

Early Prediction Model for Osteoporotic Fracture in Type 2 Diabetes Patients: A Nomogram Approach Based on a Single-Center Retrospective Study

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Background: To address the high disability and mortality rates of osteoporotic fracture (OPF), a common complication of type 2 diabetes mellitus (T2DM), this study seeks to create an early OPF risk prediction model for T2DM patients.

Methods: A single-center retrospective study was conducted on 868 T2DM patients using Multi-dimensional data. The dataset was split into training and validation sets at an 8:2 ratio. Through logistic regression analyses, key predictive factors were pinpointed and incorporated into a Nomogram prediction model. The model's reliability, validity, and generalizability were assessed using various statistical methods, including the Hosmer-Lemeshow test, Receiver Operator Characteristic (ROC) curve analysis, and decision curve analysis. The validation set was used to test the model.

Results: Female gender (OR 2.681, 95% CI 1.046–6.803, P=0.04), age (OR 1.068, 95% CI 1.023–1.115, P=0.003), body mass index (BMI) (OR 0.912, 95% CI 0.851–0.979, P=0.010), blood lactic acid level (OR 0.747, 95% CI 0.597–0.935, P=0.011), lumbar T-score (OR 0.644, 95% CI 0.499–0.833, P=0.001), and femoral neck T-score (OR 0.412, 95% CI 0.292–0.602, P<0.001) were identified as independent factors predicting OPF in T2DM patients. Based on these factors, a Nomogram model was constructed. The model showed a high degree of agreement with actual data (Hosmer-Lemeshow test, P=0.406), with an Area Under the Curve (AUC) value of 0.831. It demonstrated good clinical benefits across different thresholds and excellent generalization ability on the validation set.

Conclusion: This study integrated key factors such as gender, age, BMI, lactic acid, lumbar spine, and femoral neck T-values to construct a Nomogram for predicting the risk of OPF in T2DM patients. This model can assist doctors in accurately assessing the risk of OPF in T2DM patients, facilitating early detection and timely treatment. It has significant clinical practical value.

Keywords: type 2 diabetes mellitus, osteoporosis, bone fracture, nomogram, risk prediction

Introduction

Type 2 diabetes mellitus (T2DM), recognized as a global epidemic by the World Health Organization, induces metabolic disorders that not only directly impair the function of multiple organs but also lead to a series of complications through specific pathological mechanisms. Among these, diabetic osteoporosis (DOP) has garnered widespread attention due to its unique pathological features—clinical observations reveal that patients with T2DM typically have higher bone mineral density (BMD), yet they experience significantly increased fracture rates compared to non-diabetic individuals (“diabetic bone paradox” phenomenon).¹ In-depth research indicates that the essence of this paradoxical phenomenon lies in changes to bone quality rather than merely bone quantity: the bone fragility in T2DM patients primarily stems from factors that degrade bone quality, such as disruption of bone microstructure, deposition of advanced glycation end

products (AGEs) in the bone matrix, and decreased bone turnover rate.² Hyperglycemia-induced oxidative stress, abnormal collagen cross-linking, and bone marrow fat infiltration constitute the key molecular pathological foundations.³

Notably, the formation of fracture risk in T2DM involves multidimensional pathogenic mechanisms: in addition to the intrinsic degradation of bone quality, complications such as visual impairment due to diabetic retinopathy, decreased balance resulting from peripheral neuropathy, and syncope related to cardiovascular diseases^{4,5} collectively form a cascade risk chain of “fall-fracture”. Meanwhile, specific antidiabetic medications, such as thiazolidinediones, accelerate bone loss,⁶ and SGLT2 inhibitors interfere with calcium and phosphorus metabolism,⁷ further exacerbating the imbalance in bone metabolism. The interaction of these complex mechanisms leads to systematic biases in the traditional FRAX assessment tool based on BMD⁸ for evaluating fracture risk in T2DM, while emerging imaging technologies such as quantitative CT and trabecular bone score⁹ are difficult to popularize due to their complex operation.

This study innovatively constructs a fracture prediction model that integrates multidimensional clinical characteristics of T2DM patients: by systematically incorporating demographic features (age, gender, BMI, etc.), metabolic parameters (HbA1c, lactate, etc.), complication profiles (retinopathy/neuropathy/vascular disease), medication exposure history (use of antidiabetic drugs such as thiazolidinediones and SGLT2 inhibitors), and BMD data, a visual nomogram is developed based on large-sample clinical data. It is expected that this tool will improve the early identification rate of fracture risk in T2DM and provide quantitative decision support for clinical formulation of individualized bone health management plans.

Materials and Methods

Study Design and Population

This study is a single-center study that retrospectively collected data from 868 patients with T2DM who received treatment at the Affiliated Hospital of Southwest Medical University from January 1, 2018, to December 31, 2022. These data were divided into a training set and a validation set with a split ratio of 0.8. To ensure the rigor of the study, we set clear criteria for patient selection. Specifically, we established strict inclusion and exclusion criteria. The inclusion criteria were as follows: i) patients must be clearly diagnosed with T2DM and be aged no more than 80 years old; ii) patients must complete bone mineral density testing through dual-energy X-ray absorptiometry (DXA); iii) the presence of fractures must be confirmed by at least one method among X-ray, computed tomography (CT), or magnetic resonance imaging (MRI). Meanwhile, we set the following exclusion criteria to ensure data validity and research accuracy: patients with type 1 diabetes or other types of diabetes, diabetic ketoacidosis, hyperosmolar hyperglycemic state, hyperparathyroidism, severe infections, severe liver or kidney dysfunction, severe cardiopulmonary disease (NYHA class III–IV), severe anemia (Hb <8 g/dL), history of hysterectomy or oophorectomy, glucocorticoid treatment in the past six months, and malignant tumors were excluded from the study (Figure 1). All protocols followed the ethical guidelines of Declaration of Helsinki, the study has been approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University, with approval number KY2023142. All studies strictly adhere to ethical norms, ensuring the safety and privacy of patient data.

Data Collection

We comprehensively collected basic information about the patients, including gender, age, smoking habits, drinking habits, and the duration of T2DM. Simultaneously, we recorded various physical indicators such as body mass index (BMI), visceral fat deposition (VFD), subcutaneous fat deposition (SFD), systolic blood pressure (SBP), and diastolic blood pressure (DBP). In addition, we collected fasting morning blood samples (drawn between 06:00 and 08:00 AM after ≥ 8 hours of fasting) to measure the following parameters: glycated hemoglobin (HbA1c), blood glucose levels, blood lactate levels, blood lipids, blood cell analysis, transaminase, glomerular filtration rate (GFR), etc. To more comprehensively assess the health status of patients, we also gathered data from echocardiography, ankle-brachial index (ABI), vibration perception threshold (VPT), and bone mineral density (BMD) examinations. Furthermore, the use of anti-diabetic medications, the occurrence of diabetic complications, and comorbidities such as hypertension and coronary heart disease were also within our collection scope.

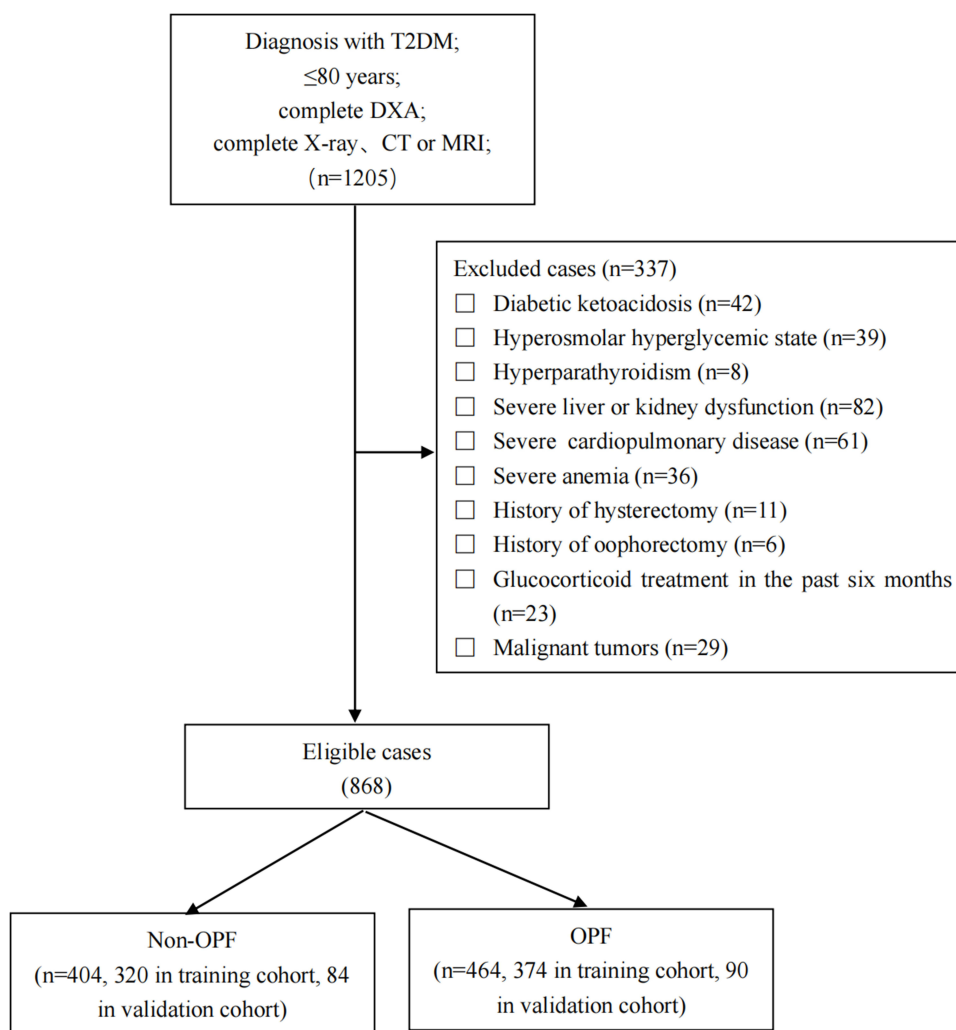


Figure 1 Flow chart for patient selection.

Diagnostic Criteria for OPFs

(1) Diagnosis based on DXA bone mineral density: $T\text{-score} = (\text{measured BMD} - \text{peak BMD of normal young adults of the same race and gender}) / \text{standard deviation of peak BMD of normal young adults of the same race and gender}$. Normal: $T\text{-score} \geq -1$; Osteopenia: $-2.5 < T\text{-score} < -1$; Osteoporosis: $T\text{-score} \leq -2.5$. (2) Diagnosis based on OPFs: A fragility fracture of the hip or vertebral body can be diagnosed as OPFs, irrespective of BMD measurements, even when the $T\text{-score}$ is ≥ -1.0 ; a fragility fracture of the proximal humerus, pelvis, or distal forearm with a BMD measurement showing low bone mass ($-2.5 < T\text{-score} < -1.0$) can also be diagnosed as OPFs. Finally, fractures caused by other underlying etiologies (such as primary or metastatic bone tumors, bone diseases, etc). need to be excluded.

Development and Evaluation of the Nomogram

Firstly, T2DM patients in the training set were divided into two groups: one with OPF and the other without (Non-OPF), serving as the control group. Through univariate logistic regression analysis, independent variables with a P-value less than 0.1 were screened out. Subsequently, these selected independent variables were incorporated into a multivariate logistic model to further identify independent variables with a P-value less than 0.05. Next, these significant independent variables were treated as predictors and integrated into the Nomogram model to construct a complete predictive framework. To more intuitively present the prediction results, prediction lines were drawn based on the scores of the predictors, and positioning was performed by accumulating them on the “total score” axis. In this way, by projecting

vertically to the bottom scale, the probability of OPFs in T2DM patients can be accurately estimated. After the model was constructed, a series of data validations were performed to ensure its reliability. First, the Hosmer-Lemeshow test was used to evaluate the goodness of fit between the model and actual data, that is, the goodness of fit of the model. Then, the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) were utilized to assess the model's discrimination, sensitivity, and specificity. Additionally, decision curve analysis (DCA) was employed to evaluate the clinical benefits of the model under different thresholds. Finally, the generalization ability of the model was tested using validation set data.

Statistical Analysis

For continuous data conforming to a normal distribution, the study accurately described them by calculating the mean and adding or subtracting the standard deviation. If the data exhibited a skewed distribution, the median (M) and interquartile range (specifically, the 25th to 75th percentiles, or P25-P75) were selected to represent the data distribution in detail. Additionally, for count data, the study adopted a percentage format for description. The study used R software version 4.2.2 for statistical analysis. When implementing statistical tests, the study consistently applied two-sided test methods and set the significance level at $P < 0.05$ to ensure that the conclusions drawn were statistically significant.

Results

General Characteristics

This study collected data from 1205 patients diagnosed with T2DM, aged no more than 80 years, and who had completed DXA scans as well as X-ray, CT, or MRI examinations. After screening, 337 patients who did not meet the inclusion criteria were excluded, leaving a total of 868 patients, including 404 patients without OPF and 464 patients with OPF (Figure 1). Subsequently, the patient dataset was split into a training cohort and a validation cohort at a ratio of 0.8. In this study, we used data from 694 T2DM patients in the training cohort to construct a nomogram and selected data from 174 patients in the validation cohort for validation. By comparing the variables of the two datasets, it was found that, apart from significant differences in EF (Ejection Fraction), UACR (Urinary Albumin/Creatinine Ratio), the use of biguanides, and prevalence of diabetic retinopathy ($P < 0.05$), most variables in the two datasets did not show significant statistical differences ($P > 0.05$) (Table 1).

Based on the diagnostic criteria for OPF, patients were divided into two groups: the OPF group, comprising 374 patients (53.9% of the total), and the Non-OPF group, consisting of 320 patients (46.1% of the total). Table 2 provides a detailed comparison of various aspects of data between these two groups. The analysis revealed significant statistical differences between the two groups in several variables ($P < 0.05$), including gender, age, duration of T2DM, drinking

Table 1 Baseline Characteristics of All Patients in the Training Cohort and Validation Cohort

Variables	Training Cohort (n=694)	Validation Cohort (n=174)	P value
OPF, n (%)			0.608
Yes	374 (53.9%)	90 (51.7%)	
No	320 (46.1%)	84 (48.3%)	
Sex, n (%)			0.710
Female	318 (45.8%)	77 (44.3%)	
Male	376 (54.2%)	97 (55.7%)	
Age (years), median (IQR)	61 (53, 69)	61 (54, 68)	0.945
Drinking, n (%)			0.844
No	480 (69.2%)	119 (68.4%)	
Yes	214 (30.8%)	55 (31.6%)	
Smoking, n (%)			0.862
No	510 (73.5%)	129 (74.1%)	
Yes	184 (26.5%)	45 (25.9%)	

(Continued)

Table 1 (Continued).

Variables	Training Cohort (n=694)	Validation Cohort (n=174)	P value
T2DM duration, n (%)			0.240
Newly	43 (6.2%)	3 (1.7%)	
<1 year	41 (5.9%)	11 (6.3%)	
1–3 years	51 (7.3%)	10 (5.7%)	
3–5 years	67 (9.7%)	20 (11.5%)	
5–10 years	138 (19.9%)	39 (22.4%)	
>10 years	354 (51%)	91 (52.3%)	
SBP (mmHg), median (IQR)	136 (125, 148)	136 (122, 147)	0.099
DBP (mmHg), median (IQR)	78 (72, 85)	77 (70, 84)	0.053
BMI (Kg/m ²), median (IQR)	24.6 (22.8, 26.5)	24.8 (23.1, 26.575)	0.509
VFD (cm ²), median (IQR)	75 (63, 95)	79 (61.5, 96.75)	0.773
SFD (cm ²), median (IQR)	144 (129.25, 167)	144 (129.25, 169.25)	0.721
HbA1c (%), median (IQR)	9 (8.3, 10.075)	8.8 (7.8, 9.7)	0.107
Glucose (mmol/L), median (IQR)	12.08 (8.2375, 16.815)	11.15 (7.4425, 15.55)	0.080
Lactate (mmol/L), median (IQR)	2.79 (2.2125, 3.5075)	2.765 (2.2125, 3.33)	0.485
EF (%), median (IQR)	65 (61, 68)	65 (63, 68)	0.049
E/A, median (IQR)	0.743 (0.637, 0.850)	0.75 (0.659, 0.939)	0.125
Right-foot VPT (V), median (IQR)	15 (12, 21)	15 (12, 20)	0.892
Left-foot VPT (V), median (IQR)	15 (12, 20)	15 (12, 20)	0.985
Right ABI, median (IQR)	1.13 (1.08, 1.1875)	1.14 (1.07, 1.17)	0.829
Left ABI, median (IQR)	1.13 (1.07, 1.17)	1.125 (1.0625, 1.18)	0.560
WBC (10 ⁹ /L), median (IQR)	6.4 (5.4, 7.5)	6.2 (5.3, 7.4)	0.448
Neu-R (%), median (IQR)	64.5 (58, 70.275)	64.15 (57.675, 70.075)	0.782
Lym-R (%), median (IQR)	26.55 (21.225, 31.9)	27 (21.925, 33.775)	0.302
Mon-R (%), median (IQR)	6 (5.1, 7.1)	5.8 (4.9, 6.9)	0.122
RBC (10 ¹² /L), median (IQR)	4.5 (4.1, 4.9)	4.5 (4.255, 4.8)	0.389
HGB (g/L), median (IQR)	137 (124, 147)	136 (128, 147.75)	0.690
PLT (10 ⁹ /L), median (IQR)	202 (165, 240.75)	195.75 (161, 234.75)	0.266
ALT (U/L), median (IQR)	20 (15.725, 30.4)	21.3 (16.05, 30.65)	0.333
AST (U/L), median (IQR)	20.25 (16.4, 25.6)	20.1 (16.425, 26.075)	0.757
GGT (U/L), median (IQR)	23.1 (16.3, 38.675)	24.9 (17, 33.7)	0.724
LDH (U/L), median (IQR)	184.55 (171.95, 184.55)	184.55 (171.95, 184.55)	0.506
Crea (μmol/L), median (IQR)	63.3 (52.5, 77.075)	64.75 (54, 77.45)	0.503
GFR (mL/min), median (IQR)	97.1 (84.3, 107)	97.1 (81.225, 106.35)	0.592
TC (mmol/L), median (IQR)	4.5 (3.8, 5.3)	4.4 (3.625, 5.2)	0.069
TG (mmol/L), median (IQR)	1.7 (1.1, 2.475)	1.6 (1.2, 2.4)	0.891
HDL-c (mmol/L), median (IQR)	1.1 (0.9, 1.3)	1.1 (0.8, 1.3)	0.109
LDL-c (mmol/L), median (IQR)	2.7 (2, 3.3)	2.6 (1.9, 3.3)	0.132
Apo-AI (mmol/L), median (IQR)	1.4 (1.2, 1.5075)	1.3 (1.1, 1.5)	0.201
Apo-B (mmol/L), median (IQR)	0.9 (0.7, 1)	0.8 (0.7, 1)	0.175
UACR (mg/gcr), median (IQR)	21.95 (10.925, 65.65)	20.2 (10.55, 29.475)	0.030
BMD			
Lumber-T score, median (IQR)	-1.375 (-1.375, -0.975)	-1.375 (-1.519, -0.956)	0.372
Femoral neck-T score, median (IQR)	-1.3 (-1.3, -1.2)	-1.3 (-1.5, -1.1)	0.621
Ward's triangle-T score, median (IQR)	-1.6 (-1.6, -1.3)	-1.6 (-1.675, -1.3)	0.692
The use of Anti-diabetes drug			
Biguanide, n (%)			0.040
No	175 (25.2%)	31 (17.8%)	
Yes	519 (74.8%)	143 (82.2%)	

(Continued)

Table 1 (Continued).

Variables	Training Cohort (n=694)	Validation Cohort (n=174)	P value
Sulfonylureas, n (%)			0.318
No	414 (59.7%)	111 (63.8%)	
Yes	280 (40.3%)	63 (36.2%)	
Glinides, n (%)			0.394
No	676 (97.4%)	172 (98.9%)	
Yes	18 (2.6%)	2 (1.1%)	
Thiazolidines, n (%)			0.397
No	647 (93.2%)	159 (91.4%)	
Yes	47 (6.8%)	15 (8.6%)	
Glycosidase Inhibitors, n (%)			0.637
No	542 (78.1%)	133 (76.4%)	
Yes	152 (21.9%)	41 (23.6%)	
SGLT2 inhibitors, n (%)			0.054
No	619 (89.2%)	146 (83.9%)	
Yes	75 (10.8%)	28 (16.1%)	
DPP4 inhibitors, n (%)			0.059
No	638 (91.9%)	152 (87.4%)	
Yes	56 (8.1%)	22 (12.6%)	
GLP1 agonists, n (%)			1.000
No	677 (97.6%)	170 (97.7%)	
Yes	17 (2.4%)	4 (2.3%)	
Insulin, n (%)			0.636
No	377 (54.3%)	98 (56.3%)	
Yes	317 (45.7%)	76 (43.7%)	
Diabetic complications			
Diabetic peripheral neuropathy, n (%)			0.199
No	146 (21%)	29 (16.7%)	
Yes	548 (79%)	145 (83.3%)	
Diabetic autonomic neuropathy, n (%)			0.739
No	460 (66.3%)	113 (64.9%)	
Yes	234 (33.7%)	61 (35.1%)	
Diabetic retinopathy, n (%)			0.022
No	535 (77.1%)	148 (85.1%)	
Yes	159 (22.9%)	26 (14.9%)	
Diabetic nephropathy, n (%)			0.113
No	463 (66.7%)	127 (73%)	
Yes	231 (33.3%)	47 (27%)	
Diabetic foot disease, n (%)			0.439
No	670 (96.5%)	170 (97.7%)	
Yes	24 (3.5%)	4 (2.3%)	
Comorbidities			
Hypertension, n (%)			0.231
No	300 (43.2%)	84 (48.3%)	
Yes	394 (56.8%)	90 (51.7%)	
Coronary heart disease, n (%)			0.835
No	575 (82.9%)	143 (82.2%)	
Yes	119 (17.1%)	31 (17.8%)	
Carotid artery plaque, n (%)			0.078
No	363 (52.3%)	78 (44.8%)	
Yes	331 (47.7%)	96 (55.2%)	

(Continued)

Table 1 (Continued).

Variables	Training Cohort (n=694)	Validation Cohort (n=174)	P value
Fatty liver, n (%)			0.841
No	401 (57.8%)	102 (58.6%)	
Yes	293 (42.2%)	72 (41.4%)	
Hyperlipidemia, n (%)			0.198
No	345 (49.7%)	77 (44.3%)	
Yes	349 (50.3%)	97 (55.7%)	

Note: Bold values: *P* value < 0.05.

Abbreviations: OPF, Osteoporotic fracture; T2DM, Type 2 diabetes mellitus; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; BMI, Body mass index; VFD, Visceral fat deposition; SFD, Subcutaneous fat deposition; HbA1c, Hemoglobin A1c; EF, Ejection fraction; VPT, Vibration perception threshold; ABI, Ankle Brachial Index; WBC, White blood cell; Neu-R, Neutrophil cell rate; Lym-R, Lymphocyte rate; Mon-R, Monocyte rate; RBC, Red blood cell; HGB, Hemoglobin; PLT, Platelets; ALT, Glutamic pyruvic transaminase; AST, Glutamic oxaloacetic transaminase; GGT, Glutamyl transpeptidase; LDH, Lactate Dehydrogenase; Crea, Creatinine; GFR, Glomerular filtration rate; TC, Total cholesterol; TG, Triglyceride; HDL-c, High-density lipoprotein; LDL-c, Low-density lipoprotein; Apo-A1, Apolipoprotein A1; Apo-B, Apolipoprotein B; UACR, Urinary Albumin/Creatinine Ratio; BMD, Bone mineral density; SGLT2, Sodium-dependent glucose transporters 2; DPP4, Dipeptidyl peptidase-4; GLP1, Glucagon-like peptide-1.

Table 2 Baseline Characteristics of All Patients in the Non-OPF Group and OPF Group

Characteristics	Non-OPF (n=320)	OPF (n=374)	P value
Sex, n (%)			< 0.001
Male	227 (70.9%)	149 (39.8%)	
Female	93 (29.1%)	225 (60.2%)	
Age (years), median (IQR)	55 (49, 66)	65 (56, 71)	< 0.001
T2DM duration, n (%)			0.012
Newly	25 (7.8%)	18 (4.8%)	
<1 year	27 (8.4%)	14 (3.7%)	
1–3 years	26 (8.1%)	25 (6.7%)	
3–5 years	34 (10.6%)	33 (8.8%)	
5–10 years	65 (20.3%)	73 (19.5%)	
>10 years	143 (44.7%)	211 (56.4%)	
Drinking, n (%)			< 0.001
No	197 (61.6%)	283 (75.7%)	
Yes	123 (38.4%)	91 (24.3%)	
Smoking, n (%)			< 0.001
No	209 (65.3%)	301 (80.5%)	
Yes	111 (34.7%)	73 (19.5%)	
SBP (mmHg), median (IQR)	136 (123, 146)	137 (126, 149)	0.098
DBP (mmHg), median (IQR)	79 (72, 86)	78 (71, 83)	0.003
BMI (Kg/m ²), median (IQR)	24.9 (23.6, 26.93)	24.4 (21.825, 25.8)	< 0.001
VFD (cm ²), median (IQR)	81 (71, 102.25)	74 (55, 88)	< 0.001
SFD (cm ²), median (IQR)	150 (138.75, 169)	144 (124, 164)	0.014
HbA1c (%), median (IQR)	9.3 (8.675, 10.5)	8.8 (8.1, 9.6)	0.006
Glucose (mmol/L), median (IQR)	12.785 (8.873, 18.267)	11.495 (7.875, 16.22)	0.003
Lactate (mmol/L), median (IQR)	2.99 (2.358, 3.715)	2.69 (2.083, 3.318)	< 0.001
EF (%), median (IQR)	65 (61, 67)	65 (61, 68)	0.686
E/A, median (IQR)	0.75 (0.648, 0.907)	0.733 (0.631, 0.824)	0.034
Right-foot VPT (V), median (IQR)	15 (12, 20)	15 (12, 22)	0.169
Left-foot VPT (V), median (IQR)	15 (12, 19)	15 (12, 22)	0.016
Right ABI, median (IQR)	1.12 (1.07, 1.18)	1.13 (1.08, 1.19)	0.233
Left ABI, median (IQR)	1.12 (1.07, 1.17)	1.13 (1.08, 1.17)	0.671

(Continued)

Table 2 (Continued).

Characteristics	Non-OPF (n=320)	OPF (n=374)	P value
WBC (10 ⁹ /L), median (IQR)	6.5 (5.5, 7.7)	6.2 (5.4, 7.2)	0.012
NEU-R (%), median (IQR)	64 (57.575, 69.875)	64.8 (58.675, 70.475)	0.166
LYM-R (%), median (IQR)	27.15 (21.475, 32.225)	26 (21.125, 31.25)	0.243
MON-R (%), median (IQR)	6.1 (5.1, 7.325)	5.9 (5, 7)	0.217
RBC (10 ¹² /L), median (IQR)	4.7 (4.3, 5.1)	4.4 (4, 4.7)	< 0.001
HGB (g/L), median (IQR)	142 (128, 155)	133.5 (121, 143)	< 0.001
PLT (10 ⁹ /L), median (IQR)	206 (167, 246.25)	196 (160.75, 238.75)	0.045
ALT (U/L), median (IQR)	20.8 (16.325, 35.025)	19.75 (15.225, 27.6)	0.003
AST (U/L), median (IQR)	20.15 (16.3, 25.6)	20.45 (16.525, 25.575)	0.981
GGT (U/L), median (IQR)	29.05 (19.275, 43.225)	20.15 (14.7, 32.2)	< 0.001
LDH (U/L), median (IQR)	179.7 (171.95, 184.55)	184.55 (171.95, 184.55)	0.043
Crea (μmol/L), median (IQR)	65.2 (54.625, 79.85)	61.6 (50.75, 75.225)	0.008
GFR (mL/min), median (IQR)	100.8 (89, 111.12)	94.25 (81.1, 103.65)	< 0.001
TC (mmol/L), median (IQR)	4.5 (3.775, 5.4)	4.4 (3.8, 5.175)	0.226
TG (mmol/L), median (IQR)	1.8 (1.3, 2.7)	1.5 (1.1, 2.1)	< 0.001
HDL-c (mmol/L), median (IQR)	1.1 (0.9, 1.2)	1.1 (1, 1.4)	< 0.001
LDL-c (mmol/L), median (IQR)	2.7 (2.1, 3.5)	2.7 (2, 3.2)	0.185
Apo-AI (mmol/L), median (IQR)	1.3 (1.1, 1.5)	1.4 (1.285, 1.6)	< 0.001
Apo-B (mmol/L), median (IQR)	0.9 (0.7, 1.1)	0.8 (0.7, 1)	< 0.001
UACR (mg/gcr), median (IQR)	23.1 (10.975, 63.25)	20.7 (10.875, 66.175)	0.839
BMD			
Lumbar-T score, median (IQR)	-0.975 (-1.375, -0.24375)	-1.375 (-1.825, -0.975)	< 0.001
Femoral neck-T score, median (IQR)	-1.2 (-1.3, -0.5)	-1.3 (-1.6, -1.2)	< 0.001
Ward's triangle-T score, median (IQR)	-1.3 (-1.6, -0.8)	-1.6 (-1.7, -1.3)	< 0.001
The use of anti-diabetes drug			
Biguanides, n (%)			0.903
No	80 (25%)	95 (25.4%)	
Yes	240 (75%)	279 (74.6%)	
Sulfonylureas, n (%)			0.864
No	192 (60%)	222 (59.4%)	
Yes	128 (40%)	152 (40.6%)	
Glinides, n (%)			0.533
No	313 (97.8%)	363 (97.1%)	
Yes	7 (2.2%)	11 (2.9%)	
Thiazolidines, n (%)			0.839
No	299 (93.4%)	348 (93%)	
Yes	21 (6.6%)	26 (7%)	
Glycosidase Inhibitors, n (%)			0.041
No	261 (81.6%)	281 (75.1%)	
Yes	59 (18.4%)	93 (24.9%)	
SGLT2 inhibitors, n (%)			0.184
No	280 (87.5%)	339 (90.6%)	
Yes	40 (12.5%)	35 (9.4%)	
DPP4 inhibitors, n (%)			0.611
No	296 (92.5%)	342 (91.4%)	
Yes	24 (7.5%)	32 (8.6%)	
GLP-1 agonists, n (%)			0.002
No	306 (95.6%)	371 (99.2%)	
Yes	14 (4.4%)	3 (0.8%)	

(Continued)

Table 2 (Continued).

Characteristics	Non-OPF (n=320)	OPF (n=374)	P value
Insulin, n (%)			0.161
No	183 (57.2%)	194 (51.9%)	
Yes	137 (42.8%)	180 (48.1%)	
Diabetic complications			
Diabetic peripheral neuropathy, n (%)			0.046
No	78 (24.4%)	68 (18.2%)	
Yes	242 (75.6%)	306 (81.8%)	
Diabetic autonomic neuropathy, n (%)			0.203
No	220 (68.8%)	240 (64.2%)	
Yes	100 (31.2%)	134 (35.8%)	
Diabetic retinopathy, n (%)			0.132
No	255 (79.7%)	280 (74.9%)	
Yes	65 (20.3%)	94 (25.1%)	
Diabetic nephropathy, n (%)			0.570
No	217 (67.8%)	246 (65.8%)	
Yes	103 (32.2%)	128 (34.2%)	
Diabetic foot disease, n (%)			0.389
No	311 (97.2%)	359 (96%)	
Yes	9 (2.8%)	15 (4%)	
Comorbidities			
Hypertension, n (%)			0.473
No	143 (44.7%)	157 (42%)	
Yes	177 (55.3%)	217 (58%)	
Coronary heart disease, n (%)			0.073
No	274 (85.6%)	301 (80.5%)	
Yes	46 (14.4%)	73 (19.5%)	
Carotid artery plaque, n (%)			0.076
No	179 (55.9%)	184 (49.2%)	
Yes	141 (44.1%)	190 (50.8%)	
Fatty liver, n (%)			0.001
No	164 (51.2%)	237 (63.4%)	
Yes	156 (48.8%)	137 (36.6%)	
Hyperlipidemia, n (%)			< 0.001
No	137 (42.8%)	208 (55.6%)	
Yes	183 (57.2%)	166 (44.4%)	

Note: Bold values: *P* value < 0.05.

Abbreviations: OPF, Osteoporotic fracture; T2DM, Type 2 diabetes mellitus; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; BMI, Body mass index; VFD, Visceral fat deposition; SFD, Subcutaneous fat deposition; HbA1c, Hemoglobin A1c; EF, Ejection fraction; VPT, Vibration perception threshold; ABI, Ankle Brachial Index; WBC, White blood cell; Neu-R, Neutrophil cell rate; Lym-R, Lymphocyte rate; Mon-R, Monocyte rate; RBC, Red blood cell; HGB, Hemoglobin; PLT, Platelets; ALT, Glutamic pyruvic transaminase; AST, Glutamic oxaloacetic transaminase; GGT, Glutamyl transpeptidase; LDH, Lactate Dehydrogenase; Crea, Creatinine; GFR, Glomerular filtration rate; TC, Total cholesterol; TG, Triglyceride; HDL-c, High-density lipoprotein; LDL-c, Low-density lipoprotein; Apo-A1, Apolipoprotein A1; Apo-B, Apolipoprotein B; UACR, Urinary Albumin/Creatinine Ratio; BMD, Bone mineral density; SGLT2, Sodium-dependent glucose transporters 2; DPP4, Dipeptidyl peptidase-4; GLP1, Glucagon-like peptide-1.

and smoking habits, DBP, BMI VFD, SFD, HbA1c, blood glucose and lactic acid levels, E/A ratio, left foot VPT, white blood cell and red blood cell counts, hemoglobin concentration, platelet count, and biochemical indicators such as Alanine Aminotransferase (ALT), Gamma-Glutamyl Transferase (GGT), Lactate Dehydrogenase (LDH), serum creatinine, and GFR. Additionally, there were significant differences in Triglyceride (TG) and HDL-c (High-Density Lipoprotein Cholesterol) concentrations, Apolipoprotein A1 (Apo-A1) and Apolipoprotein B (Apo-B), BMD, the use of hypoglycemic drugs such as alpha-glucosidase inhibitors and Glucagon-Like Peptide-1 (GLP-1) agonists, and the prevalence of diabetic peripheral neuropathy, fatty liver, and hyperlipidemia.

Predictive Factor Screening

Given the significant differences between the OPF and Non-OPF groups in multiple variables, independent predictive factors were identified through univariate and multivariate logistic regression analyses. The results, presented in Table 3, indicate that female gender and “old” age are risk factors (OR>1, P<0.05), and the other four (“higher” BMI, serum lactic acid concentration, lumber T-score, and femoral T-score) are protective factors (OR<1, P<0.05). Particularly noteworthy is that this study, for the first time, reveals the correlation between serum lactic acid levels and the occurrence of OPF in patients with T2DM (OR 0.747, 95% CI 0.597–0.935, P = 0.011). This finding provides a new perspective and basis for predicting models of OPF in T2DM.

Table 3 Univariate and Multivariate Logistic Regression Analyses for Screening Predictors

Characteristics	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Sex				
Male	Reference		Reference	
Female	3.686 (2.682–5.065)	< 0.001	2.681 (1.046–6.803)	0.040
Age (years)	1.075 (1.058–1.092)	< 0.001	1.068 (1.023–1.115)	0.003
T2DM duration				
Newly	Reference		Reference	
<1 year	0.720 (0.297–1.745)	0.467	0.491 (0.161–1.497)	0.211
1–3 years	1.335 (0.590–3.025)	0.488	0.824 (0.290–2.338)	0.715
3–5 years	1.348 (0.623–2.918)	0.449	0.601 (0.221–1.636)	0.319
5–10 years	1.560 (0.781–3.116)	0.208	0.799 (0.326–1.959)	0.625
>10 years	2.049 (1.078–3.894)	0.028	0.654 (0.277–1.544)	0.333
Drinking				
No	Reference		Reference	
Yes	0.515 (0.372–0.714)	< 0.001	1.492 (0.856–2.603)	0.158
Smoking				
No	Reference		Reference	
Yes	0.457 (0.324–0.644)	< 0.001	0.915 (0.515–1.626)	0.762
SBP (mmHg)	1.007 (0.999–1.015)	0.096	0.995 (0.977–1.012)	0.533
DBP (mmHg)	0.980 (0.966–0.995)	0.007	1.004 (0.976–1.033)	0.767
BMI (Kg/m ²)	0.895 (0.853–0.939)	< 0.001	0.912 (0.851–0.979)	0.010
VFD (cm ²)	0.991 (0.986–0.996)	< 0.001	0.999 (0.991–1.006)	0.763
SFD (cm ²)	0.998 (0.995–1.001)	0.111		
HbA1c (%)	0.944 (0.877–1.015)	0.121		
Glucose (mmol/L)	0.973 (0.953–0.993)	0.010	1.014 (0.986–1.043)	0.323
Lactate (mmol/L)	0.624 (0.525–0.741)	< 0.001	0.747 (0.597–0.935)	0.011
EF (%)	1.008 (0.978–1.038)	0.610		
E/A	0.522 (0.318–0.859)	0.010	1.042 (0.556–1.921)	0.894
Right-foot VPT (V)	1.010 (0.992–1.029)	0.263		
Left-foot VPT (V)	1.017 (0.999–1.036)	0.063		
Right ABI	1.271 (0.318–5.086)	0.735		
Left ABI	0.689 (0.173–2.738)	0.596		
WBC (10 ⁹ /L)	0.874 (0.802–0.953)	0.002	0.979 (0.873–1.099)	0.722
NEU-R (%)	1.008 (0.993–1.024)	0.293		
LYM-R (%)	0.994 (0.976–1.012)	0.483		
MON-R (%)	0.957 (0.886–1.035)	0.276		
RBC (10 ¹² /L)	0.867 (0.711–1.058)	0.161		
HGB (g/L)	0.975 (0.967–0.983)	< 0.001	1.002 (0.990–1.015)	0.724

(Continued)

Table 3 (Continued).

Characteristics	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
PLT (10 ⁹ /L)	0.999 (0.998–1.001)	0.276		
ALT (U/L)	0.984 (0.976–0.993)	< 0.001	0.998 (0.986–1.011)	0.806
AST (U/L)	0.997 (0.986–1.009)	0.628		
GGT (U/L)	0.994 (0.989–0.998)	0.006	1.000 (0.994–1.005)	0.873
LDH (U/L)	1.001 (0.993–1.010)	0.726		
Crea (μmol/L)	0.991 (0.983–0.998)	0.013	0.984 (0.941–1.029)	0.484
GFR (mL/min)	0.981 (0.973–0.988)	< 0.001	0.986 (0.937–1.038)	0.596
TC (mmol/L)	0.893 (0.796–1.002)	0.053	0.870 (0.730–1.038)	0.122
TG (mmol/L)	0.821 (0.741–0.910)	< 0.001	1.143 (0.985–1.327)	0.079
HDL-c (mmol/L)	4.248 (2.529–7.134)	< 0.001	1.333 (0.666–2.670)	0.417
LDL-c (mmol/L)	0.875 (0.752–1.019)	0.086	1.202 (0.864–1.672)	0.274
Apo-A1 (mmol/L)	4.797 (2.658–8.658)	< 0.001	1.749 (0.620–4.932)	0.291
Apo-B (mmol/L)	0.354 (0.199–0.630)	< 0.001	0.560 (0.212–1.478)	0.242
UACR (mg/gcr)	1.000 (1.000–1.000)	0.757		
BMD				
Lumbar-T score	0.386 (0.311–0.479)	< 0.001	0.644 (0.499–0.833)	0.001
Femoral neck-T score	0.259 (0.189–0.354)	< 0.001	0.412 (0.292–0.602)	< 0.001
Ward's triangle-T score	0.355 (0.272–0.463)	< 0.001	0.984 (0.668–1.451)	0.935
The use of anti-diabetes drug				
Biguanide				
No	Reference			
Yes	0.979 (0.694–1.381)	0.903		
Sulfonylureas				
No	Reference			
Yes	1.027 (0.758–1.392)	0.864		
Glinides				
No	Reference			
Yes	1.355 (0.519–3.537)	0.535		
Thiazolidines				
No	Reference			
Yes	1.064 (0.586–1.930)	0.839		
Glycosidase Inhibitors				
No	Reference		Reference	
Yes	1.464 (1.014–2.114)	0.042	1.267 (0.792–2.025)	0.324
SGLT2 inhibitors				
No	Reference			
Yes	0.723 (0.447–1.168)	0.185		
DPP4 inhibitors				
No	Reference			
Yes	1.154 (0.665–2.003)	0.611		
GLP1 agonists				
No	Reference		Reference	
Yes	0.177 (0.050–0.621)	0.007	0.300 (0.069–1.293)	0.106
Insulin				
No	Reference			
Yes	1.239 (0.918–1.673)	0.161		

(Continued)

Table 3 (Continued).

Characteristics	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Diabetic complications				
Diabetic peripheral neuropathy				
No	Reference		Reference	
Yes	1.450 (1.006–2.092)	0.047	0.833 (0.496–1.398)	0.489
Diabetic autonomic neuropathy				
No	Reference			
Yes	1.228 (0.895–1.687)	0.204		
Diabetic retinopathy				
No	Reference			
Yes	1.317 (0.920–1.886)	0.133		
Diabetic nephropathy				
No	Reference			
Yes	1.096 (0.798–1.505)	0.570		
Diabetic foot disease				
No	Reference			
Yes	1.444 (0.623–3.345)	0.392		
Comorbidities				
Hypertension				
No	Reference			
Yes	1.117 (0.826–1.509)	0.473		
Coronary heart disease				
No	Reference		Reference	
Yes	1.445 (0.965–2.163)	0.074	0.756 (0.445–1.285)	0.302
Carotid artery plaque				
No	Reference		Reference	
Yes	1.311 (0.971–1.769)	0.077	1.453 (0.967–2.182)	0.072
Fatty liver				
No	Reference		Reference	
Yes	0.608 (0.448–0.823)	0.001	0.839 (0.548–1.286)	0.422
Hyperlipidemia				
No	Reference		Reference	
Yes	0.597 (0.442–0.807)	< 0.001	0.791 (0.506–1.235)	0.302

Note: Bold values: *P* value < 0.05.

Abbreviations: OPF, Osteoporotic fracture; T2DM, Type 2 diabetes mellitus; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; BMI, Body mass index; VFD, Visceral fat deposition; SFD, Subcutaneous fat deposition; HbA1c, Hemoglobin A1c; EF, Ejection fraction; VPT, Vibration perception threshold; ABI, Ankle Brachial Index; WBC, White blood cell; Neu-R, Neutrophil cell rate; Lym-R, Lymphocyte rate; Mon-R, Monocyte rate; RBC, Red blood cell; HGB, Hemoglobin; PLT, Platelets; ALT, Glutamic pyruvic transaminase; AST, Glutamic oxaloacetic transaminase; GGT, Glutamyl transpeptidase; LDH, Lactate Dehydrogenase; Crea, Creatinine; GFR, Glomerular filtration rate; TC, Total cholesterol; TG, Triglyceride; HDL-c, High-density lipoprotein; LDL-c, Low-density lipoprotein; Apo-A1, Apolipoprotein A1; Apo-B, Apolipoprotein B; UACR, Urinary Albumin/Creatinine Ratio; BMD, Bone mineral density; SGLT2, Sodium-dependent glucose transporters 2; DPP4, Dipeptidyl peptidase-4; GLP1, Glucagon-like peptide-1.

Development of a Risk Prediction Nomogram

Based on the six key risk factors, a multivariable logistic regression model was constructed (Table 4). These factors were then integrated into the nomogram (Figure 2). For patients with T2DM, the nomogram model demonstrates that a patient's total score is directly proportional to their probability of having OPF. To quantify the risk of OPF, the following prediction formula was adopted: OPF linear predictor = 0.884 (if the patient is female) + 0.065 × age (years) – 0.305 × serum lactic acid concentration (mmol/L) – 0.070 × BMI (Kg/m²) – 0.476 × lumbar spine T-score – 0.788 × femoral neck T-score – 2.974. Furthermore, to calculate a patient's probability of developing OPF, the following formula was used: OPF probability = 1 / (1 + e^{-(linear predictor)}). These calculations allow for a more precise assessment of the risk of OPF in patients with T2DM.

Table 4 The Logistic Regression of Six Factors for Constructing Model

Characteristics	Beta	OR	95% CI Low	95% CI High	P value
Sex					
Male		Reference			
Female	0.884	2.422	1.656	3.542	<0.001
Age (years)	0.065	1.067	1.048	1.087	<0.001
BMI (Kg/m ²)	-0.070	0.933	0.881	0.987	0.017
Lactate (mmol/L)	-0.305	0.737	0.602	0.90903	0.003
Lumbar-T score	-0.476	0.621	0.487	0.793	<0.001
Femoral neck-T score	-0.788	0.455	0.322	0.642	<0.001

Note: Bold values: P value < 0.05.

Predictive Accuracy and Net Benefit of the Nomogram

In this study, the Hosmer-Lemeshow test was used to verify the agreement between the constructed OPF prediction nomogram and actual data. The resulting P-value of 0.406 indicates no significant difference between the predicted and actual observed values, demonstrating good model fit (Figure 3A). Subsequently, the ROC curve and AUC value were employed to evaluate the model's discriminatory ability, sensitivity, and specificity. The results showed an AUC of 0.831 (95% CI 0.801–0.861), a sensitivity of 0.802, and a specificity of 0.697, indicating high diagnostic performance of the model in predicting OPF (Figure 3B). Additionally, DCA analysis revealed that the prediction model exhibits good clinical net benefit across different thresholds (Figure 3C).

Finally, the generalization ability of the model was tested on validation dataset using the aforementioned methods. The test results showed a Hosmer-Lemeshow test P-value of 0.138 (Figure 3D) and an AUC value of 0.847 (95% CI 0.791–0.902) (Figure 3E). Furthermore, DCA analysis further confirmed the model's good net benefit performance (Figure 3F). These results demonstrate the good generalization ability of the prediction model on the validation dataset.

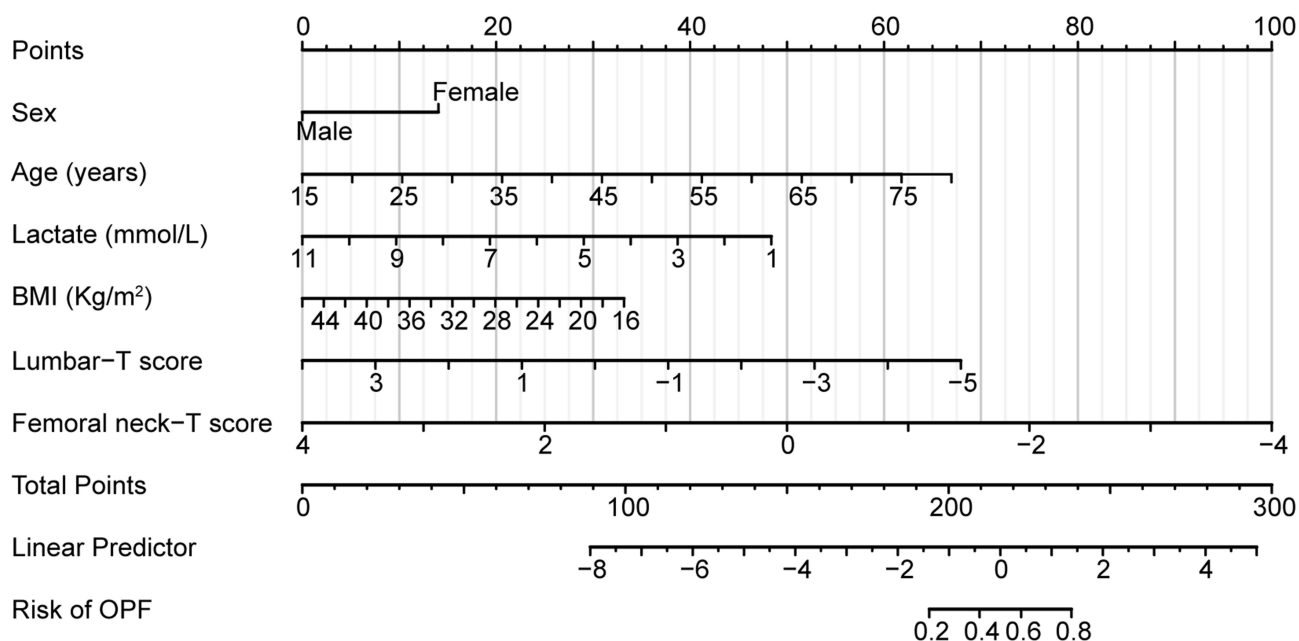


Figure 2 Nomogram for the prediction of osteoporotic fracture (OPF) in patients with type 2 diabetes.

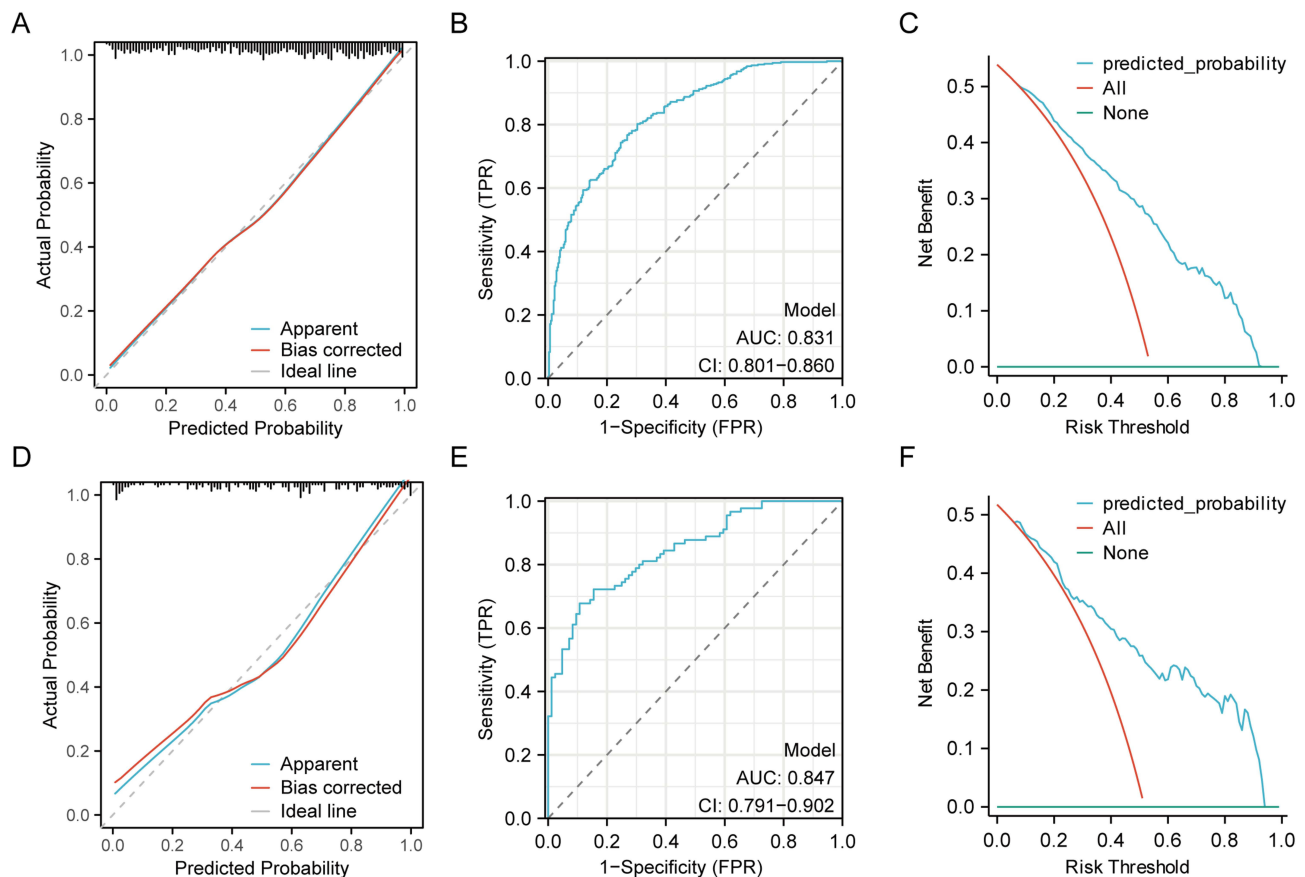


Figure 3 (A) Calibration curve of training cohort; (B) ROC curve of training cohort; (C) Decision curve analysis of training cohort; (D) Calibration curve of validation cohort; (E) ROC curve of validation cohort; (F) Decision curve analysis of validation cohort.

Discussion and Conclusion

This study constructed the predictive model specifically for OPF risk in patients with T2DM by systematically integrating multidimensional data, including demographic baselines (age, gender, BMI, etc), metabolic dynamic indicators (HbA1c, lactic acid, etc), diabetes-specific complications (retinal/nerve/vascular lesions), exposure history to hypoglycemic medications (thiazolidinediones, SGLT2 inhibitors, etc), and bone mineral density (BMD). Gender, age, BMI, serum lactic acid, and lumbar spine/femoral neck BMD were identified as independent predictors. The model showed a high degree of agreement with actual data (Hosmer-Lemeshow test, $P=0.406$), with an Area Under the Curve (AUC) value of 0.831. It demonstrated good clinical benefits across different thresholds and excellent generalization ability on the validation set. Compared to existing general fracture risk assessment tools (such as FRAX, QFracture, Garvan, etc),¹⁰ this model focuses on the interaction between the metabolic disturbances and bone microstructural abnormalities unique to T2DM, addressing the specific assessment need for this population that remains at high fracture risk even with normal BMD. The OPF model for early elderly diabetic nephropathy developed by Youyuan Gao's team is limited to specific ages and stages of kidney disease,¹¹ whereas our study transcends age stratification and covers renal function status across the entire disease course. Although the eight-variable model proposed by Xiao-ke Kong et al¹² includes diabetes-related parameters such as insulin use, it does not incorporate BMD, a key biomarker. By jointly modeling BMD with other metabolic indicators, our model not only validates the independent predictive power of BMD in T2DM patients but also achieves a clinical breakthrough in explaining the “BMD paradox” phenomenon observed in traditional tools (ie, high BMD accompanied by high fracture risk).

Osteoporosis is more prevalent in women, particularly those with T2DM. According to Sharma et al, up to 35.5% of adult patients with T2DM suffer from osteoporosis. Notably, women experience more severe osteoporosis and bone loss

in the spine and hip compared to men.¹³ Furthermore, female T2DM patients with microvascular complications face a higher risk of fractures.¹⁴ Although Schwartz et al found that elderly female T2DM patients have relatively high bone mineral density, their fracture rate is surprisingly high.¹⁵ Therefore, timely detection of fracture susceptibility is crucial for preventing fractures and improving prognosis in female T2DM patients. Consistent with the findings of the Xiao-ke Kong,¹² our study also confirms that female gender is a significant predictor of OPF in patients with T2DM, and we have incorporated this factor into our predictive model.

With advancing age, skeletal fragility increases concomitant with reductions in both bone mass and structure.¹⁶ Prior investigations have underscored the propensity for females to experience earlier onset of bone mass loss, while males, upon encountering osteoporosis, typically face heightened probabilities and severity of fractures.¹⁷ The elderly, particularly vulnerable to osteoporosis and pathological fractures, are further compounded in bone health detriment by T2DM, known to diminish bone formation and escalate fracture risks.¹⁸ Furthermore, age-associated inflammatory and oxidative stress processes have been pinpointed as facilitators in osteoporosis development primarily through impeding bone formation.¹⁹ Therefore, in line with other predictive models for OPF, this study also incorporates age as a key factor in predicting OPF in patients with T2DM into our predictive model.

Previous research has elucidated a direct association between BMI and BMD.²⁰ Specifically, lower BMI tends to correlate with diminished BMD, thereby augmenting the risk of accelerated bone loss among osteoporosis patients.²¹ Conversely, individuals with obesity often exhibit higher BMD, partly attributable to increased mechanical loading on the body. Additionally, studies indicate that aromatase enzymes in obese women may elevate serum estrogen levels.²² However, it is noteworthy that excess adiposity in obese individuals may exert deleterious effects on skeletal metabolism, potentially heightening fracture risks.²³ Compared to non-diabetic counterparts, individuals with T2DM generally present with higher BMI, albeit with correspondingly elevated BMD, yet with a relatively higher incidence of OPF.³ Our study further reveals that OPF patients exhibit significantly lower BMI and visceral fat area compared to non-OPF patients. Multivariable logistic regression analysis demonstrates a significant negative correlation between BMI and OPF risk. Consequently, low BMI has been identified as a crucial independent risk factor for predicting OPF among T2DM patients and has been incorporated into our predictive model.

Serum lactic acid, once regarded as a waste product of glycolytic metabolism, actually serves multiple vital functions, including acting as an energy substrate, regulating energy metabolism, participating in redox reactions, and serving as a signaling molecule.²⁴ In recent years, relevant studies have shown that lactic acid can modulate the joint immune environment by influencing the differentiation of specific immune cells and osteoclasts, as well as the migration and phenotypic polarization of macrophages, thereby affecting joint function.^{25,26} Although the specific mechanism of lactic acid's role in osteoporosis is not yet fully understood, studies have demonstrated that lactic acid bacteria and their fermentation products can enhance calcium absorption, reduce bone loss, and have a positive impact on osteoporosis.^{27–30} Notably, patients with osteoporosis often have lower levels of lactic acid. Recent research has further revealed that lactic acid produced by glycolysis in endothelial cells may promote the differentiation of mesenchymal stem cells into osteoblasts through histone lactylation,³¹ providing a new perspective on how exercise can improve osteoporosis. In this context, our study found a significant association between serum lactic acid levels and the risk of OPF in patients with T2DM. Specifically, the serum lactic acid levels in the OPF group were significantly lower than those in the non-OPF group ($P < 0.05$). Multivariate regression analysis further confirmed that serum lactic acid levels are a protective factor against OPF in patients with T2DM, with an OR of 0.747 and a 95% CI of 0.597 to 0.935. This important finding not only provides strong evidence for lactic acid as a predictive indicator of osteoporotic fractures but also offers new ideas for the prevention and treatment of related diseases. In terms of methodological design, this study excluded patients with diabetic ketoacidosis, hyperosmolar state, and severe cardiopulmonary diseases through strict inclusion criteria. Additionally, a morning fasting blood collection strategy was adopted to effectively avoid the interference of exercise, diet, hypoxia, and acute metabolic disorders on lactic acid levels. It should be specifically noted that, although lactic acid shows potential as a predictive biomarker for OPF, its clinical application still needs to consider individual differences. As a dynamic product of glucose metabolism, lactic acid levels may still be influenced by factors such as long-term exercise patterns, gut microbiota status, and hypoglycemic medications (such as metformin). Therefore, it is recommended to combine steady-state assessments (such as continuous dynamic monitoring) with metabolic background analysis in clinical monitoring to improve the accuracy of risk prediction.

This model utilizes the T-scores of lumbar spine and femoral neck BMD as core parameters for predicting the risk of OPF in patients with T2DM. Its clinical value is manifested in a dual paradox: Although T2DM patients often exhibit higher BMD due to overweight/obesity, their incidence of OPF is elevated compared to non-diabetic populations. This “BMD-fracture risk” paradox stems from the unique pathological mechanisms of diabetes – the accumulation of advanced glycation end products (AGEs) leads to abnormal collagen cross-linking in bone matrix and decreased bone turnover rate, significantly weakening bone biomechanical strength.^{32,33} Notably, the mortality risk after OPF is increased in T2DM patients compared to non-diabetic individuals, highlighting the special need for precise assessment in this population. Compared to general tools like FRAX, this study achieves a breakthrough in mechanism adaptability while retaining BMD indicators. Although trabecular bone score (TBS) is theoretically more suitable for assessing diabetic bone microstructural damage, BMD measurement based on DXA offers advantages such as strong clinical applicability and low data acquisition cost. By establishing a correlation model between BMD and metabolic parameters including lactate, BMI, age, and gender, this approach not only overcomes the risk of misjudgment by traditional tools regarding the “bone quality-BMD” dissociation phenomenon in the T2DM population but also addresses the practical dilemma of limited promotion of novel biomarkers.

In our study, we thoroughly investigated predictive factors for OPF in T2DM patients and developed a risk prediction model. This intuitive and personalized tool can assist clinicians in more convenient predictions. However, notable limitations exist in this study. Firstly, we did not account for whether patients had previously used anti-osteoporosis medications, which could potentially influence the outcomes. Secondly, we did not comprehensively explore the association between the duration of hypoglycemic drug use and osteoporotic fractures. Thirdly, since we did not compare the performance of this model with traditional assessment tools such as FRAX, we cannot demonstrate its superiority. Fourthly, our study did not include indicators such as the nature of physical activity and diet, which may affect the research results. Fifth, despite the limitation of the Hosmer-Lemeshow test’s sensitivity to sample size, where significant results may be obtained even with minor deviations in fit for larger samples, this study still chose to adopt this method. Finally, the training and validation data for this study were both derived from the same hospital, lacking broader external validation, thereby affecting the generalizability of the research. In the future, we suggest incorporating more relevant factors and seeking multicenter collaborations to enhance the reliability and applicability of the study. At the same time, in order to quickly fill the gap in this field, it is recommended to apply the existing osteoporosis prediction model to the population of type 2 diabetes patients to evaluate its effectiveness in clinical practice. This method is both feasible and full of potential.

The predictive model for OPF in patients with T2DM developed in this study demonstrates significant advantages for future clinical application. Firstly, the model incorporates a relatively small number of indicators, which are highly prevalent in clinical practice and for which data is easily obtainable. This means that even primary hospitals can readily adopt this model for prediction. However, there are also some notable limitations to this predictive model. On one hand, the study still relies on BMD, and in some remote areas, the availability of DXA is inadequate. On the other hand, one of the key predictive indicators in the model, serum lactate concentration, is susceptible to various factors such as physical activity, diet, hypoxia, and glycemic control. Therefore, when collecting and applying this indicator for disease assessment, it is essential to fully consider the aforementioned interfering factors.

In summary, this study elucidates several core predictive factors influencing OPFs in T2DM patients: gender, age, BMI, serum lactate concentration, as well as T-scores of lumbar spine and femoral neck bone density. Based on these elements, this study innovatively designs a predictive nomogram capable of accurately forecasting the risk of osteoporotic fractures in T2DM patients. Presented in an intuitive graphical format, this model enables clinicians to swiftly assess patients’ fracture risks and provides crucial basis for timely intervention. Thus, this model holds promise in reducing the incidence of OPF in T2DM patients and demonstrates significant potential in alleviating healthcare economic burdens.

Data Sharing Statement

The datasets are available from the corresponding author on reasonable request.

Statement of Ethics

All protocols followed the ethical guidelines of Declaration of Helsinki, the study has been approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University, with approval number KY2023142. When we retrospectively collected the data of previous cases, written informed consent was waived due to the retrospective nature and low risk of the study. We obtained informed consent when collecting blood and urine from patients.

Consent for Publication

All authors have read the paper and agree that it can be published.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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