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Development and validation of a novel glucolipid metabolism-related nomogram to enhance the predictive performance for osteoporosis complications in prediabetic and diabetic patients

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Abstract

Background Diabetes is the most prevalent metabolic disorder worldwide, imposing a significant economic burden on society. Prediabetes has not received as much attention as diabetes, and among its complications, osteoporosis has been relatively under-researched compared to cardiovascular disease. Recent studies have identified nine indices related to glucose and lipid metabolism that may enhance osteoporosis risk assessment in diabetic and prediabetic individuals. The research examined the osteoporosis risk prediction potential of these indices and developed a nomogram to enhance predictive performance.

Methods 2,735 prediabetic and diabetic subjects were derived from National Health and Nutrition Examination Survey (NHANES) dataset collected between 2011 and 2020, then randomly assigned to development and validation cohorts in 7:3. The predictive capacity of glucolipid metabolism-related indices for osteoporosis risk was evaluated using receiver operating characteristic (ROC) curve analysis. The least absolute shrinkage and selection operator (LASSO) and multivariate logistic regression were used to identify predictors for constructing the risk model, which was visualized using a nomogram. The model's performance was further validated.

Results All the glucolipid metabolism-related indices showed predictive ability, and the best-performing index was metabolic score for insulin resistance (METS-IR). Multivariate logistic regression identified 5 predictors [Triglyceride-glucose index (TyG), age, METS-IR, TyG-waist circumference, and TyG-body mass index] with good predictive

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performance. These predictors were selected to establish the nomogram. ROC curve, calibration plot, as well as decision curve analysis (DCA) collectively demonstrated fairly good predictive ability of the nomogram.

Conclusions Glucolipid metabolism-related indices are the predictors of osteoporosis risk. This newly developed nomogram based on glucolipid metabolism indices demonstrates optimal predictive accuracy for assessing combined osteoporosis risk in individuals with prediabetes and diabetes.

Keywords Osteoporosis, Diabetes, Prediabetes, Glucolipid metabolism, Nomogram

Background

Diabetes is the most prevalent metabolic disorder worldwide and causes a huge economic burden on society [1, 2]. In 2021, approximately 10.5% of the global population were affected by diabetes, the proportion would increase to 12.2% in 2045 [2]. The global cost associated with diabetes is expected to increase from 966 billion dollars in 2021 to 1,054 billion dollars in 2045 [2]. Prediabetes is a stage of glucose dysregulation and is defined as a fasting glucose level higher than normal glucose but lower than the level of diabetes [3]. Diabetes and prediabetes are inseparable and represent a pathophysiologic continuum, given their shared diagnostic methods and pathogenic mechanisms [4]. It is reported that, in the U.S. population, 1 in 3 has been diagnosed with prediabetes and nearly 1 in 10 prediabetic patients would progress to type 2 diabetes annually [3]. Globally, 1 billion people are projected to be affected by prediabetes by 2045 [2]. Both diabetes and prediabetes have a huge impact on health. Patients with diabetes showed twice the mortality risk than people with normoglycemia [4]. Similarly, many studies also have described that prediabetic patients showed damaged function of many organs, higher rates of hospitalization, and higher mortality risk compared with individuals with normal glucose levels [5, 6]. However, most previous studies have predominantly examined diabetes while paying scant attention to prediabetes. Prediabetic individuals were frequently classified alongside normoglycemic subjects under the broad category of "non-diabetic", thus ignoring the effect of prediabetes on health and making primary prevention difficult for these patients [7]. Therefore, due to the similarity of pathophysiology in diabetic and prediabetic patients, when planning to explore the adverse consequences of uncontrolled blood glucose, diabetic and prediabetic patients should be taken into consideration as a whole.

It is well known that diabetes and prediabetes are tightly associated with many comorbidities [8–11]. A large percentage of studies were focused on cardiovascular complications, including devastating macrovascular complications (such as coronary artery disease) as well as microvascular pathologies (particularly diabetic retinopathy) [12]. However, compared with cardiovascular complications, the putative association between diabetes/prediabetes and osteoporosis complications risk has been less extensively studied. According to previous research, long-term hyperglycemia increases the risk of bone loss, while prediabetes or diabetes is often found in individuals diagnosed with osteoporosis [13, 14]. Importantly, the risk of coexisting osteoporosis was more pronounced in prediabetes compared with diabetes, suggesting that the negative effects of uncontrolled blood glucose may start before a diabetes diagnosis [15]. Extensive research has shown that patients with impaired glucose metabolism (diabetes as well as prediabetes) exhibit significantly elevated osteoporosis risk compared with the general population, with greater disability and mortality rates linked to this complication [16, 17]. Nonetheless, prediabetes has not received the same level of attention as diabetes, and among the complications, osteoporosis has received relatively little attention compared with the research enthusiasm of cardiovascular disease. Clinically, early screening and then treating patients with higher osteoporosis complication risk would be valuable for the more efficient management of osteoporosis and prevent them from causing more disastrous events, such as osteoporotic fractures.

Recently, the potential association between glucose or lipid metabolism disorders and bone metabolism has garnered increasing attention. Various indicators have been proposed in the past to predict the osteoporosis risk in patients with diabetes and prediabetes, such as triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) [18–20]. However, existing literature has reported the limited predictive performance of TG or HDL-C, and conflicting relationships between TG or HDL-C and osteoporosis risk [21]. Therefore, composite indices based on glucose or lipid parameters have been developed. Over the past two years, numerous journals have continuously published studies on emerging glucolipid metabolism-related indicators designed to enhance predictive effectiveness. The following is a list of new glucolipid metabolism-related indicators, which integrate multiple parameters: atherogenic index of plasma (AIP) [15], triglyceride-glucose (TyG) index [22], lipid accumulation products (LAP) [23], TyG-waist circumference (TyG-WC) [22], homeostasis model assessment of insulin resistance (HOMA-IR) [24], TyG-WC/height (TyG-WHtR) index [22], visceral adiposity index (VAI) [25], TyG-body mass index (TyG-BMI) [22,

26], as well as metabolic score for IR (METS-IR) [24]. Despite existing literature confirms the osteoporosis predictive ability of all 9 biomarkers, it remains unclear which glucolipid metabolism-related indicator offers the best predictive efficacy for clinical use. A systematic comparative analysis of these indicators could better address clinical needs than the ongoing development of new composite measures. Besides, previous studies indicate that the areas under the curves (AUC) for these 9 indicators generally range from 0.6 to 0.7, with only a few indicators having an AUC exceeding 0.7 [27–30]. Hence, after evaluating the efficacy of every biomarker, it is essential to integrate the most effective ones to construct a nomogram to enhance the osteoporosis risk prediction in prediabetic or diabetic populations.

Employing the National Health and Nutrition Examination Survey (NHANES) data, this investigation evaluated and compared the predictive capacity of 9 glucolipid metabolic indices for osteoporosis risk assessment in glucose-impaired populations (diabetes as well as prediabetes), subsequently constructing a nomogram to optimize risk stratification.

Methods

Study population

The investigation employed a cross-sectional design with all data sourced from NHANES 2011–2020 database. The NHANES database, offering open access through its website (https://www.cdc.gov/nchs/nhanes/index.htm), covers a demographically representative cross-section of U.S. civilian residents [31]. Each enrolled individual provided documented informed consent. Therefore, institutional review board approval was exempted as this observational analysis exclusively utilized de-identified NHANES data publicly available.

The study enrollment criteria consisted of: (1) data from NHANES 2011–2020; (2) diagnosed with prediabetes or diabetes. According to the 2013 American Diabetes Association guidelines, patients with glycosylated hemoglobin A1c (HbA1c) level between 5.7% and 6.4%, or fasting blood glucose (FBG) level between 5.6 mmol/L and 7.0 mmol/L were diagnosed with prediabetes. Patients with HbA1c level higher than 6.5%, or FBG level higher than 7 mmol/L, or self-reported doctor-diagnosed diabetes, or the use of insulin or oral hypoglycemic agents were defined as diabetes. Exclusion criteria were as follows: (1) subjects aged ≤ 18 years; (2) probable type 1 diabetes (defined as subjects younger than 20 years managed solely with insulin); (3) with incomplete study variables, including FBG, TG, HbA1c, and HDL-C; (4) documented malignancies, renal failure, or any liver-related disease, including potential liver disease (aspartate/alanine aminotransferase ≥ 120 U/L) or renal insufficiency [serum creatinine (SCr) ≥ 133 μmol/L]; (5) continuous variables with abnormal values; (6) lack of bone mineral density (BMD) data; (7) individuals with normal blood glucose or who cannot be diagnosed with diabetes or prediabetes. Finally, 2,735 subjects were included in the following analysis and were further randomly allocated to development (1,914) as well as validation cohort (821) in 7:3. The detailed screening process of participants was shown in Supplementary Fig. 1.

Glucolipid metabolism-related indices measurement

Nine glucolipid metabolism-related indicators were included in this study, all of which can be used to reflect IR. The HOMA-IR is calculated by FBG and insulin concentration and is regarded as a validated marker of IR. Because insulin concentration is not one marker that is routinely tested, other biomarkers without insulin concentrations, such as TyG, are developed. METS-IR computation involves four parameters: FBG, TG, BMI, as well as HDL-C [24]. Calculation of TyG requires TG and FBG. A few biomarkers combining TyG and adiposity indices, including TyG-BMI and TyG-WHtR, have shown superior predictive performance for certain clinical conditions [32]. The AIP is regarded as a marker for plasma atherosclerosis and is derived from the combination of TG and HDL-C [33]. Two novel metabolic markers were also studied. The LAP is calculated by WC and TG. The VAI is calculated by WC, BMI, TG, and HDL-C [34]. The detailed calculation formulas of glucolipid metabolism-related indices were shown in Supplementary Table 1.

Osteoporosis assessment

All the data of BMD collected in the NHANES database were scanned and measured through dual-energy X-ray absorptiometry (HOLOGIC Discovery A, U.S.). This study was limited by the missing values and discontinuities for BMD data collection in the NHANES database during the period 2011–2020, and ultimately only BMD data of the whole body as well as the total femur (TF), pelvis and lumber spine (LS) sites were included as study parameters. The T-score of BMD was defined as the difference between an individual's BMD and the BMD of the young healthy population divided by the standard deviation (SD) of the BMD of the young healthy population. Following the recommendations in the previous literature [35, 36], the mean BMD values at the corresponding sites in non-Hispanic White males and females aged 20–29 years from the NHANES database were used as a reference value for BMD in the young healthy population. Based on the World Health Organization diagnostic criteria, individuals with a BMD T-score less than or equal to -2.5 SD from the reference value are diagnosed with osteoporosis. Moreover, those with a BMD T-score between −1.0 SD and −2.5 SD are diagnosed with

osteopenia, while a score of ≥ -1.0 SD is regarded as normal BMD.

Covariates selection

A total of 32 covariates were included, including 4 demographic factors, 3 anthropometric factors, 9 laboratory factors, 7 questionnaire factors, and 9 composite indicators. Age, family income-to-poverty ratio, all the anthropometric data (BMI, height, and WC), all the laboratory data [TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), FBG, fasting serum insulin (FSIN), HbA1c, serum calcium and phosphorus, and SCr], as well as all the composite indicators (TyG-WHtR, VAI, AIP, TyG-BMI, METS-IR, LAP, TyG-WC, HOMA-IR, and TyG) were treated as continuous variables, other factors were regarded as categorical variables. Sex was categorized as male and female. Race was divided into Non-Hispanic White, Non-Hispanic Black, Mexican-American, and Other Race. Smoking status was divided into former, never as well as current. The variables of alcohol consumption, hypertension, and drug interventions (including the use of insulin, oral hypoglycemic agents, lipid-lowering agents, and antihypertensive agents) were respectively divided into yes or no. The NHANES official website (https://www.cdc.gov/nchs/nhanes/index.htm) provides complete details regarding all study variables.

Construction and validation of the nomogram

The 1,914 participants in the development cohort were employed to build the model. The least absolute shrinkage and selection operator (LASSO) regression was first used to select the variables. Based on the result of LASSO regression, multivariate logistic regression analysis was further employed to determine osteoporosis risk factors with statistical significance. Multicollinearity was assessed using the variance inflation factor (VIF). A nomogram containing the significant variables in the multivariable analysis was used to visualize this model. Restricted cubic splines (RCS) analysis was used to analyze the non-linear relationships between variables included in the nomogram and osteoporosis risk.

Next, the predictive performance of this nomogram needs to be further assessed. Model validation included bootstrap resampling and internal validation with the validation cohort. During the bootstrap resampling process, the regression model was fitted with 500 repeated samplings based on the bootstrap resampling technique, that is, resampling was performed by centrally extracting and replacing from the development cohort, and each repetition reperforms the predictor selection and model fitting so that it can be tested on the original development cohort for model performance evaluation. The 821 participants in validation cohort were further employed to validate this model. Model discrimination was assessed through ROC curve and AUC. Calibration curves evaluated the model's predictive accuracy against observed outcomes. The clinical utility of the model was evaluated by the decision curve analysis (DCA). Net reclassification improvement (NRI) was used to quantify the predictive improvement between single indicators and integrated models.

Statistical analysis

R-software (version 4.4.0) and IBM SPSS Statistical software 23.0 (SPSS, Chicago, IL, USA) were employed for statistical analyses. Based on the results of Kolmogorov-Smirnov test, continuous variables were classified as normally distributed continuous variables, such as height, and non-normally distributed continuous variables. The former was reported as mean ± SD, and the latter was reported as median (first interquartile range [IQR], third IQR). Categorical variables, such as male, race, and smoking status, were reported as frequencies and proportions. All the categorical variables in overall cohort, development cohort, and validation cohort were analyzed by chi-squared test.

ROC curve and the AUC were used for assessment of the predictive performance of glucolipid metabolism-related indices for osteoporosis complications in prediabetic or diabetic populations. Statistical significance was defined as a two-tailed *P* value below 0.05.

Results

Baseline characteristics of the study population

2,735 participants with prediabetes or diabetes were finally included. Among them, 1,914 participants were randomly assigned to the development cohort and 821 to the validation cohort. In the overall cohort, 56.1% were male, 17.2% were Mexican-American, the family income-to-poverty ratio was 2.17 (1.10, 3.70), and the average age was 45 (35, 54) years. Among all the participants, the mean FBG was 5.94 (5.61, 6.44) mmol/L, the HbA1c was 5.7% (5.4%, 6.0%), 39.0% were treated with oral hypoglycemic drugs, 4% were treated with insulin. In the development cohort, the mean FBG and HbA1c were 5.94 (5.61, 6.49) and 5.7% (5.4%, 6.0%), respectively. While in the validation cohort, the mean FBG and HbA1c were 5.93 (5.61, 6.44) and 5.7% (5.4%, 6.1%), respectively. Specifically, all evaluated baseline characteristics demonstrated statistical equivalence across both cohorts (all *P* values exceeding 0.05). Table 1 presents comprehensive baseline data.

The predictive performance of glucolipid metabolism-related indices for osteoporosis risk

To systematically examine the predictive capability of these parameters, as well as to identify the best-performing indicators, the predictive utility of nine glucolipid

Table 1 Baseline characteristics of patients with prediabetes and diabetes in the development cohort and validation cohort

Variables	All cohort (*n* = 2735)	Development cohort (*n* = 1914)	Validation Cohort (*n* = 821)	*P*
Demographics data				
Age (years)	45 (35, 54)	45 (35, 54)	46 (36, 55)	0.263
Male, n (%)	1534 (56.1)	1084 (56.7)	450 (54.8)	0.401
Race, n (%)				0.391
Non-Hispanic White	818 (29.9)	582 (30.4)	236 (28.8)	
Non-Hispanic Black	624 (22.8)	426 (22.3)	198 (24.1)	
Mexican-American	471 (17.2)	320 (16.7)	151 (18.4)	
Other Race	822 (30.1)	586 (30.6)	236 (28.8)	
Family income-to-poverty ratio	2.17 (1.10, 3.70)	2.20 (1.10, 3.67)	2.13 (1.10, 3.73)	0.646
Anthropometric data				
BMI (kg/m^2)	29.3 (25.6, 34.2)	29.2 (25.6, 34.1)	29.6 (25.6, 34.5)	0.229
Height (cm)	168.1 ± 10.0	168.1 ± 9.9	168.1 ± 10.3	0.859
WC (cm)	100.2 (91.4, 111.5)	100.1 (91.2, 111.0)	100.7 (91.7, 112.8)	0.508
Laboratory data				
TG (mmol/L)	1.19 (0.82, 1.78)	1.20 (0.82, 1.80)	1.17 (0.80, 1.76)	0.582
HDL-C (mmol/L)	1.24 (1.06, 1.50)	1.24 (1.03, 1.50)	1.27 (1.06, 1.47)	0.688
LDL-C (mmol/L)	3.03 (2.46, 3.65)	3.04 (2.43, 3.65)	3.03 (2.48, 3.67)	0.717
FBG (mmol/L)	5.94 (5.61, 6.44)	5.94 (5.61, 6.49)	5.93 (5.61, 6.44)	0.589
HbA1c (%)	5.7 (5.4, 6.0)	5.7 (5.4, 6.0)	5.7 (5.4, 6.1)	0.981
FINS (μU/mL)	11.65 (7.48, 18.22)	11.69 (7.63, 17.94)	11.61 (6.93, 18.47)	0.739
SCr (μmol/L)	73.37 (61.00, 84.86)	73.37 (61.00, 84.86)	72.49 (61.88, 83.98)	0.741
Serum calcium (mmol/L)	2.33 (2.28, 2.38)	2.33 (2.28, 2.38)	2.33 (2.28, 2.38)	0.472
Serum P (mmol/L)	1.16 (1.03, 1.26)	1.16 (1.04, 1.26)	1.16 (1.03, 1.26)	0.530
Questionnaire data				
Smoking status, n (%)				0.198
Never	1519 (55.5)	1045 (54.6)	474 (57.7)	
Former	588 (21.5)	428 (22.4)	160 (19.5)	
Current	628 (23.0)	441 (23.0)	187 (22.8)	
Alcohol consumption, n (%)	1829 (66.9)	1288 (67.3)	541 (65.9)	0.504
Hypertension, n (%)	938 (34.3)	640 (33.4)	298 (36.3)	0.162
Drug interventions, n (%)				
Antihypertensive agents	2300 (84.1)	1611 (84.2)	689 (83.9)	0.916
Oral hypoglycemic agents	1067 (39.0)	744 (38.9)	323 (39.3)	0.850
Insulin	110 (4.0)	71 (3.7)	39 (4.8)	0.245
Lipid-lowering agents	871 (31.9)	618 (32.3)	253 (30.8)	0.476
Composite indicators				
TyG	8.62 (8.20, 9.07)	8.63 (8.22, 9.08)	8.62 (8.16, 9.06)	0.304
TyG-BMI	256.15 (219.23, 302.22)	255.28 (218.95, 299.45)	256.74 (219.91, 312.68)	0.136
TyG-WC	871.97 (772.72, 990.49)	869.19 (771.89, 982.50)	876.91 (774.54, 1006.80)	0.183
TyG-WHtR	5.21 (4.58, 5.91)	5.20 (4.57, 5.90)	5.24 (4.61, 5.95)	0.419
AIP	-0.03 (-0.25, 0.21)	-0.03 (-0.24, 0.21)	-0.02 (-0.26, 0.22)	0.872
HOMA-IR	3.20 (1.99, 5.21)	3.22 (2.03, 5.15)	3.14 (1.88, 5.28)	0.546
METS-IR	48.13 (40.66, 57.57)	47.87 (40.87, 57.15)	48.34 (40.50, 57.89)	0.341
LAP	47.36 (27.45, 77.19)	47.61 (27.64, 76.52)	46.73 (26.78, 79.36)	0.282
VAI	1.53 (0.93, 2.60)	1.54 (0.94, 2.64)	1.52 (0.91, 2.50)	0.775

Normally distributed continuous variables were reported as mean ± SD, non-normally distributed continuous variable was reported as median (first IQR, third IQR), categorical variables were reported as frequencies and proportions. $P < 0.05$ was considered significant

metabolism-related indices (TyG, TyG-WC, TyG-WHtR, AIP, LAP, VAI, TyG-BMI, HOMA-IR, as well as METS-IR) for osteoporosis complications in prediabetic or diabetic populations were further compared. As shown in Table 2; Fig. 1A, the AUCs of all the parameters were more than 0.5 ($P < 0.05$ for all), indicating all the gluco-lipid metabolism-related indices have predictive ability for osteoporosis complications in prediabetic or diabetic populations. The best-performing index was METS-IR (AUC:0.685, $P < 0.001$), and the worst-performing index

Table 2 The results of ROC curves in the development cohort

Variables	OP							
	Cut-off value	AUC (95% CI)	*P*	Youden	Sensitivity	Specificity	PPV	NPV
TyG-WHtR	4.84	0.577 (0.550–0.603)	<0.001	0.162	0.773	0.389	0.341	0.808
AIP	0.07	0.578 (0.548–0.608)	0.011	0.209	0.535	0.674	0.401	0.780
TyG	8.42	0.639 (0.613–0.666)	0.004	0.216	0.784	0.432	0.360	0.830
TyG-WC	741.03	0.563 (0.534–0.591)	<0.001	0.119	0.890	0.229	0.320	0.836
TyG-BMI	226.54	0.619 (0.591–0.646)	0.026	0.193	0.838	0.355	0.347	0.843
HOMA-IR	5.01	0.574 (0.546–0.602)	0.001	0.137	0.832	0.305	0.328	0.817
METS-IR	51.18	0.685 (0.657–0.712)	<0.001	0.388	0.661	0.727	0.497	0.840
LAP	67.55	0.522 (0.493–0.550)	<0.001	0.054	0.353	0.701	0.326	0.726
VAI	1.83	0.560 (0.531–0.589)	0.034	0.141	0.510	0.631	0.361	0.759

P < 0.05 was considered significant. Youden index was defined as sensitivity + specificity − 1

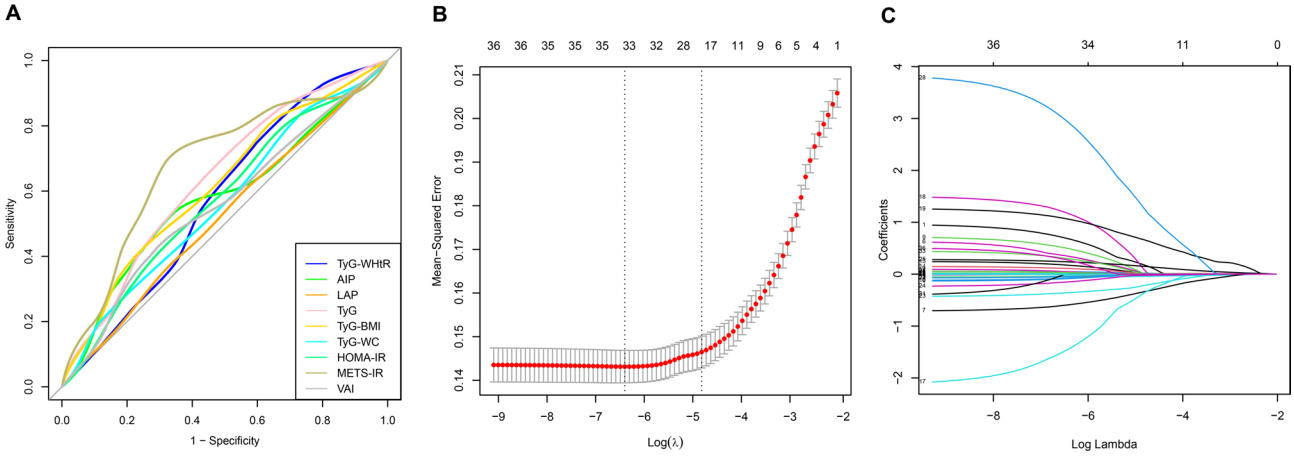


Fig. 1 The predictive ability of indices and LASSO regression analysis. (**A**) The predictive performance of glucolipid metabolism-related indices for osteoporosis complications was evaluated by ROC curve and AUC. (**B**) 32 basic characteristics were first screened by LASSO regression analysis. The plot for LASSO regression coefficients. (**C**) The optimal lambda in the LASSO model was selected by 10-fold cross-validation. LASSO, least absolute shrinkage and selection operator

was LAP (AUC: 0.522, $P < 0.001$). The detailed AUC value of all the indices were shown in Table 2. However, the AUC of any index was lower than 0.7, indicating the relatively limited predictive performance of all the single indices.

LASSO regression analysis

To prevent overfitting of the model and to screen the predictors that are strongly associated with the osteoporosis risk in prediabetic or diabetic populations, LASSO regression analysis was first conducted on all the basic characteristics of the study participants in the development cohort. As shown in Fig. 1B and C, LASSO regression analysis (λ-1se = 0.008) identified 12 candidate predictors of osteoporosis risk in diabetic and prediabetic populations, as detailed subsequently: age, TyG, BMI, TyG-WC, sex, serum calcium, TyG-BMI, LDL-C, HOMA-IR, oral hypoglycemic agents, TG, and METS-IR.

Multivariate logistic regression analysis

Subsequently, multivariate logistic regression analysis was further employed to screen and confirm the 12 predictors identified by the LASSO regression analysis. As shown in Table 3, age, TyG, TyG-BMI, TyG-WC, as well as METS-IR ($P < 0.05$ for all) were positively associated with the osteoporosis risk, while BMI, TG, serum calcium, oral hypoglycemic agents, as well as HOMA-IR ($P < 0.05$ for all) were inversely associated with osteoporosis risk. Compared with male participants, female participants showed higher osteoporosis risk, nevertheless, this difference failed to achieve statistical significance ($P = 0.114$). LDL-C ($P = 0.281$) also did not show statistical significance.

Nomogram construction

LASSO and multivariate logistic regression analyses identified 10 significant osteoporosis risk factors. To establish the novel glucolipid metabolism-related model and simplify the model as much as possible for convenient application, five out of ten predictors of interest

Table 3 Multivariate logistic regression analysis in the development cohort

Variables	OR	95% CI	*P*
Age (years)	1.017	1.005–1.028	**0.004**
Gener			0.114
Male	1.000	Reference	
Female	1.338	0.933–1.924	
BMI (kg/m^2)	0.582	0.536–0.627	**<0.001**
TG (mmol/L)	0.926	0.908–0.944	**<0.001**
LDL-C (mmol/L)	1.077	0.941–1.233	0.281
Serum calcium (mmol/L)	0.670	0.612–0.730	**<0.001**
Oral hypoglycemic agents			**<0.001**
No	1.000	Reference	
Yes	0.339	0.264–0.425	
TyG	3.186	2.220–4.705	**<0.001**
TyG-BMI	1.021	1.016–1.029	**<0.001**
TyG-WC	1.005	1.004–1.007	**<0.001**
HOMA-IR	0.953	0.919–0.983	**0.006**
METS-IR	1.205	1.171–1.242	**<0.001**

Data were analyzed by multivariate logistic regression model. $P<0.05$ was considered significant

Table 4 Quantitative assessment of the stability and predictive improvement of the integrated model

Variables	Age	TyG	TyG-WC	TyG-BMI	METS-IR
VIF	1.029	1.202	1.620	1.535	1.513
NRI	0.920	0.914	1.000	0.953	0.821

VIF: variance inflation factor; NRI: Net reclassification improvement

with good predictive performance were selected in the present study. Since the inclusion of too many variables may compromise model simplicity and clinical utility, and affect the interpretability, this work considered incorporating some of the most explanatory and meaningful variables to construct nomogram that was employed to visualize the model. Ultimately, the nomogram was constructed based on five predictors, including age and four glucolipid metabolism indices (TyG, TyG-WC, METS-IR, as well as TyG-BMI). As shown in Table 4, VIF values for the five variables in the nomogram were calculated—age (VIF = 1.029), TyG (VIF = 1.202), TyG-WC (VIF = 1.620), TyG-BMI (VIF = 1.535), and METS-IR (VIF = 1.513)—and concluded that all values fall within an acceptable range, indicating no multicollinearity issues in the final model. The nomogram was presented in Fig. 2. To predict osteoporosis risk in prediabetic or diabetic populations, one doctor can first add the total points obtained in age, TyG, TyG-BMI, TyG-WC, as well as METS-IR, next, draw a perpendicular line originating at the "total points" axis and terminating at the "predicted value" axis. Finally, the corresponding predicted value of osteoporosis risk is obtained. Moreover, to facilitate reader use, we have provided an online dynamic nomogram that was accessible at https://evosaber.shinyapps.io/myAppName/.

Restricted cubic splines analysis

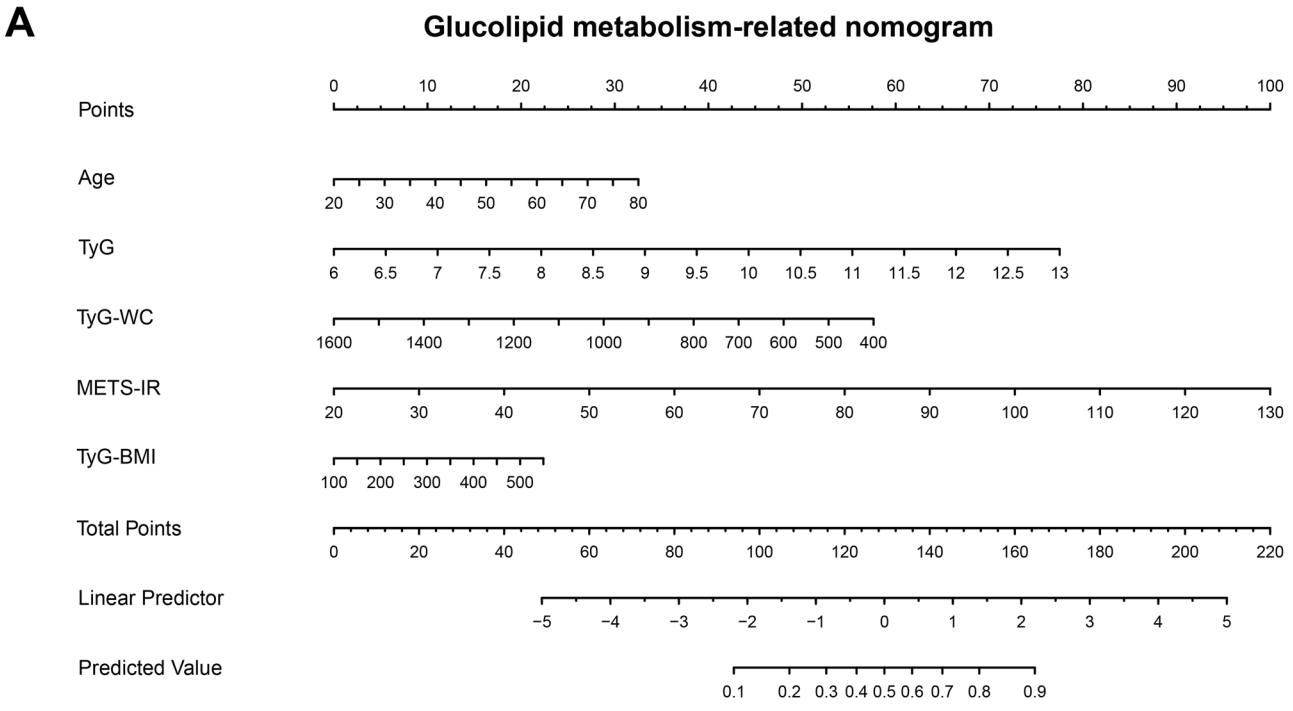
The relationships between age, four glucolipid metabolism-related indices, including TyG, TyG-BMI, TyG-WC, and METS-IR, and osteoporosis risk were visualized by RCS analysis (Fig. 3). The results of RCS analysis showed a nonlinear relationship between the risk of concurrent osteoporosis in diabetic and prediabetic patients and TyG (Fig. 3B), as well as METS-IR (an approximate "U-shape" pattern, Fig. 3E), respectively. In contrast, age (Fig. 3A), TyG-BMI (Fig. 3C), as well as TyG-WC (Fig. 3D) demonstrated linear association with the osteoporosis risk.

Nomogram validation

The predictive performance of the final diagnostic model was assessed by AUC, calibration plots, and DCA. As shown in Fig. 4A-C, the AUC in development cohort, bootstrap resampling, as well as internal validation with the validation cohort were 0.802, 0.8, and 0.82, indicating fairly good discrimination ability and predictive performance of this nomogram. As shown in Fig. 4D-F, the calibration plots in the three cohorts demonstrated good consistency between the predicted probability predicted by the novel glucolipid metabolism-related nomogram and observed probability, facilitating precise prediction of osteoporosis complications risk in prediabetic and diabetic patients. As shown in Fig. 4G-I, the DCA analysis demonstrated significant net benefit across extensive probability thresholds for concurrent osteoporosis risk prediction, showing well clinical practicality of the new model. As shown in Supplementary Fig. 2, this work evaluated the net benefit across a range of threshold probabilities (0.1, 0.2, 0.4, and 0.5). The full model consistently demonstrated higher net benefit compared to individual predictors at each threshold. As shown in Table 4, the NRI analyses of single predictors and the integrated model yielded the following values: age (0.919), TyG (0.913), TyG-WC (1.000), TyG-BMI (0.952), and METS-IR (0.820), demonstrating that the integrated model significantly improves risk classification, with all NRI values above 0.8 and TyG-WC reaching the maximum value of 1, indicating a substantial net gain in reclassification and strong evidence that the new model enhances predictive ability.

Discussion

This study is the first to systematically demonstrate that various glucolipid metabolism-related indices (TyG-WC, TyG-WHtR, TyG, HOMA-IR, AIP, METS-IR, LAP, VAI, as well as TyG-BMI) are the predictors of the osteoporosis risk ($P<0.05$ for all) in prediabetic and diabetic patients, and the best-performing index is METS-IR (AUC: 0.685). Furthermore, this work innovatively constructed the novel glucolipid metabolic nomogram to enhance combined osteoporosis risk prediction in



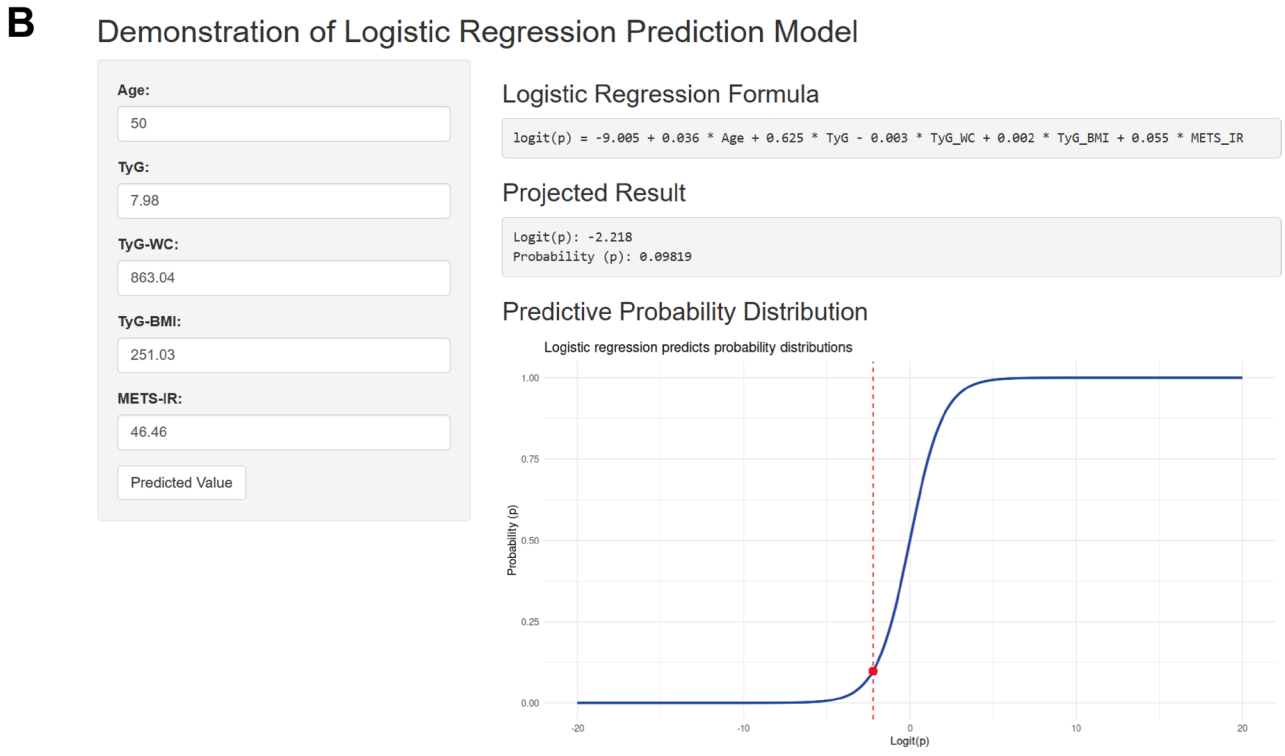


Fig. 2 The novel glucolipid metabolism-related nomogram. (**A**) The novel nomogram to enhance the predictive performance for osteoporosis complications in prediabetic and diabetic patients. (**B**) An online dynamic nomogram was accessible at https://evosaber.shinyapps.io/myAppName/

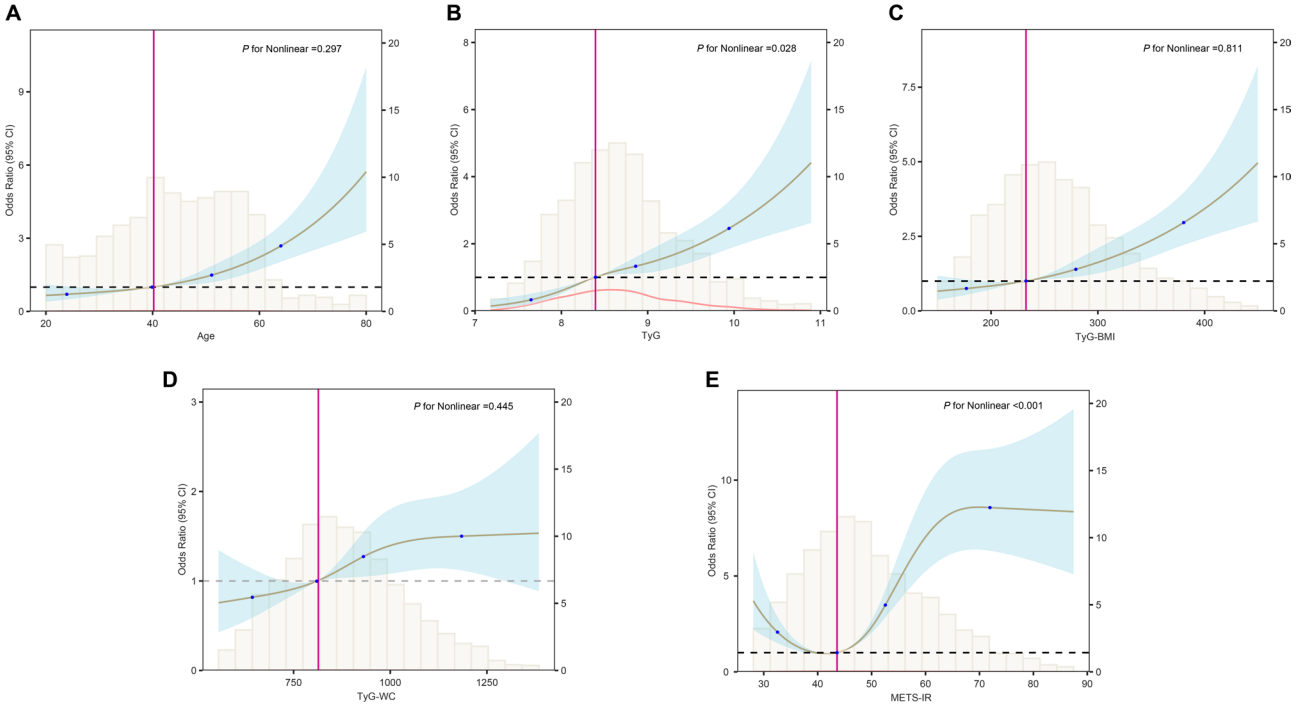


Fig. 3 RCS analysis on the non-linear association between predictors and the risk of osteoporosis. (**A**) The RCS analysis on the association between age and osteoporosis. (**B**) The RCS analysis on the association between TyG and osteoporosis. (**C**) The RCS analysis on the association between TyG-BMI and osteoporosis. (**D**) The RCS analysis on the association between TyG-WC and osteoporosis. (**E**) The RCS analysis on the association between METS-IR and osteoporosis. RCS, restricted cubic spline

individuals with impaired glucose metabolism (prediabetes as well as diabetes). The AUC, calibration plots, and DCA analysis together demonstrated fairly good predictive ability of the nomogram.

Glucolipid metabolism-related indices were widely used to predict complications in prediabetic and diabetic patients [37–41]. For example, one cross-sectional study by Liu et al. [37] indicated that elevated TyG correlated with increased cardiovascular disease risk in prediabetic and diabetic patients. Utilizing NHANES-derived data, this work confirmed the predictive ability of these indices to predict osteoporosis risk in prediabetic and diabetic patients. However, similar to previous studies, each index only showed limited predictive performance (METS-IR showed the highest AUC: 0.685). Therefore, this work further combined a couple of significant parameters to construct a novel nomogram for improved osteoporosis complication risk assessment. The results of model validation demonstrated the good performance of the nomogram. Recently, several models have been constructed and validated for predicting osteoporosis complications in diabetic patients [7, 42]. Ji et al. [7] developed a prediction model for osteoporosis risk screening in patients with type 2 diabetes, incorporating 9 factors such as age, fasting C-peptide and type I collagen carboxy-terminal peptide, based on data from 817 patients. The AUC of the nomogram was 0.828. Another nomogram was built and validated by Li et al. [42], by utilizing 6 independent predictors, including gender and serum calcium. A total of 379 type 2 diabetic participants were finally included in their study and the reported AUC in the model-development cohort was 0.844. However, they have merely focused on the osteoporosis risk of elderly diabetic patients (age ≥ 60 years), while neglecting those of younger diabetic patients. Although both models employed the LASSO and multivariate logistic regression models to rigorously screen for statistically significant variables, they were both limited by relatively small sample sizes. Moreover, neither of the two studies included patients with prediabetes. Compared with the two previous models, the present nomogram was built by only five predictors but showed fairly good predictive performance (AUC: 0.802, 0.8, as well as 0.82 in the three cohorts).

The possible mechanisms between glucolipid metabolism-related indices and osteoporosis need to be discussed. All the glucolipid metabolism-related indices included in this study were reliable surrogate indicators for IR [43–45], which was widely regarded as the core pathology in diabetic patients [46]. IR, defined as attenuated biological responsiveness to physiological circulating insulin levels, typically precedes diabetes onset by several years [47]. Some recent evidence has established IR as a significant contributor to osteoporotic pathogenesis in

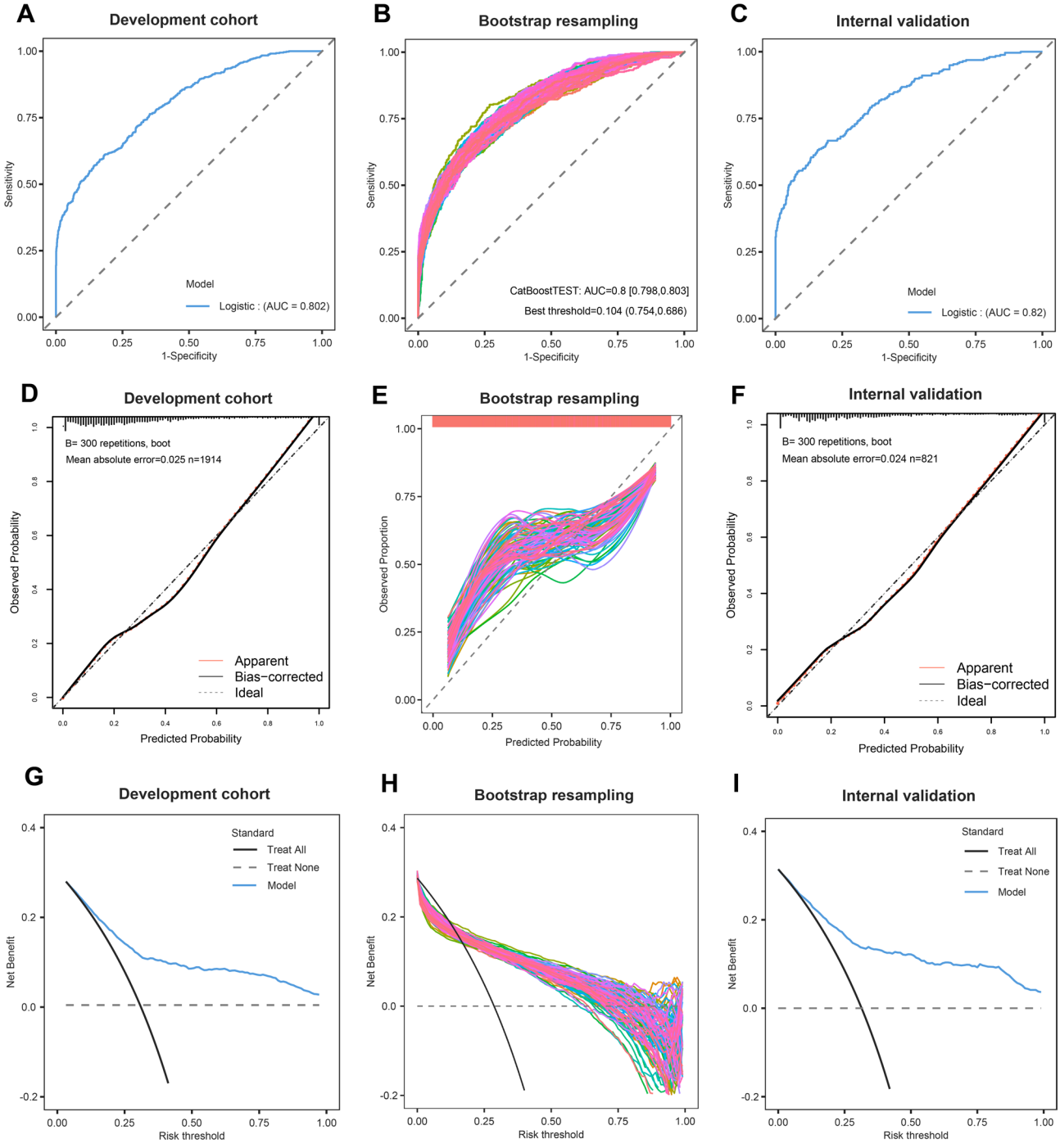


Fig. 4 Performance evaluation of the novel glucolipid metabolism-related nomogram. (**A**, **B**, and **C**) The ROC curve and AUC in the development cohort, bootstrap resampling, and internal validation with the validation cohort. (**D**, **E**, and **F**) The calibration plot in the development cohort, bootstrap resampling, and internal validation with the validation cohort. (**G**, **H**, and **I**) The DCA analysis in the development cohort, bootstrap resampling, and internal validation with the validation cohort

individuals with diabetes [48–52]. On the one hand, clinical studies have shown the close associations between IR and osteoporosis in diabetic patients. By retrospectively analyzing 234 Chinese type 2 diabetic patients, Wang et al. [49] demonstrated that the higher level of IR (assessed by HOMA-IR) was significantly and nonlinearly related to the higher risk of osteoporosis complications only in female patients. One cross-sectional study by Shin et al. [50] indicated that IR as well as the level of plasma insulin were associated with elevated risk of bone mass loss in Korean male patients. On the other hand, although the exact cellular and molecular mechanisms between IR and

osteoporosis remain unclear, basic research has proposed a possible mechanism. IR was regarded as one crucial factor that resulted in the malfunctions of osteoblasts and osteoclasts, causing decreased bone turnover as well as decreased bone quality [53]. Besides, type 2 diabetes-associated IR could not only enhance bone resorption, but also induce glucotoxicity in osteoblasts, and further lead to osteoblast apoptosis [54, 55]. Collectively, by synthesizing the present research outcomes with existing evidence, this work propose that the predictive ability of nine glucolipid metabolism-related indices for osteoporosis complications risk may be attributed to IR.

Strengths and limitations

It is critical to note that this work has several strengths. Firstly, this work was the first to systematically evaluate the predictive ability of nine glucolipid metabolism-related indices on the risk of osteoporosis complications in prediabetic and diabetic patients and demonstrated that METS-IR has the best predictive performance. Secondly, this work innovatively developed and validated a novel glucolipid metabolism-related nomogram with good predictive performance for osteoporosis complications in prediabetic and diabetic patients. Thirdly, the predictors used to build the nomogram were age and four glucolipid metabolism-related indices. These indices were calculated by TG, FBG, BMI, HDL-C, and WC, which were routinely tested and easily obtained by laboratory tests and physical examination, making it convenient for clinicians to screen the high-risk populations of osteoporosis complications in prediabetic and diabetic patients, particularly in economically underdeveloped countries and regions. Fourthly, the current cross-sectional analysis incorporated data from 2,735 subjects, which was a fairly large sample size compared with previous studies. Fifthly, neither of the previous studies included prediabetic patients, neglecting the high risk for osteoporosis complications in prediabetic patients and making early diagnosis and treatment of osteoporosis complications or osteoporotic fractures in patients with impaired fasting glucose difficult [56–58]. This study innovatively combined consideration of prediabetic patients and diabetic patients, to evaluate the osteoporosis risk in patients with impaired fasting glucose comprehensively and systematically. Finally, LASSO coupled with logistic regression models ensured methodologically robust variable selection process, making the results more reliable. Based on this, clinicians are strongly advised to use this novel glucolipid metabolism-related nomogram for precise prediction of osteoporosis complications in prediabetic and diabetic patients.

This work still has some limitations. First, because all the data were extracted from NHANES database, populations outside U.S. may be used to externally validate this model to confirm its generalizability. Second, the cross-sectional nature of this study precludes definitive causal inferences between metabolic health parameters and concurrent osteoporosis risk. Third, most of the parameters that constitute metabolic health-related indices, including FBG, TG, as well as HDL-C, actually fluctuate dynamically. However, NHANES primarily obtained these parameters based on a single laboratory measurement, causing inability of this work to capture the full picture of these dynamic changes. Therefore, bias could be introduced by a single measurement. Fourth, the discontinuity and numerous missing values of the database when collecting BMD from other sites of the body might lead to an underestimation of the prevalence of osteoporosis. Finally, considering osteoporosis is one multifactorial disorder, a few confounders that were not included in this study may still exist, despite 32 covariates being included. Continuation of multicenter, larger prospective studies is necessary to validate these findings.

Conclusion

Glucolipid metabolism-related indices serve as predictors of osteoporosis risk. This newly developed glucolipid-based nomogram demonstrates superior predictive accuracy for assessing concurrent osteoporosis risk among prediabetic and diabetic populations. This risk assessment tool provides clinicians with a novel, convenient, and effective strategy for screening osteoporosis complications, thus promising to optimize clinical decision-making.

Abbreviations

AUC	Area under the curve
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
DCA	Decision curve analysis
DXA	Dual-energy x-ray absorptiometry
FBG	Fasting blood glucose
FINS	Fasting insulin
HDL-C	High-density lipoprotein cholesterol
IR	Insulin resistance
LASSO	The least absolute shrinkage and selection operator
LDL-C	Low-density lipoprotein cholesterol
LS	Lumber spine
NHANES	The National Health and Nutrition Examination Survey
NPV	Negative predictive value
NRI	Net reclassification improvement
OP	Osteoporosis
OR	Odds ratio
PPV	Positive predictive value
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
SD	Standard deviation
SCr	Serum creatinine
TF	Total femur
TG	Triglycerides
TyG	The Triglyceride-glucose index
VIF	Variance inflation factor
WC	Waist circumference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02602-w.

Supplementary Material 1

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Author contributions
MZ and PL designed the study and amended the paper. JL (Junhong Li) was the primary writer of the paper and was responsible for the statistical analysis. CM made critical revisions to the manuscript and created all tables and figures. JL (Junhong Li), CM, XW, JL (Jianwen Li), PL, and MZ performed the literature search. All authors read and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was performed according to the guidelines of the *Helsinki Declaration*. The original protocol of the NHANES survey adhered to the STROBE statement and was approved by the Ethics Review Committee of the National Center for Health Statistics. All participants signed informed consent forms. The data is publicly available, therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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