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ORIGINAL RESEARCH

Clinical Manifestations and Risk Factors of Osteoporosis in Patients with Type 2 Diabetes Mellitus

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Purpose: To investigate the clinical manifestations and modifiable risk factors of osteoporosis in patients with type 2 diabetes mellitus (T2DM), with emphasis on the interplay between metabolic dysregulation, inflammation, and bone health.

Patients and Methods: This retrospective cohort study included 241 middle-aged and older T2DM patients from the Second Affiliated Hospital of Army Medical University (2016–2020). The participants underwent dual-energy X-ray absorptiometry for bone mineral density (BMD) assessment. Osteoporosis was defined as a BMD T-score of ≤ −2.5. Data on demographic, anthropometric, metabolic, inflammatory, and bone turnover marker levels were collected. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors. Restricted cubic spline (RCS) and receiver operating characteristic (ROC) curves were used to evaluate nonlinear associations and predictive accuracy.

Results: Of 241 patients, those with osteoporosis were significantly older (64.1 vs 59.0, $p = 0.021$) and more likely female. Lower body mass index (BMI), higher total cholesterol (TCH), elevated N-terminal mid-fragment of osteocalcin (N-MID), elevated high-density lipoprotein cholesterol (HDL-C), and lower monocyte-to-HDL ratio (MHR) and platelet-to-HDL ratio (PHR) were significantly associated with osteoporosis ($p = 0.015$, 0.024, 0.019, 0.013, 0.027, and 0.039, respectively). Multivariate analysis revealed that advanced age (odds ratio [OR] = 1.036, $p = 0.020$), low BMI (OR = 0.897, $p = 0.017$), and elevated TCH levels (OR = 1.381, $p = 0.021$) were independently associated with an increased risk of osteoporosis. Although HDL-C levels and MHR showed initial associations, they lost significance after adjustment. RCS showed a linear correlation between BMI and osteoporosis risk in patients with T2DM (p for overall = 0.020; p for nonlinear = 0.351). ROC analysis showed modest predictive power for individual markers (AUC < 0.60); however, a composite model (including age, sex, BMI, TCH, HDL-C, and MHR) improved the AUC to 0.692.

Conclusion: In T2DM patients, age, low BMI, and elevated TCH were independent risk factors for osteoporosis. Routine inflammatory indices showed limited predictive value. A multimodal model integrating demographic and metabolic factors offers better predictive accuracy, supporting a comprehensive risk assessment in clinical practice.

Keywords: osteoporosis, type 2 diabetes mellitus, risk factors, bone mineral density, dyslipidemia, inflammation

Introduction

Osteoporosis is a systemic skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture. It increases bone fragility and fracture risk.[1] It imposes a substantial public health burden worldwide, especially among the elderly, leading to higher morbidity, mortality, and healthcare costs.[2] Osteoporosis can occur in different sexes or ages, especially in older men and postmenopausal women. Early osteoporosis generally lacks obvious clinical manifestations, manifesting only as low back pain or generalized bone pain, and some patients are diagnosed with serious consequences, such as fragility fractures. The Chinese national epidemiological survey of osteoporosis shows that

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the prevalence of osteoporosis in people over 50 years old is 19.2% including 32.1% in women and 6.9% in men, the prevalence of osteoporosis in people over 65 years of age is 32.0%, including 51.6% in women and 10.7% in men.[3,4] Although the prevalence of osteoporosis in our country is high, the public awareness and diagnosis rates of osteoporosis are very low, only 7.4% and 6.4%, respectively. Even after fragility fractures, the treatment rate for osteoporosis is only 30%.[3] Therefore, there is an urgent need to improve the diagnosis and treatment of this debilitating disease.

Diabetes is a serious health concern worldwide. In 2024, it is estimated that nearly 589 million adults globally will have diabetes.[5] And it is estimated that as many as 233 million people in China will have this disease by 2023. This is nearly a 50% increase compared with the last report by China, increasing from 7.53% to 13.7%.[6] Type 2 diabetes mellitus (T2DM) is also the most common type of diabetes worldwide, which accounts for more than 90% of all diabetes. Both T2DM and osteoporosis are affected by lifestyle changes and ageing. However, these two diseases will appear simultaneously, especially in older patients, resulting in a higher or even worse bone fracture risk. This conclusion was supported by a recent meta-analysis. There is a 27.67% prevalence of osteoporosis in people with T2DM around the world.[7] Ironically, even though with normal or elevated bone mineral density (BMD) people with T2DM still have a higher chance of fragility fracture than non-diabetics. Compared with non-diabetic individuals, there is an increased fracture risk of up to 20%–70%.[8] Bone tissue quality, rather than merely quantity, is responsible for this difference.

Many mechanisms have been proposed in relation to T2DM and osteoporosis. Chronic hyperglycemia, insulin resistance, advanced glycation end-product accumulation, excessive oxidative stress, and increased low-grade systemic inflammation can cause altered osteoblast/osteoclast functions, and finally, bone loss in the skeletal system.[9–13] In addition, diabetic complications such as neuropathy and retinopathy can increase the probability of falling and increase the incidence of fractures easily.[14] But we do not know the clinical features of patients with T2DM who suffer fractures and the change in these indicators for the prevention and control of related T2DM-related osteoporosis. However, the effects of prevention and treatment in clinical settings remain unclear. Thus, early diagnosis and further clarification of possible risk factors in their management are limited to a few scenarios.

Dyslipidemia is also associated with T2DM. Lipid metabolism also participates in the regulation of calcium metabolism, which indirectly affects T2DM-induced osteoporosis. The effects of lipid metabolism disturbances in patients with T2DM have long attracted interest. Serum levels of triglycerides (TG) and total cholesterol (TCH) in patients with T2DM have often been studied. Elevated TCH and lower high-density lipoprotein cholesterol (HDL-C) levels indicate lower BMD.[15,16] Cholesterol serves as a precursor to some steroid hormones, including vitamin D and its precursor sex hormones. They are required to maintain steady-state blood calcium levels and to regulate bone mass turnover. Furthermore, oxidized low-density lipoproteins drive the proliferation and differentiation of monocytes/macrophages into osteoclasts, while suppressing bone marrow mesenchymal stem cells/osteosperm/bone marrow progenitor cells into osteoblasts or osteocytes via ligands.[17] But the uncertainty remains when lipid metabolism is altered in elderly individuals with T2DM.

Recent studies have highlighted routine- blood-derived inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), monocyte-to-HDL ratio (MHR), and systemic immune-inflammation index (SII) as markers of chronic inflammation and predictors of adverse outcomes in metabolic and cardiovascular diseases.[18,19] Given the shared low-grade inflammation in T2DM and osteoporosis, these ratios may serve as surrogate markers for bone loss. For example, monocytes are osteoclast precursors, while HDL possesses anti-inflammatory and antioxidant properties; thus, MHR may reflect the balance between resorptive and protective forces affecting bone integrity.[20] Data on the association between these novel indices and osteoporosis in T2DM patients are still scarce.

According to the fracture risk caused by osteoporosis, many studies had developed prediction model for early warning.[21,22] Most of the previous studies on osteoporosis in patients with T2DM were single factor related risk factors, had small sample sizes, and were not generally applicable; they needed to evaluate traditional age, sex, and diabetes duration as risk factors together with newly emerging biological parameters to obtain a better model that improves accuracy in prediction and diagnosis. Some studies have included demographic, metabolic, and bone-related factors to evaluate integrated factors to screen for independent risk factors for osteoporosis. Our study aimed to develop a new diagnostic method to evaluate the situation and risk factors of the middle-aged population and among older adults

suffering from osteoporosis with T2DM, combined with other indicators, to observe changes with new data to generate a more refined diagnostic approach in the real world.

Materials and Methods

Study Design and Patients

This retrospective cohort study adhered to the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Army Medical University (approval number: 2025-YANDI278-01). The requirement for informed consent was waived because of the retrospective nature of the study. All patient information and data used in this study were handled with strict confidence and de-identified to protect patient privacy in compliance with the relevant ethical and legal standards.

We extracted the clinical records of patients with T2DM who underwent dual-energy X-ray bone density screening at the Second Affiliated Hospital of the Army Medical University between 2016 and 2020. Patients with complete clinical and laboratory examination data were enrolled in the study. We aimed to focus on the population at highest risk for primary osteoporosis, the exclusion criteria were as follows: (1) men aged < 50 years and premenopausal women; (2) serious and unstable health conditions [severe cardiovascular or cerebrovascular diseases, obvious liver or renal dysfunction (AST ≥ 120 U/L, ALT ≥ 120 U/L, or eGFR ≤ 60 mL/min/1.73m^2), severe anemia (hemoglobin ≤ 60 g/L), or malignant tumors]; (3) acute or chronic infections; (4) thyroid or rheumatic diseases; and (5) any form of glucocorticoid administration.

Data Collection

Demographic data and clinical information were collected from electronic medical records in the hospital by trained interviewers who provided detailed guidance to collect the questionnaire by themselves. Anthropometric data, including height and weight, were collected by the research nurses. Body mass index (BMI) was calculated using the following formula: BMI (kg/m^2) = weight (kg)/height^2 (m^2).

Routine blood examinations included white blood cell (WBCs), neutrophil, monocyte, lymphocyte, monocyte, platelet (PLTs), and hemoglobin (Hb) counts. Biochemical indicators included TG, TCH, HDL-C, low-density lipoprotein (LDL-C), albumin (ALB), serum creatinine (SCr), uric acid (UA) levels, serum calcium, serum phosphorus, bone turnover markers (BTMs), 25-hydroxyvitamin D (25-OHD), N-terminal mid-fragment of osteocalcin (N-MID), procollagen type I N-terminal propeptide (P1NP), β-crosslaps, and parathyroid hormone (PTH). Based on these values, the following systemic inflammatory indices and composite indices (related to metabolic and inflammatory status) were calculated: 1) NLR = Neutrophils (×109/L)/lymphocytes (×109/L); 2) MLR = Monocytes (×109/L)/lymphocytes (×109/L); 3) PLR= Platelets (×109/L)/lymphocytes (×109/L); 4) NHR = Neutrophils (×109/L)/HDL (mmol/L); 5) MHR = Monocytes (×109/L)/HDL (mmol/L); 6) PHR = Platelets (×109/L)/HDL (mmol/L); 7) SII = Neutrophils (×109/L) × platelets (×109/L))/lymphocytes (×109/L); and 8) SIRI = Neutrophils (×109/L) × Monocytes (×109/L))/Lymphocytes (×109/L).

Assessment of Bone Mineral Density

The participants underwent BMD assessment by dual-energy X-ray absorptiometry (GE Healthcare) in the supine position, performed by a single experienced operator. BMD measurements were obtained at the lumbar vertebrae (L1–L4) and bilateral femoral necks. Standardized quality-control phantoms were employed prior to each day's scans, and the operator was blinded to all clinical data. BMD values were expressed as grams of mineral per scanned area (g/cm^2) and subsequently converted to T-scores using the appropriate reference coefficients. The coefficient of variation for BMD measurements was 1.0%. Osteoporosis was defined according to the World Health Organization (WHO, 2011) criteria as a BMD T-score ≤ −2.5 SD relative to the mean of a healthy reference population matched for race, age, and sex. Participants with T-scores ≤ −2.5 were assigned to the osteoporosis group, whereas those with T-scores > −2.5 were assigned to the non-osteoporotic group.

Statistical Analyses

All statistical analyses were conducted with IBM SPSS Statistics version 26.0. Continuous variables were presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were expressed as counts and percentages. The one-sample Kolmogorov–Smirnov test assessed the normality of data distributions. Depending on normality, continuous variables were compared using independent-samples t-tests, paired-samples t-tests, or Mann–Whitney *U*-tests. Categorical variables were analyzed with chi-squared tests or Fisher's exact tests. Correlations between continuous variables and BMD were evaluated using Pearson's correlation coefficient for normally distributed data and Spearman's rank-order correlation for non-normally distributed data. To identify factors influencing disease, both univariate and multivariate logistic regression analyses were performed. For multicollinearity evaluation, we calculated the Variance Inflation Factor (VIF) for all independent variables, with a threshold of VIF > 5 indicating potential multicollinearity; variables exceeding this threshold will be further examined for correlation and adjusted based on clinical priority. We used the Hosmer–Lemeshow test to assess goodness-of-fit, with a non-significant result ($p > 0.05$) indicating adequate calibration. For internal validation, we performed 10-fold cross-validation to estimate the model's predictive performance across different subsets of the dataset, ensuring the model's stability and generalizability within the study population. Heterogeneity among subgroups was assessed by multivariate logistic regression, and interactions between subgroups and gender were examined by likelihood ratio testing. Restricted cubic spline (RCS) functions were incorporated into the regression models to accommodate potential nonlinear relationships between predictors and osteoporosis outcomes, thereby avoiding linearity assumptions. Receiver operating characteristic (ROC) curve analysis quantified the predictive performance of laboratory parameters for osteoporosis, with optimal cut-off values determined by the maximum Youden index. Statistical significance was defined as a two-tailed p-value < 0.05.

Results

Clinical Characteristics of the Patients

The participant enrolment process is shown in Figure 1. The final evaluation included 241 middle-aged or older individuals (138 males and 103 females). The demographic characteristics of the participants, based on the presence of osteoporosis, are presented in Table 1. All patients had a median age of 62 years, with a significantly older age observed in individuals with osteoporosis than in those without osteoporosis ($p = 0.021$). A marked sex disparity was evident, as females constituted a significantly larger proportion of the osteoporosis group (57.7% vs 30.8% in non-osteoporosis; $p < 0.001$). BMI was slightly lower in the osteoporosis group than in the non-osteoporosis group (23.96 vs

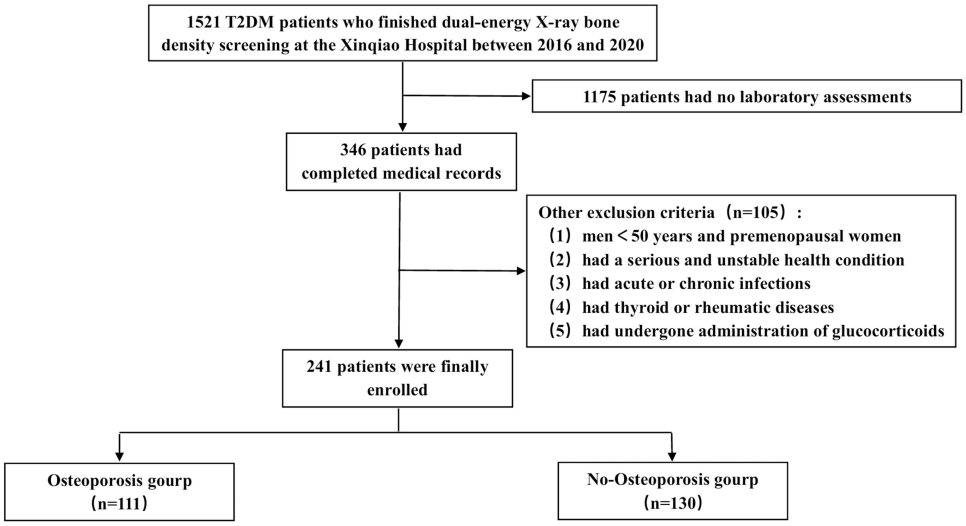

Figure 1 The flowchart of the study population.
Abbreviation: T2DM, type 2 diabetes mellitus.

Table 1 Demographic Characteristics of Individuals Based on the Presence of Osteoporosis

Parameters	All (n=241)	Osteoporosis (n=111)	No-Osteoporosis (n=130)	t/Z/χ^2	*P* value
Age, year	62 (55, 70)	64.10 ± 8.56	59.00(54.00, 68.25)	2.308	0.021
Gender (n)				16.523	0.000
Male	138	48	90		
Female	103	63	40		
BMI kg/m^2	24.40 (22.46, 26.47)	23.96 ± 3.01	24.95(22.97, 26.59)	2.442	0.015
Education (n)				1.285	0.733
Less than 9th grade	43	22	21		
9-11th grade	112	53	59		
High school grad or equivalent	31	15	16		
College graduate or above	29	11	18		
Smoking (n)				0.189	0.664
Yes	86	38	48		
No	155	73	82		
Drinking alcohol (n)				1.776	0.183
Yes	71	28	43		
No	170	83	87		
Combined with hypertension (n)				0.044	0.834
Yes	83	39	44		
No	159	72	86		
Diabetes duration (n)				1.491	0.684
1 year	17	9	8		
1 year to 5years	46	20	26		
5 years to 10years	54	28	26		
10 years above	124	54	70		

Abbreviation: BMI, Body mass index.

24.95, $p = 0.015$). No significant differences were found between the groups in terms of education level, smoking status, alcohol consumption, prevalence of hypertension, or diabetes duration.

Table 2 presents a comprehensive comparative analysis of laboratory parameters between the two groups. No significant differences were observed in hematological indices such as WBCs count ($p = 0.636$), neutrophil count ($p = 0.536$), lymphocyte count ($p = 0.833$), monocyte count ($p = 0.134$), RBCs count ($p = 0.186$), Hb level ($p = 0.109$), or PLTs ($p = 0.585$). The metabolic and inflammatory markers showed limited divergence. Glycosylated hemoglobin (HbA1c), an indicator of long-term glycemic control, did not differ significantly between the groups ($p = 0.342$), uric acid ($p = 0.184$), serum creatinine ($p = 0.108$), calcium ($p = 0.647$), phosphorus ($p = 0.598$), 25-OHD ($p = 0.500$), PTH ($p = 0.424$), or alkaline phosphatase ($p = 0.126$). Similarly, bone turnover markers, including β-crosslaps ($p = 0.420$) and P1NP ($p = 0.534$), showed no significant variation. However, notable differences were observed in the lipid profiles and

Table 2 Laboratory Examination of Individuals Based on the Presence of Osteoporosis

Parameters	All (n=241)	Osteoporosis (n=111)	No-Osteoporosis (n=130)	t/Z	*P* value
WBCs ($\times10^9$/L)	5.72 (5.04, 6.87)	5.70 (4.81, 7.08)	5.73 (5.10, 6.48)	0.474	0.636
Neutrophils ($\times10^9$/L)	3.39 (2.71, 4.38)	3.48 (2.67, 4.46)	3.33 (2.77, 4.20)	0.618	0.536
RBCs ($\times10^{12}$/L)	4.32 ± 0.62	4.27 ± 0.64	4.37 ± 0.60	1.325	0.186
Lymphocytes ($\times10^9$/L)	1.62 (1.30, 2.01)	1.57 (1.28, 2.04)	1.65 (1.31, 2.00)	0.211	0.833
Monocytes ($\times10^9$/L)	0.45 (0.35, 0.57)	0.42 (0.34, 0.57)	0.47 (0.37, 0.57)	1.499	0.134
Hb (g/L)	128.52 ± 17.90	126.91 ± 18.17	129.90 ± 17.62	1.604	0.109
PLTs ($\times10^9$/L)	171.00 (139.50, 221.50)	171.00 (133.00, 220.00)	170.50 (141.00, 223.25)	0.546	0.585
HbA1c (%)	8.15 (6.90, 9.80)	7.90 (6.90, 9.60)	8.30 (6.90, 10.00)	0.950	0.342
ALB (g/L)	41.30 (38.60, 44.05)	41.20 (38.80, 44.10)	41.35 (38.20, 44.02)	0.230	0.818
UA (μmol/L)	310.40 (242.00, 384.65)	304.30 (237.00, 365.50)	312.20 (245.07, 403.80)	1.327	0.184
SCr (μmol/L)	68.00 (58.55, 85.25)	67.50 (57.20, 82.30)	68.30 (59.18, 91.25)	1.607	0.108
TCH (mmol/L)	4.36 ± 1.12	4.54 ± 1.17	4.22 ± 1.05	2.275	0.024
TG (mmol/L)	1.41 (1.01, 2.07)	1.46 (1.04, 2.10)	1.22 (0.97, 1.82)	1.081	0.281
HDL-C (mmol/L)	1.01 (0.85, 1.22)	1.08 (0.87, 1.26)	0.95 (0.83, 1.19)	2.471	0.013
LDL-C (mmol/L)	2.42 ± 0.81	2.48 ± 0.85	2.26 ± 0.73	0.901	0.368
Ca (mmol/L)	2.26 (2.17, 2.34)	2.27 (2.17, 2.34)	2.25 (2.18, 2.34)	0.457	0.647
P (mmol/L)	1.10 (0.99, 1.22)	1.10 (0.99, 1.21)	1.10 (0.99, 1.22)	0.527	0.598
25-OHD (ng/mL)	19.90 (14.85, 25.65)	18.90 (15.30, 25.00)	20.40 (14.40, 26.75)	0.674	0.500
PTH (pg/mL)	52.10 (39.05, 73.65)	52.10 (38.20, 70.50)	52.00 (40.08, 75.42)	0.799	0.424
ALP (U/L)	69.80 (55.85, 86.00)	73.10 (57.30, 91.80)	68.20 (54.00, 81.80)	1.528	0.126
β-cross (pg/mL)	304.20 (190.95, 477.90)	336.10 (189.40, 515.30)	278.80 (189.30, 445.50)	0.806	0.420
N-MID (ng/mL)	12.62 (9.54, 17.91)	13.81 (10.08, 19.72)	11.58 (8.88, 16.63)	2.345	0.019
P1NP (ng/mL)	33.21 (25.30, 47.56)	34.66 (24.61, 51.67)	33.08 (25.90, 45.79)	0.622	0.534
BMD (g/cm^3)	0.968 ± 0.184	0.844 (0.765, 0.884)	1.07 (1.00, 1.17)	13.072	<0.001
NLR	2.03 (1.56, 2.93)	2.04 (1.45, 2.96)	2.03(1.59, 2.89)	0.366	0.714
MLR	0.27 (0.21, 0.38)	0.25 (0.20, 0.35)	0.30 (0.22, 0.40)	1.921	0.055
PLR	108.84 (81.50, 141.98)	107.56 (79.41, 139.34)	109.55 (82.79, 144.56)	1.008	0.314
NHR	3.31 (2.43, 4.50)	3.00 (2.28, 4.45)	3.48 (2.51, 4.62)	0.937	0.349
MHR	0.45 (0.32, 0.60)	0.42 (0.31, 0.54)	0.47 (0.35, 0.65)	2.214	0.027
PHR	171.88 (127.80, 227.38)	158.96 (123.31, 213.46)	179.15 (134.91, 237.93)	2.063	0.039
LHR	1.55 (1.10, 2.06)	1.46 (1.14, 2.02)	1.61 (1.08, 2.13)	0.684	0.494

(*Continued*)

Table 2 (Continued).

Parameters	All (n=241)	Osteoporosis (n=111)	No-Osteoporosis (n=130)	t/Z	*P* value
SII	353.73 (236.26, 533.87)	353.73 (237.43, 530.31)	353.71 (234.38, 542.35)	0.291	0.771
SIRI	0.95 (0.62, 1.38)	0.89 (0.60, 1.33)	1.02 (0.63, 1.40)	1.133	0.257

Abbreviations: 25-OHD, 25-hydroxyvitamin D; Hb, haemoglobin; PLTs, platelets; HbA1c, glycosylated hemoglobin; ALB, albumin; UA, uric acid; SCr, serum creatinine; TCH, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone; ALP, alkaline phosphatase; N-MID, N-terminal mid-fragment of osteocalcin; P1NP, procollagen type I N-terminal propeptide; BMD, bone mineral density; NLR, neutrophil to lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NHR, neutrophil-to-high-density lipoprotein cholesterol ratio; MHR, monocyte-to-high-density lipoprotein cholesterol ratio; PHR, platele-to-high-density lipoprotein cholesterol ratio; LHR, lymphocyte-to-high-density lipoprotein ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

certain inflammatory ratios. TCH was significantly higher in the osteoporosis group (4.54 mmol/L vs 4.22 mmol/L, $p = 0.024$), HDL-C was lower (1.08 mmol/L vs 0.95 mmol/L, $p = 0.013$), indicating a possible association between dyslipidemia and reduced bone mass. Additionally, N-MID, a marker of osteoblastic activity, was significantly elevated in osteoporotic individuals (13.81 ng/mL vs 11.58 ng/mL, $p = 0.019$). Several hematological ratios demonstrated marginal significance: MLR ($p = 0.055$), MHR ($p = 0.027$), PHR ($p = 0.039$), and SII, SIRI, and NHR approached statistical significance. Most critically, lumbar spine (L1–L4) BMD was markedly lower in the osteoporosis group (0.844 g/cm^2 vs 1.07 g/cm^2, $p < 0.001$), confirming effective group stratification.

Correlations of the Factors and BMD at Different Sites

Table 3 shows the correlations between demographic, hematological, biochemical, and bone turnover markers and BMD at the lumbar vertebrae and bilateral femoral necks. Age was significantly negatively correlated with BMD at all sites (right femoral neck: r = −0.395, $p < 0.0001$; left femoral neck: r = −0.365, $p < 0.001$). BMI was positively correlated with

Table 3 Correlations of the Factors and BMD at Different Sites

Variable	Lumbar Vertebrae		Left Femoral Neck		Right Femoral Neck	
	r	*P*	r	*P*	r	*P*
Age	−0.211	0.001	−0.365	<0.0001	−0.395	<0.0001
BMI	0.264	<0.0001	0.099	0.126	0.063	0.327
WBCs	−0.001	0.983	−0.071	0.272	−0.032	0.621
Neutrophils	−0.029	0.649	−0.115	0.075	−0.062	0.341
RBCs	0.158	0.014	0.167	0.009	0.170	0.008
Lymphocytes	0.002	0.970	0.021	0.746	0.025	0.704
Monocytes	0.131	0.042	−0.001	0.991	0.037	0.572
Hb	0.199	0.002	0.173	0.007	0.201	0.002
PLTs	0.005	0.943	0.010	0.875	0.063	0.334
HbA1c	0.056	0.387	0.058	0.375	0.035	0.595
ALB	0.030	0.643	0.024	0.711	0.063	0.333
UA	0.205	0.001	0.084	0.192	0.080	0.216

(*Continued*)

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Table 3 (Continued).

Variable	Lumbar Vertebrae		Left Femoral Neck		Right Femoral Neck	
	r	*P*	r	*P*	r	*P*
SCr	0.253	<0.0001	0.066	0.309	0.101	0.119
TCH	−0.102	0.114	−0.074	0.255	−0.027	0.676
TG	0.036	0.583	0.069	0.286	0.095	0.141
HDL-C	−0.175	0.007	−0.167	0.009	−0.169	0.009
LDL-C	−0.068	0.293	−0.062	0.341	−0.027	0.681
Ca	−0.031	0.643	0.006	0.927	−0.057	0.395
P	0.000	0.997	0.141	0.034	0.174	0.008
25-OHD	0.095	0.143	0.136	0.035	0.165	0.010
PTH	0.034	0.598	−0.045	0.490	−0.051	0.435
ALP	−0.144	0.025	−0.138	0.033	−0.142	0.028
β-cross	−0.113	0.085	−0.129	0.048	−0.096	0.143
N-MID	−0.177	0.006	−0.127	0.051	−0.131	0.044
P1NP	−0.090	0.167	−0.202	0.002	−0.185	0.004
NLR	−0.012	0.856	−0.079	0.220	−0.046	0.476
MLR	0.129	0.046	0.009	0.891	0.032	0.618
PLR	0.015	0.811	0.000	0.997	0.047	0.469
NHR	0.060	0.351	0.012	0.851	0.048	0.461
MHR	0.170	0.008	0.066	0.310	0.088	0.172
PHR	0.104	0.107	0.093	0.151	0.134	0.038
LHR	0.055	0.392	0.086	0.184	0.072	0.263
SII	−0.028	0.669	−0.074	0.255	−0.009	0.889
SIRI	0.062	0.335	−0.064	0.323	−0.018	0.779

Abbreviations: 25-OHD, 25-hydroxyvitamin D; Hb, haemoglobin; PLTs, platelets; HbA1c, glycosylated hemoglobin; ALB, albumin; UA, uric acid; SCr, serum creatinine; TCH, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone; ALP, alkaline phosphatase; N-MID, N-terminal mid-fragment of osteocalcin; P1NP, procollagen type 1 N-terminal propeptide; BMD, bone mineral density; NLR, neutrophil to lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NHR, neutrophil-to-high-density lipoprotein cholesterol ratio; MHR, monocyte-to-high-density lipoprotein cholesterol ratio; PHR, platele-to-high-density lipoprotein cholesterol ratio; LHR, lymphocyte-to-high-density lipoprotein ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

lumbar BMD (r = 0.264, $p < 0.001$), but not with femoral neck BMD. RBCs demonstrated weak positive correlations with BMD (lumbar: r = 0.158, $p = 0.014$; left femoral neck: r = 0.167, $p = 0.009$; right femoral neck: r = 0.170, $p = 0.008$). Hb levels also positively correlated with BMD at all sites (lumbar: r = 0.199, $p = 0.002$; left: r = 0.173, $p = 0.007$; right: r = 0.201, $p = 0.002$). Serum creatinine was positive correlated with lumbar BMD (r = 0.253, $p < 0.001$), but not with femoral neck BMD. HbA1c levels were not significantly correlated with BMD. HDL-C levels consistently negatively correlated with BMD (lumbar: r = −0.175, $p = 0.007$; left: r = −0.167, $p = 0.009$; right: r = −0.169, $p = 0.009$). Phosphorus positive correlated with the femoral neck (left: r = 0.141, $p = 0.034$; right: r = 0.174, $p = 0.008$). The

25-OHD level was moderately positive correlated (right femoral neck: r = 0.165, $p = 0.010$; left femoral neck: r = 0.136, $p = 0.035$). Alkaline phosphatase negatively correlated with BMD at all sites (lumbar: r = −0.144, $p = 0.025$; left: r = −0.138, $p = 0.033$; right: r = −0.142, $p = 0.028$). P1NP showed a strong negative correlation with femoral neck BMD (left: r = −0.202, $p = 0.002$; right: r = −0.185, $p = 0.004$). Parathyroid hormone levels and inflammatory indices (NLR, PLR, SII, and SIRI) showed no significant correlations, whereas MLR (r = 0.129, $p = 0.046$) and MHR (r = 0.170, $p = 0.008$) showed weak positive associations only in the lumbar spine. PHR was positive correlated with the right femoral neck BMD (r = 0.134, $p = 0.038$).

Logistic Regression of the Risk Factors for Osteoporosis

The univariate logistic regression analysis presented in Table 4 identifies several significant risk factors associated with osteoporosis. Among the variables examined, BMI emerged as a statistically significant protective factor, with a negative

Table 4 Univariate Logistic Regression of the Risk Factors for Osteoporosis

Variables	β	SE	z	OR (95% CI)	*p*
BMI	−0.112	0.043	2.579	0.894 (0.821~0.974)	0.010
Age	0.026	0.014	1.866	1.027 (0.999~1.056)	0.062
Hb	−0.009	0.007	1.291	0.991 (0.977~1.005)	0.197
UA	−0.002	0.001	1.411	0.998 (0.996~1.001)	0.158
VD25-OH	−0.009	0.011	0.864	0.991 (0.970~1.012)	0.388
PTH	−0.004	0.003	1.522	0.996 (0.990~1.001)	0.128
ALP	−0.000	0.002	0.203	1.000 (0.996~1.003)	0.839
SCr	−0.005	0.003	1.607	0.995 (0.990~1.001)	0.108
ALB	−0.005	0.028	0.164	0.995 (0.943~1.051)	0.870
TG	−0.022	0.081	0.277	0.978 (0.834~1.146)	0.782
TCH	0.268	0.120	2.233	1.307 (1.033~1.654)	0.026
LDL-C	0.173	0.161	1.079	1.189 (0.868~1.630)	0.281
HDL-C	0.981	0.467	2.103	2.667 (1.069~6.656)	0.035
WBC	0.088	0.086	1.027	1.093 (0.923~1.293)	0.304
RBC	−0.278	0.211	1.321	0.757 (0.501~1.144)	0.187
Neutrophil	0.088	0.097	0.907	1.092 (0.903~1.321)	0.365
Lymphocyte	0.245	0.210	1.168	1.278 (0.847~1.929)	0.243
Monocyte	−0.718	0.805	0.891	0.488 (0.101~2.364)	0.373
PLts	−0.001	0.002	0.463	0.999 (0.996~1.003)	0.644
NLR	0.021	0.049	0.432	1.022 (0.927~1.126)	0.666
MLR	−1.030	0.794	1.297	0.357 (0.075~1.694)	0.195
PLR	−0.003	0.002	1.355	0.997 (0.994~1.001)	0.175
NHR	−0.052	0.072	0.719	0.950 (0.825~1.093)	0.472

(*Continued*)

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Table 4 (Continued).

Variables	β	SE	z	OR (95% CI)	p
MHR	−1.370	0.644	2.128	0.254 (0.072~0.897)	0.033
PHR	−0.003	0.002	1.722	0.997 (0.994~1.000)	0.085
LHR	−0.100	0.189	0.530	0.904 (0.624~1.311)	0.596
SII	−0.000	0.000	0.125	1.000 (0.999~1.000)	0.901
SIRI	−0.013	0.129	0.105	0.987 (0.767~1.269)	0.917

Abbreviations: 25-OHD, 25-hydroxyvitamin D; BMI, body mass index; Hb, haemoglobin; PLTs, platelets; ALB, albumin; UA, uric acid; SCr, serum creatinine; TCH, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone; ALP, alkaline phosphatase; BMD, bone mineral density; NLR, neutrophil to lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NHR, neutrophil-to-high-density lipoprotein cholesterol ratio; MHR, monocyte-to-high-density lipoprotein cholesterol ratio; PHR, platele-to-high-density lipoprotein cholesterol ratio; LHR, lymphocyte-to-high-density lipoprotein ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; OR, odds ratio; SE, standard error.

β coefficient of −0.112 ($p = 0.010$) and an odds ratio (OR) of 0.894 [95% confidence interval (CI): 0.821–0.974]. Age was positive associated with osteoporosis risk (β = 0.026, $p = 0.062$); however, this association was not reached conventional levels of statistically significant. TCH was significantly associated with increased odds of osteoporosis (β = 0.268, $p = 0.026$), yielding an OR of 1.307 (95% CI: 1.033–1.654). HDL-C also showed a significant positive effect (β = 0.981, $p = 0.035$), with an OR of 2.667 (95% CI: 1.069–6.656). MHR was identified as a significant predictor, with a large negative β value (−1.370, $p = 0.033$) and an OR of 0.254 (95% CI: 0.072–0.897). Other inflammatory indices, such as the SII, SIRI, NLR, MLR, PLR, and LHR, did not demonstrate statistically significant associations (all $p > 0.05$). Hematological parameters, including hemoglobin, RBCs, WBCs, neutrophils, lymphocytes, monocytes, and platelets, were not significantly associated with osteoporosis risk. Similarly, markers of renal function (serum creatinine), liver function (alkaline phosphatase), nutritional status (albumin), glucose metabolism (uric acid), parathyroid hormone, 25-OHD, LDL-C, and TG showed no significant predictive value in the model.

Osteoporosis was used as the dependent variable. After excluding repeated indicator calculations, all factors were incorporated into the multivariate logistic regression analysis. The multivariate logistic regression analysis (Table 5) demonstrated that the elderly age was more likely increased risk of developing osteoporosis compared with other groups

Table 5 Multivariable Logistic Regression of the Risk Factors for Osteoporosis

Variables	β	SE	OR (95% CI)	p
(Intercept)	−0.631	1.828	0.532	0.532
Age	0.036	0.015	1.036 (1.006~1.068)	0.020
BMI	−0.108	0.045	0.897 (0.821~0.981)	0.017
TCH	0.323	0.140	1.381 (1.050~1.817)	0.021
HDL-C	−0.058	0.622	0.944 (0.279~3.196)	0.926
MHR	−0.997	0.813	0.369 (0.075~1.815)	0.220

Abbreviations: BMI, body mass index; TCH, total cholesterol; HDL-C, high-density lipoprotein cholesterol; MHR, monocyte-to-high-density lipoprotein cholesterol ratio; OR, odds ratio; SE, standard error; CI, confidence interval.

(OR = 1.036, 95% CI, 1.006–1.068, $p = 0.020$). TCH was significantly positively correlated with higher increased risk of developing osteoporosis compared with those at lower levels (OR = 1.381, 95% CI, 1.050–1.817, $p = 0.021$); low BMI had highly contributed to increased risk of developing osteoporosis than others, which included (OR = 0.897, 95% CI: 0.821–0.981, $p = 0.017$). Conversely, HDL-C (OR = 0.944, 95% CI: 0.279–3.196, $p = 0.926$) and MHR (OR = 0.369, 95% CI: 0.075–1.815, $p = 0.220$) did not show statistically significant associations after adjusting for covariates. These findings emphasize the independent predictive roles of age, TCH, and BMI in osteoporosis risk in the study cohort.

Table 6 showed subgroup analysis of osteoporosis prevalence in males versus females across various demographic and clinical parameters. Overall, a higher proportion of women have osteoporosis compared to men within most age groups, with the disparity increasing with age—particularly evident in those over 50 years. OR indicate that females consistently have significantly higher odds of osteoporosis than males, especially in the 51–60 (OR = 2.37), 61–70 (OR = 2.64), and >70 years (OR = 4.46) age ranges. Similar patterns are observed when stratified by BMI, TCH, HDL-C, and MHR, where low levels of protective factors (BMI ≤24.4, HDL-C ≤1.01) are associated with increased osteoporosis risk, particularly among women. Although interaction tests for most subgroups were not statistically significant (all *P* for interaction >0.05), the results suggest that sex may modify the effect of certain metabolic and inflammatory markers on osteoporosis risk.

Table 6 Subgroup Analysis for Osteoporosis in Male versus Female

Subgroup	Male	Female	OR (95% CI)	*P* value	*P* for Interaction
	(Osteoporosis n, %)	(Osteoporosis n, %)			
Age					0.677
≤50 years	4 (50.0)	2 (50.0)	1.00 (0.09~11.03)	1.000	
51-60 years	18 (27.3)	16 (47.1)	2.37 (1.00~5.63)	0.050	
61-70 years	17 (47.2)	26 (70.3)	2.64 (1.01~6.91)	0.048	
>70 years	9 (32.1)	19 (67.9)	4.46 (1.45~13.68)	0.009	
BMI ≤24.4 kg/m^2					0.830
Yes	24 (42.1)	43 (67.2)	2.82 (1.34~5.91)	0.006	
No	24 (29.6)	20 (51.3)	2.50 (1.14~5.50)	0.023	
TCH ≤4.36 mmol/L					0.379
Yes	21 (28.8)	27 (60.0)	3.71 (1.70~8.12)	0.001	
No	27 (41.5)	36 (62.1)	2.30 (1.12~4.75)	0.024	
HDL-C ≤1.01 mmol/L					0.172
Yes	29 (32.6)	14 (43.8)	1.61 (0.70~3.68)	0.260	
No	19 (38.8)	49 (69.0)	3.52 (1.64~7.55)	0.001	
MHR ≤0.45					0.272
Yes	22 (41.5)	39 (60.0)	2.11 (1.01~4.42)	0.047	
No	26 (30.6)	24 (63.2)	3.89 (1.74~8.70)	0.001	

Abbreviations: BMI, body mass index; TCH, total cholesterol; HDL-C, high-density lipoprotein cholesterol; MHR, monocyte-to-high-density lipoprotein cholesterol ratio; OR, odds ratio; CI, confidence interval.

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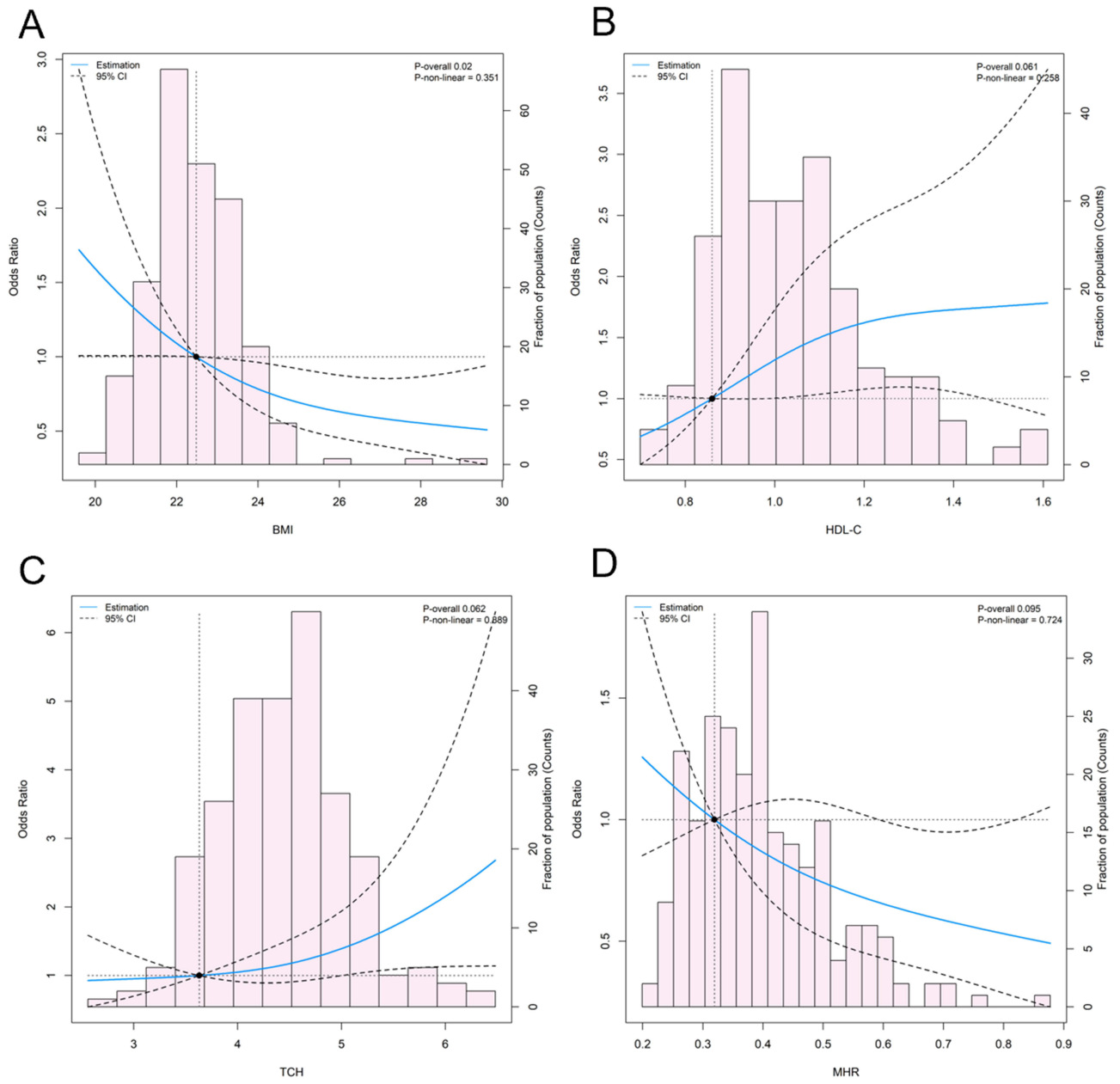

Figure 2 Restricted cubic spline analysis of the relationship between osteoporosis and BMI (**A**), HDL-C (**B**), TCH (**C**), MHR (**D**).
Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; TCH, total cholesterol; MHR, monocyte-to-high-density lipoprotein cholesterol ratio.

The Almost Linear Relationship Between BMI, TCH, HDL-C, MHR and Osteoporosis

RCS represents a specialized spline function designed to fit data by strategically selecting both the placement and number of knots. This method addresses complex nonlinear relationships, while remaining equally effective in describing linear regression analyses. To further validate the association between BMI, TCH, HDL-C, MHR and Osteoporosis in patients with type 2 diabetes, we performed RCS analysis (showed in Figure 2). The results showed a linear correlation between BMI and osteoporosis risk in patients with type 2 diabetes (p for overall = 0.02; p for nonlinear = 0.351; Figure 2A). Notably, with a threshold of 22.3, lower BMI was associated with an increased risk of osteoporosis, suggesting a potential link between BMI and the occurrence of osteoporosis. However, TCH, HDL-C, and MHR were not linearly correlated with osteoporosis (all $p > 0.05$).

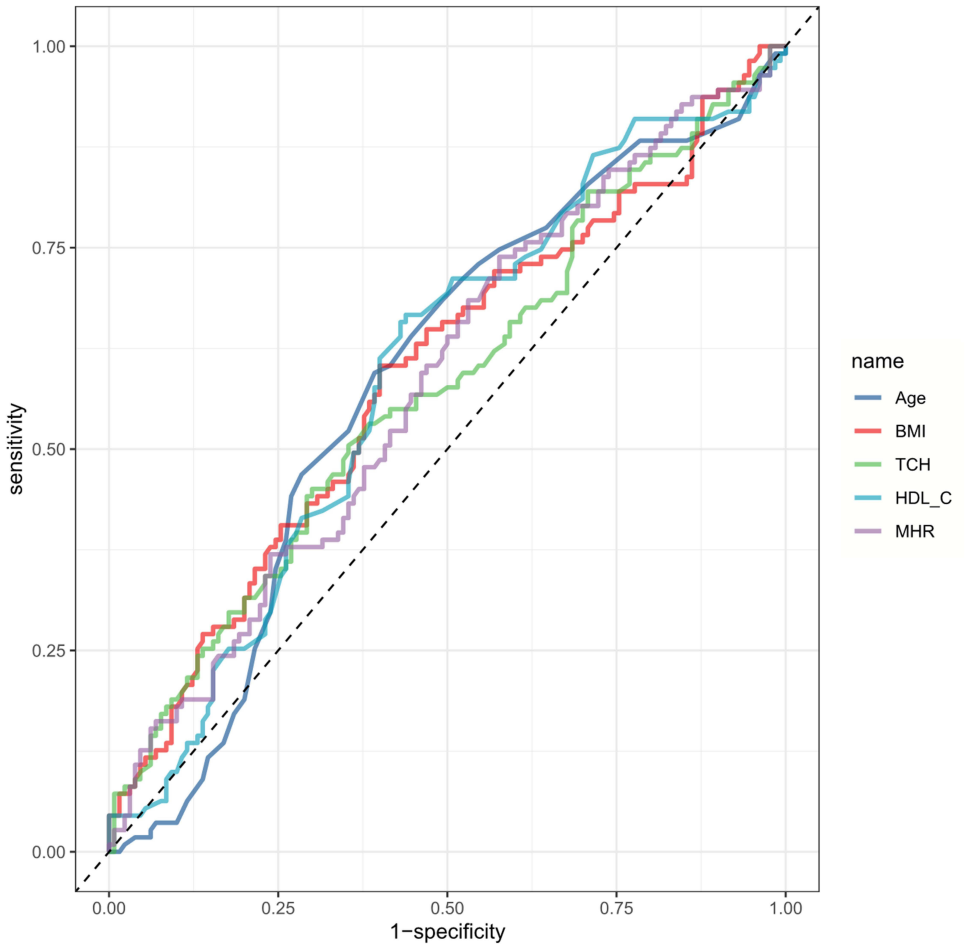

Figure 3 Receiver operating characteristic curves analysis to determine risk factors' predictive capacity for osteoporosis.
Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; TCH, total cholesterol; MHR, monocyte-to-high-density lipoprotein cholesterol ratio.

Analysis of ROC Curves

The identified risk factors were further evaluated using ROC curve analysis to determine their predictive capacity for osteoporosis. Among the parameters assessed (showed in Figure 3 and Table 7), HDL-C had the highest AUC (0.592, 95% CI: 0.520–0.665), with BMI next AUC (0.591, 95% CI: 0.519–0.664), followed by age AUC (0.586, 95% CI: 0.513–0.659). HDL had the highest sensitivity (66.67%), but average negative value (66.36%) among all, MHR had the highest sensitivity (73.87%), but the lowest specificity of all (42.31%). Although BMI had the highest specificity

Table 7 Prediction Performance of Parameters for Osteoporosis

Scale	Cut Point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)	*P*
Age	62.5	59.46	60.77	56.41	63.71	0.586 (0.513–0.659)	0.021
BMI	24.33	60.36	60.00	56.30	63.93	0.591 (0.519–0.664)	0.015
TCH	4.55	50.45	64.62	54.90	60.43	0.575 (0.502–0.648)	0.044
HDL-C	0.97	66.67	56.15	56.49	66.36	0.592 (0.520–0.665)	0.013
MHR	0.52	73.87	42.31	52.23	65.48	0.583 (0.511–0.655)	0.027

Abbreviations: BMI, body mass index; TCH, total cholesterol; HDL-C, high-density lipoprotein cholesterol; MHR, monocyte-to-high-density lipoprotein cholesterol ratio; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

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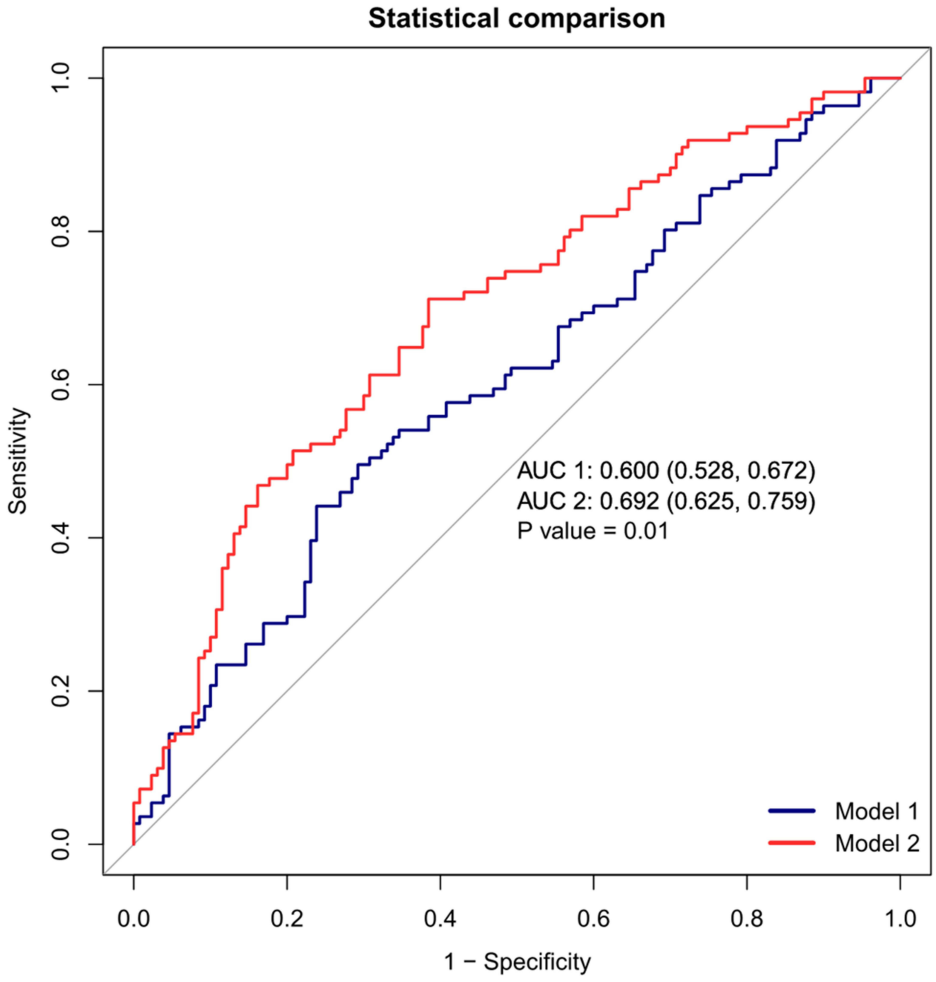
(60.00%) and positive prediction value (56.30%), but no indicator obtained an AUC greater than 0.6, the model's accuracy in distinguishing individuals at high and low risk for osteoporosis was poor. The results indicated that there are indeed some metabolic and physical indicators with clinical significance as screening indicators for predicting osteoporosis, but there were no indicators with independent diagnostic values. Therefore, two predictive models were constructed (showed in Figure 4). Model 1 combined the biochemical indicators, TCH, HDL-C, and MHR, as predictive factors. With the expanded parameters in Model 1, we designed Model 2, which included sex, age, and BMI as the predictive factors. Compared with Model 1, the prediction effect improved significantly, the first result was predictive of Model 1 with an AUC (0.600, 95% CI: 0.528–0.672), sensitivity of 49.55%, specificity 70.77%. Model 2 demonstrated a substantial increase in predictive accuracy, AUC (0.692, 95% CI: 0.625–0.759), sensitivity of 71.77%, specificity 61.54%, indicating when adding demographic and metabolic characteristics of T2DM into prediction model, the effect showed improvement in screening individuals with potential risk for osteoporosis in middle elderly patients.



Model	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)
Model 1	49.55	70.77	59.14	62.16	0.600 (0.528-0.672)
Model 2	71.77	61.54	61.24	71.43	0.692 (0.625-0.759)

Figure 4 The AUC (Area Under the Curve) analysis of model performance.
Notes: Model 1: TCH, HDL-C, and MHR; Model 2: Added sex, age, and BMI to Model 1.
Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; TCH, total cholesterol; MHR, monocyte-to-high-density lipoprotein cholesterol ratio.

Discussion

Osteoporosis remains a major public health issue, especially in aging individuals and patients with long-standing metabolic dysregulation such as T2DM. Although regarded as a condition related with aging, postmenopausal status, and hormonal disturbances, researchers now highlight the vital role of chronic low-grade inflammation and metabolic issues during the process of diabetic osteoporosis.[23] Our study was retrospective, aimed at investigating the association between clinical parameters, particularly inflammatory parameters drawn from commonly performed routine blood tests, and presence of osteoporosis in middle-aged or older patients with T2DM. The findings reveal that age, TCH, and BMI are independently associated with osteoporosis risk. Conversely, HDL-C and MHR initially showed promise, but lost significance after multivariate adjustment. RCS showed a linear correlation between BMI and osteoporosis risk in patients with T2DM. A multimodal model integrating demographic and metabolic factors (age, sex, BMI, TCH, HDL-C, and MHR) offers better predictive accuracy.

One of the most consistent findings of epidemiological and clinical studies is the strong inverse relationship between advanced age and BMD. Our data corroborate this trend, showing a significant negative correlation between age and BMD at both the lumbar and femoral sites.[24] Multivariate logistic regression confirmed age as an independent risk factor for osteoporosis. This aligns with the natural process of skeletal aging, which is characterized by declining osteoblast activity, increased adipogenesis in the bone marrow, and cumulative oxidative stress, all of which contribute to progressive bone loss. In the context of T2DM, age-related bone deterioration may be exacerbated by prolonged hyperglycemia, advanced glycation end products, and mitochondrial dysfunction, collectively impairing bone remodeling and reducing bone quality, even when BMD is preserved.

In our study, TCH was an independent predictor of osteoporosis. However, other studies have suggested that cholesterol has a protective effect on bones, supporting bone formation to a certain extent. Previously, it was believed that cholesterol was essential for the production of steroid hormones, such as vitamin D and sex hormones, which can help build bones in our bodies. However, a recent long-tracking study reported that excessive amounts of serum cholesterol cause oxidative stress and proinflammatory signals within the bones, which accelerates the production of osteoclasts while simultaneously suppressing the differentiation of osteoblasts.[25] A cohort study performed by Cao et al showed a U-shaped association between TCH and BMD values; both very low and high levels of TCH were associated with worse bone microarchitecture.[26] In our participants, higher levels of TCH indicated some kind of low-grade underlining dyslipidemia as a result of insulin-resistant states, the concurrent presence of which might promote further fracture as a result of impairing the vessels inside the patient's body (vascular endothelial cell injury, inflammation, and even disruption).

BMI is strongly protective against bone mineral loss and osteoporosis, in both single and multiple variables. This may be due to the mechanical load hypothesis, where higher physical weight leads to a normal strain to a healthy human bearing weight bones, promoting the development of the structures in a mechanical fashion itself.[27] Also present among the fats is a group of enzymes called aromatase, which is responsible for converting androgens into estrogens. Androgen and estrogen are key components in the production of other forms of steroid hormones necessary for healthy bones, especially postmenopausal female.[28] But yet this so-called positive role for obesity is more complicated than what previous theory would lead people to think, since we could argue that higher levels of adiposity and fat distribution would negatively interfere with a person's health, especially over the years. People thought BMI helps to produce more bone mass which protects from developing brittle bones and fractures, but recent epidemiological research contradicts this notion where subjects with higher central obesity or visceral adipose tissue had lower level of bone density despite regular BMI range and might have even higher T score, furthermore they would also tend to fracture easily.[29] Since in our study we used BMI not directly measuring or calculating body composition factors, future studies should involve body measurements for body compositions and possible interaction of visceral fats or lean body mass in combination with bone mass, all of these information will help to understand their relationship and predict risk of getting poor results such as osteopenia and fractures.

HDL-C has been known for its role in bone homeostasis as having anti-inflammatory, antioxidant, and endothelial protective functions.[30] Preclinical studies suggested that HDL could inhibit the RANKL mediated osteoclast

differentiation and could increase osteoblast survival through PI3K/Akt signaling.[31] In our univariate analysis, the risk of osteoporosis was positively correlated with HDL-C. This seemingly paradoxical result may be due to other factors such as age, sex, or BMI, which are related to bone status instead of HDL-C itself in the multivariate logistic analysis. This can also reflect dysfunction of HDL particles, also referred to as "HDL dysfunction", which refers to the loss of capacity of HDL despite normal or even high levels of HDL.[32] Such a commonly exists in T2DM, where HDL is dysfunctional. Thus, although the serum HDL-C level alone may not reliably predict bone status, its functional quality warrants further exploration as a potential biomarker of diabetic osteoporosis.

Among the other novel inflammatory indices, MHR showed a borderline significant association between HDL-C and osteoporosis in univariate analysis but lost significance after adjustment. Higher levels of monocytes are associated with higher production of cytokines, such as TNF-α and IL-1β, which stimulate osteoclast formation and suppress osteoblast proliferation.[33] As discussed before, inhibitory effects against these proinflammatory stimuli could possibly be achieved by HDL on monocytes with respect to adhesion and migration, preventing inflammation-associated osteolysis. Similar to some findings seen in research on cardiovascular disease, MHR only yielded marginal predictive power and did not have better performance than traditional scores.[34] Conversely, traditional indices, such as NLR, MLR, PLR, NHR, PHR, SII and SIRI, showed no significant association between osteoporosis, related fractures, and those parameters. We suppose that the indices were more likely representative of acute or subacute period inflammatory status than chronic, low-grade inflammation typical for patients affected by bone turnover. The absence of significant differences in the counts of blood elements, such as WBC, neutrophils, lymphocytes, and platelets, showed a relatively consistent status of inflammatory markers in the two groups of participants, explaining the lower discriminatory capacity of the generated indexes derived by them.

ROC curve analysis revealed modest discriminatory accuracy for individual predictors, with AUCs < 0.6 for age, BMI, and HDL-C. This highlights the limitations of relying on a single biomarker for screening osteoporosis. However, when integrated into a composite model incorporating demographic, anthropometric, and biochemical variables, the AUC improved to 0.692, indicating that multimodal assessment enhanced the predictive performance. Nowadays, there are some studies on machine learning models for predicting osteoporosis in patients with T2DM, most studies found sex, age were predictors, but laboratory indicators were changeable, including alkaline phosphatase, uric acid, and hemoglobin.[35–38] Our study found the model combined age, sex, BMI, TCH, HDL-C, and MHR predicted better, indicating the metabolic and inflammatory indices may play a role in the osteoporosis with T2DM. Due to multiple factors leading to the occurrence of osteoporosis in T2DM, future studies could explore the integration of additional parameters, such as glycated albumin, urinary N-terminal telopeptide, or genetic polymorphisms related to bone metabolism, to further refine the predictive models.

As mentioned before, many mechanisms, such as chronic hyperglycemia, insulin resistance, advanced glycation end-product accumulation, excessive oxidative stress, and increased low-grade systemic inflammation, have been proposed in relation to T2DM and osteoporosis. Some new therapeutic targets have been gradually discovered and shown potential. AGEs inhibitors such as aminoguanidine and can improve the structure and function of bone matrix by inhibiting the formation of AGEs.[39] In addition, anti-RAGE drugs are expected to reduce inflammation and oxidative stress by blocking the binding of AGEs to their receptors.[40] Another potential therapeutic target is oxidative stress regulators, which can indirectly slow down osteoclast activation and osteoblast dysfunction.[41] The development of new targeted drugs is expected to provide more precise and effective solutions for the treatment of osteoporosis in T2DM.

Our study has several strengths. First, we utilized dual-energy X-ray absorptiometry, the gold standard for BMD measurement, with strict quality control protocols.[42] Second, our analytical approach included restricted cubic spline modeling to account for potential nonlinearity, enhancing the robustness of the observed associations. Third, we systematically evaluated a broad panel of hematological and metabolic markers, allowing comprehensive risk factor profiling. However, the limitations of this study must be acknowledged. The retrospective design limits causal inference and selection bias may exist because of the single-center nature of the study. Although adequate for primary analyses, the sample size may lack the power to detect smaller effect sizes, particularly in subgroup comparisons. Some residual confounders, such as antidiabetic medications, lipid-lowering therapy, menopausal duration, and calcium/vitamin D supplementation, were not clearly found in the record information. Additionally, we did not assess fracture incidence

or the ultimate clinical outcome of osteoporosis, nor did we evaluate bone microarchitecture using advanced techniques, such as trabecular bone score or high-resolution peripheral quantitative computed tomography. However, we speculated that our study could help clinicians identify high-risk T2DM patients with osteoporosis.

Conclusion

In conclusion, our findings indicate that among patients with T2DM, advancing age, lower BMI, and elevated TCH are independent risk factors for osteoporosis. Although the univariate analyses suggested potential links between certain inflammatory markers and osteoporosis risk, these associations did not persist after adjusting for confounding variables. This observation implies that traditional metabolic and anthropometric parameters may play critical roles in predicting osteoporosis in this patient population. Additionally, we developed a composite predictive model integrating demographic and biochemical data, which significantly improved diagnostic accuracy. However, the current model was derived from a single-center cohort with limited ethnic diversity, potentially limiting its applicability to broader populations, and residual confounders may have masked subtle associations between inflammatory markers and osteoporosis, future studies should adopt a prospective design, include larger and more diverse cohorts, extend follow-up periods, and incorporate advanced bone-imaging modalities. The composite model also should be validated in real-world population and we can develop AI-integrated electronic health record tools that automatically apply the predictive model to flag high-risk patients, enabling personalized bone health management.

Data Sharing Statement

The data supporting the findings of this study are available on request from the corresponding author Hui Wang.

Author Contributions

YW: Conceptualization; Writing-Original Draft; Methodology; Investigation. YXD; JZ: Visualization; Software; Data Curation. LHH; YS: Data Curation; Formal analysis; YY; YL: Investigation; Data Curation. HTZ; HW: Writing-Review & Editing; Project administration; Conceptualization; Resources.

All authors made a significant contribution to the work reported, whether 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 conflicts of interest in this work.

References

1. Kanis JA, Judson I, Verweij J, et al. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet*. 2001;358(9290):1421–1424. doi:10.1016/s0140-6736(01)06535-7
2. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int*. 2006;17(12):1726–1733. doi:10.1007/s00198-006-0172-4
3. Chinese Society for Osteoporosis and Bone Mineral Research. Guidelines for the diagnosis and treatment of primary osteoporosis (2022). *Chin J Osteoporosis Bone Miner Res*. 2022;15(06):573–611.
4. Wang L, Yu W, Yin X, et al. Prevalence of osteoporosis and fracture in China: the China osteoporosis prevalence study. *JAMA Network Open*. 2021;4(8):e2121106. doi:10.1001/jamanetworkopen.2021.21106
5. Ceriello A, Colagiuri S. IDF global clinical practice recommendations for managing type 2 diabetes - 2025. *Diabet Res Clin Pract*. 2025;222 Suppl 1:112152. doi:10.1016/j.diabres.2025.112152

6. Zhou Y, Liu J, Zhao Z, et al. The national and provincial prevalence and non-fatal burdens of diabetes in China from 2005 to 2023 with projections of prevalence to 2050. *Mil Med Res*. 2025;12(1):28. doi:10.1186/s40779-025-00615-1
7. Liu X, Chen F, Liu L, et al. Prevalence of osteoporosis in patients with diabetes mellitus: a systematic review and meta-analysis of observational studies. *BMC Endocr Disord*. 2023;23(1):1. doi:10.1186/s12902-022-01260-8
8. Sheu A, Greenfield JR, White CP, et al. Assessment and treatment of osteoporosis and fractures in type 2 diabetes. *Trends Endocrinol Metab*. 2022;33(5):333–344. doi:10.1016/j.tem.2022.02.006
9. Napoli N, Chandran M, Pierroz DD, et al. Mechanisms of diabetes mellitus-induced bone fragility. *Nat Rev Endocrinol*. 2017;13(4):208–219. doi:10.1038/nrendo.2016.153
10. Su S, Lee Y, Tsai Y, et al. Glycemic control and fracture risk in patients with type 2 diabetes mellitus. *Int J Rheum Dis*. 2025;28(2):e70103. doi:10.1111/1756-185X.70103
11. Zhang X, Xu D, Zhang R, Wang H, Yang G. Interaction between diabetes and osteoporosis: imbalance between inflammation and bone remodeling. *Osteoporos Int*. 2025;36(12):2401–2409. doi:10.1007/s00198-025-07636-5
12. Nayak SPRR, Haridevamuthu B, Murugan R, et al. Furan-based chalcone protects β-cell damage and improves glucose uptake in alloxan-induced zebrafish diabetic model via influencing peroxisome proliferator-activated receptor agonists (PPAR-γ) signaling. *Process Biochem*. 2024;142:149–161. doi:10.1016/j.procbio.2024.04.012
13. Pohokar P, Nayak SPRR, G K, et al. Protective role of dibenzylideneacetone derivative (MBK2) against diabetic pathophysiology via PTGS2-PGE2 signaling modulation and redox homeostasis. *Biochem Pharmacol*. 2026;243(Pt 1):117526. doi:10.1016/j.bcp.2025.117526
14. Rasmussen NH, Dal J. Falls and fractures in diabetes-more than bone fragility. *Curr Osteoporos Rep*. 2019;17(3):147–156. doi:10.1007/s11914-019-00513-1
15. Trimpou P, Oden A, Simonsson T, et al. High serum total cholesterol is a long-term cause of osteoporotic fracture. *Osteoporos Int*. 2011;22(5):1615–1620. doi:10.1007/s00198-010-1367-2
16. Kan B, Zhao Q, Wang L, et al. Association between lipid biomarkers and osteoporosis: a cross-sectional study. *BMC Musculoskelet Disord*. 2021;22(1):759. doi:10.1186/s12891-021-04643-5
17. Qi S, Peng B, Xu Z, et al. The relationship between non-HDL-C/HDL-C ratio and bone mineral density: an NHANES study. *Front Nutr*. 2024;11:1486370. doi:10.3389/fnut.2024.1486370
18. He L, Xie X, Xue J, et al. Association of the systemic immune-inflammation index with all-cause mortality in patients with arteriosclerotic cardiovascular disease. *Front Cardiovasc Med*. 2022;9:952953. doi:10.3389/fcvm.2022.952953
19. Huang L, Li X, Zhou W, et al. The clinical value of the neutrophil-to-lymphocyte ratio, the C-reactive protein-to-albumin ratio, the systemic inflammatory index, and the systemic inflammatory response index in patients with the anti-synthetase syndrome. *J Inflammation Res*. 2024;17:3617–3628. doi:10.2147/JIR.S460610
20. Zhu L, Yuan X. Associations between monocyte to HDL-C ratio and lumbar bone mineral density in alcohol dependent individuals with depression. *Sci Rep*. 2025;15(1):15817. doi:10.1038/s41598-025-00885-8
21. Xia P, Jiang Y, Cai F, Peng S, Xu Z. Construction and verification of risk prediction model of osteoporotic fractures in patients with osteoporosis in China. *Front Public Health*. 2024;12:1380218. doi:10.3389/fpubh.2024.1380218
22. Moldovan F, Moldovan L. A modeling study for hip fracture rates in Romania. *J Clin Med*. 2025;14(9):3162. doi:10.3390/jcm14093162
23. Li C, Gong H, Shi P, Liu S, Zhang Q. Different forms of regulated cell death in type-2-diabetes-mellitus-related osteoporosis: a focus on mechanisms and therapeutic strategies. *Int J Mol Sci*. 2025;26(9):4417. doi:10.3390/ijms26094417
24. Lee CY, Kim HJ, Kim TH, et al. Relationship between type 2 diabetes mellitus and lumbar bone mineral density in postmenopausal women. *Asian Spine J*. 2021;15(6):721–727. doi:10.31616/asj.2021.0099
25. Anagnostis P, Florentin M, Livadas S, Lambrinoudaki I, Goulis DG. Bone health in patients with dyslipidemias: an underestimated aspect. *Int J Mol Sci*. 2022;23(3):1639. doi:10.3390/ijms23031639
26. Cao L, Wu W, Deng X, et al. Association between total cholesterol and total bone mineral density in US adults: national health and nutrition examination survey (NHANES), 2011-2018. *J Orthopaedic Surg Res*. 2023;18(1):40. doi:10.1186/s13018-022-03485-8
27. Dytfeld J, Ignaszak-Szczepaniak M, Gowin E, Michalak M, Horst-Sikorska W. Influence of lean and fat mass on bone mineral density (BMD) in postmenopausal women with osteoporosis. *Arch Gerontol Geriatr*. 2011;53(2):e237–42. doi:10.1016/j.archger.2011.01.002
28. Yeom S, Lee DH, Song J. Therapeutic potential of anti-diabetes drugs and anti-dyslipidemia drugs to mitigate head and neck cancer risk in metabolic syndrome. *CNS Neurosci Ther*. 2025;31(5):e70446. doi:10.1111/cns.70446
29. Ha J, Baek KH. Body mass index at the crossroads of osteoporosis and type 2 diabetes. *Korean J Internal Med*. 2020;35(6):1333–1335. doi:10.3904/kjim.2020.540
30. Li S, Liu Y, Sun G, et al. The predictive value of hsCRP/HDL-C ratio for cardiometabolic multimorbidity in middle-aged and elderly people: evidence from a large national cohort study. *Front Nutr*. 2025;12:1580904. doi:10.3389/fnut.2025.1580904
31. Jiang C, Wang Y, Zhang M, Xu J. Cholesterol inhibits autophagy in RANKL-induced osteoclast differentiation through activating the PI3K/AKT/mTOR signaling pathway. *Mol Biol Rep*. 2022;49(10):9217–9229. doi:10.1007/s11033-022-07747-w
32. Dule S, Barchetta I, Cimini FA, et al. Reduced high-density lipoprotein cholesterol is an independent determinant of altered bone quality in women with type 2 diabetes. *Int J Mol Sci*. 2023;24(7):6474. doi:10.3390/ijms24076474
33. Tsukasaki M, Takayanagi H. Osteoimmunology: evolving concepts in bone-immune interactions in health and disease. *Nat Rev Immunol*. 2019;19(10):626–642. doi:10.1038/s41577-019-0178-8
34. Lin N, Li D, Lin S, et al. The monocyte-to-high-density lipoprotein cholesterol ratio as a novel predictor of the prevalence of senile osteoporosis. *Clin Interv Aging*. 2024;19:1773–1788. doi:10.2147/CIA.S478461
35. Wu X, Zhai F, Chang A, et al. Development of machine learning models for predicting osteoporosis in patients with type 2 diabetes mellitus—a preliminary study. *Diab Metab Syndrome Obes*. 2023;16:1987–2003. doi:10.2147/DMSO.S406695
36. Yu X, Liu W, Chen X, et al. Construction of a novel online calculator for prediction of osteoporosis risk in Chinese type 2 diabetes patients. *Exp Gerontol*. 2025;208:112819. doi:10.1016/j.exger.2025.112819
37. Zhan J, Wei Q, Guo W, et al. Evaluating the triglyceride glucose index as a predictive biomarker for osteoporosis in patients with type 2 diabetes. *Front Endocrinol*. 2025;16:1534232. doi:10.3389/fendo.2025.1534232

38. Wei Q, Liu Z, Chen X, et al. Development and validation of an explainable machine learning model for predicting osteoporosis in patients with type 2 diabetes mellitus. *Front Endocrinol*. 2025;16:1611499. doi:10.3389/fendo.2025.1611499
39. Gurbuz N, Gurkan R, Ender Caylan A, Surmen Usta S, Usta MF. The therapeutic effect of ALT-711 on erectile function in rats treated with high-level AGEs (advanced glycation end products) containing diet. *Int J Impot Res*. 2022;34(2):222–228. doi:10.1038/s41443-021-00417-8
40. El-Far AH, Sroga G, Jaouni SKA, Mousa SA. Role and mechanisms of RAGE-ligand complexes and RAGE-inhibitors in cancer progression. *Int J Mol Sci*. 2020;21(10):3613. doi:10.3390/ijms21103613
41. Priya PS, Nayak SPRR, Margesan T, et al. Investigating the osteoprotective effects of quercetin and rutin from Terminalia chebula in glucocorticoid-induced osteoporosis in vitro cell line and in vivo zebrafish model. *S Afr J Bot*. 2024;175:712–722. doi:10.1016/j.sajb.2024.10.060
42. Gani LU, McClung MR, Binkley N, et al. Follow-up bone mineral density testing: 2023 official positions of the international society for clinical densitometry. *J Clin Densitom*. 2024;27(1):101440. doi:10.1016/j.jocd.2023.101440