening for any possible secondary causes should be applied to all patients suspected of osteoporosis. Several studies demonstrated that various evaluations for secondary osteoporosis were beneficial in the diagnostic utility and cost-effectiveness [13–15]. For that reason, we developed a diagnostic model for secondary osteoporosis using six simple predictors, including the patient's age, BMI, FRAX-H calculated by BMI-based FRAX®, corrected calcium level, phosphate level, and TSH level. FRAX-M was not included in the model due to the insufficient data regarding the use of FRAX-M in predicting the risk of osteoporotic fractures in the Thai population [6, 7]. We believe that the developed diagnostic model could provide useful guidance for clinicians to provide further investigations in fragility fracture patients, entailing an appropriate treatment for re-fracture prevention. As we intended to use this predictive model as a screening tool, high sensitivity is crucial for early detection or ruling out a case with secondary osteoporosis. Patients with a risk for secondary osteoporosis of greater than 22% were classified as high-risk, for whom further investigation and specialist consultation were recommended. This cut-off level provides not only high sensitivity

but also high NPV. Therefore, if a patient was classified as low risk from our screening tool, the patient is 89% likely to have primary osteoporosis. The developed predictive model is practical since all predictors are simple and available in most scenarios, even in settings where healthcare resources are limited. Patient's age, BMI, and FRAX-H calculated by BMI-based FRAX® can be collected in routine patient evaluation. At the same time, calcium, phosphate, and TSH levels are simple laboratory tests that can be measured without special patient preparation. Therefore, we can assume that all predictors in the developed prediction model can be easily obtained during hospitalization for fragility fractures.

The older age and corrected calcium level of 9–10 mg/dL were protective factors for secondary osteoporosis. In contrast, the higher BMI, phosphate level, TSH level, and FRAX-H calculated by BMI-based FRAX® were risk factors for secondary osteoporosis. All of them contributed to the power of the predictive model; the power of the model significantly decreased if anyone was deleted. Age and weight are commonly recognized as traditional contributing factors for primary osteoporosis [36, 37]. Accordingly, patients with younger ages or higher BMI demonstrated higher risk and should be suspected of secondary osteoporosis [36]. In terms of FRAX-H, the high probability of hip fracture would derive from older age and a lower BMI [36]. A high probability of fractures in the context of a younger age and a higher BMI, according to our model, would indicate secondary osteoporosis.

Calcium and phosphate levels represent mineral homeostasis, which is tightly controlled by various hormones. Abnormal calcium and phosphate levels indicate abnormal mineral metabolism that usually associates with metabolic bone diseases. For example, hyperphosphatemia is usually demonstrated in chronic kidney disease-related metabolic bone disease (CKD-MBD) [27, 38]. Hypocalcemia usually indicates vitamin D deficiency [32] or SHPT [27, 38], while hypercalcemia is found in PHPT [26]. Multiple studies found high bone turnover and increased fracture risk in cases of hyperthyroidism or subclinical hyperthyroidism, whereas adults with hypothyroidism theoretically had a low bone turnover and a prolonged bone remodeling cycle [39, 40]. However, the adverse skeletal consequences of hypothyroidism in adults have never been established [39, 41]. TSH levels have been previously shown to be useful and cost-effective as part of secondary osteoporosis screening panels in determining overt and subclinical thyroid disease [14, 15]. Although the TSH level itself did not show a statistically significant correlation to secondary osteoporosis in this study, we decided to include this parameter due to its effects on bone turnover and its impact on the power of our constructed predictive model. In our study, 51 (13.9%) patients had elevated TSH with normal free thyroxine (free T4) and free triiodothyronine (free T3). In addition, most of

them had mild subclinical hypothyroidism (TSH elevation of <10 mIU/L) and were not indicated for thyroid hormone supplementation. No patients had been previously treated with thionamides or radioiodine therapy. This mild subclinical hypothyroidism could be from aging, since an increased prevalence of elevated TSH up to 15% in the population at the age of 70 years or older [42].

There are several strengths in this study. Our web-based diagnostic screening tool is simple and easy to use. With only six simple parameters, our tool allows clinicians to evaluate fragility fracture patients' risk of secondary osteoporosis. However, there are some limitations to be addressed. First, our prediction tool was developed using a relatively small number of patients, which included only a minimal number for model optimism. Second, our tool was based on a retrospective study, which is subjected to several biases. Excluding patients who received an incomplete evaluation for secondary osteoporosis has the potential for selection bias and could affect the incidence and probability of cases. Third, the method for evaluation for 25(OH)D levels was electrochemiluminescence immunoassay (ECLIA), not the liquid chromatography-tandem mass spectrometry (LC-MS) which is the gold-standard test for 25(OH)D levels. However, the Roche Elecsys® Vitamin D total III assay was also valid and reliable [43]. In addition, 25(OH)D levels were not available in all patients, which might alter the true prevalence of vitamin D deficiency in our study. Finally, although the developed model demonstrated good internal validity, external validation is mandatory to evaluate the generalizability of the tool.

In conclusion, specific causes of osteoporosis were demonstrated in 26.5% of apparent healthy elderly individuals presented with fragility fractures. The most common contributing factor for secondary osteoporosis was vitamin D deficiency, followed by GIO. We identified the patient's age, BMI, corrected calcium level, phosphate level, TSH level, and FRAX-H calculated by FRAX® as potential predictors for secondary osteoporosis. Subsequently, a diagnostic model for screening secondary osteoporosis was constructed using these simple clinical and biochemical parameters. This diagnostic screening tool may provide clinicians with guidance for further advanced investigations for secondary causes of osteoporosis.

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Data availability All data generated or analyzed during this study are included in this published article and supplementary online resource.

Declarations

Conflicts of interest Pitchaporn Phudphong, Mattabhorn Phimphilai, Worapaka Manosroi, Nath Adulkasem, and Tawika Kaewchur declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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