

RESEARCH

Novel nomogram for predicting the 3-year incidence risk of osteoporosis in a Chinese male population

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Abstract

Objective: To establish a rapid, cost-effective, accurate, and acceptable osteoporosis (OP) screening model for the Chinese male population (age ≥ 40 years) based on data mining technology.

Materials and methods: This was a 3-year retrospective cohort study, which belonged to the sub-cohort of the Chinese Reaction Study. The research period was from March 2011 to December 2014. A total of 1834 subjects who did not have OP at the baseline and completed a 3-year follow-up were included in this study. All subjects underwent quantitative ultrasound examinations for calcaneus at the baseline and follow-ups that lasted for 3 years. We utilized the least absolute shrinkage and selection operator (LASSO) regression model to select feature variables. The characteristic variables selected in the LASSO regression were analyzed by multivariable logistic regression (MLR) to construct the predictive model. This predictive model was displayed through a nomogram. We used the receiver operating characteristic (ROC) curve, C-index, calibration curve, and clinical decision curve analysis (DCA) to evaluate model performance and the bootstrapping validation to internally validate the model.

Results: The predictive factors included in the prediction model were age, neck circumference, waist-to-height ratio, BMI, triglyceride, impaired fasting glucose, dyslipidemia, osteopenia, smoking history, and strenuous exercise. The area under the ROC (AUC) curve of the risk nomogram was 0.882 (95% CI, 0.858–0.907), exhibiting good predictive ability and performance. The C-index for the risk nomogram was 0.882 in the prediction model, which presented good refinement. In addition, the nomogram calibration curve indicated that the prediction model was consistent. The DCA showed that when the threshold probability was between 1 and 100%, the nomogram had a good clinical application value. More importantly, the internally verified C-index of the nomogram was still very high, at 0.870.

Conclusions: This novel nomogram can effectively predict the 3-year incidence risk of OP in the male population. It also helps clinicians to identify groups at high risk of OP early and formulate personalized intervention measures.

Key Words

- ▶ male patients
- ▶ osteoporosis
- ▶ risk factors
- ▶ nomogram
- ▶ data mining

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Introduction

Osteoporosis (OP) refers to a systemic bone metabolic syndrome in which bone strength is reduced and bone fragility is increased due to the loss of bone mass and destruction of bone tissue microstructure (1). In the United States, OP affects approximately 10 million people, including 2 million men (2). It is estimated that one in five white men will suffer from osteoporosis-related fractures in their lifetimes (3). In China, the overall prevalence rate of OP in people over 50 years old is 19.2%, and the prevalence rate in men is 6.0% (4); the overall prevalence rate in people with low bone mass who need prevention and treatment is 46.4%, and in men, it is as high as 46.9% (4). China is one of the countries with the largest elderly population in the world (5). Currently, OP has become a major public health issue in China, and it is estimated that by 2050, the number of OP patients will reach 120 million (6). In addition, some studies have found that osteoporotic fractures in men have more serious consequences, and their morbidity and mortality are significantly higher than those in women (7, 8, 9). Unfortunately, the diagnosis rates and treatment rates of males suffering from the OP are insufficient (10).

The research of Si *et al.* (11) showed that osteoporosis-related fractures will cause a huge economic burden, and it will increase significantly with the increase of aging. So, the health care system must urgently identify cost-effective screening and intervention measures. OP has become one of the chronic diseases that seriously threaten the health and life safety of middle-aged and elderly people. Dual-energy X-ray absorptiometry (DXA) is the gold standard for diagnosing OP. However, due to its high operating costs and inconvenience to carry, it has not yet been popularized among the population. In addition, in some countries and regions with less economic development, screening and testing capabilities OP are even more inadequate. Therefore, in clinical work, it is very important to identify and intercept OP-related risk factors as early as possible.

The current assessment tools that have been adopted for early OP screening are primarily for female patients, and similar effective measurement tools for men are not available. Data mining technology is a new method widely used in disease diagnosis and prediction. In recent years, most methods for disease risk assessment involve data mining. Machine learning (ML), as a branch of artificial intelligence (AI), has been widely applied to solve complex problems in the scientific field (12, 13, 14). Logistic regression (LR) is one of the most commonly used ML techniques in the medical field. It can be used to analyze the risk factors related to the occurrence of a disease and

to construct a clinical prediction model. Among the various models for predicting disease risk, the nomogram transforms the complex regression equation into a simple and visual graph. Its prediction results are highly readable and have very promising clinical application value (15). This study will combine the least absolute shrinkage and selection operator (LASSO) regression analysis and multiple LR analysis incorporate them into data mining technology to establish an OP prediction model and visualize it through a nomogram. To our knowledge, this article is the first study to use a nomogram to predict OP risk factors in male patients and provide guidance for early prevention.

Materials and methods

Participants

This study is a 3-year retrospective cohort study, which is part of the China REACTION study (16). The REACTION study is the largest prospective study of diabetes and cancer in China. From March 2011 to December 2011, we selected 1988 male residents aged 40 and above in Wuyishan City, Fujian Province as the research objects. All subjects were fully informed and voluntarily signed the informed consent form before taking the test. The following cases were excluded: (i) patients who had been diagnosed with OP at baseline ($n = 59$); (ii) those with missing baseline data ($n=80$); (iii) those who took drugs that affect bone metabolism within 2 week before the examination ($n=0$). Finally, 1849 non-OP patients at the baseline were included for a 3-year non-interventional follow-up. The follow-up period was from December 2011 to December 2014. Ultimately, 1834 participants completed the second survey and were included in the study. The follow-up response rate was 99.2%, and the detailed research flow chart is shown in Fig. 1. At present, the study has been approved by the ethics committee of Fujian Provincial Hospital (ID: K2020-10-002).

Data collection

All patients completed a questionnaire survey. The survey content included age, past medical history (hypertension, diabetes, prediabetes, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), dyslipidemia, obesity, abdominal obesity, osteopenia, fractures), personal history (histories of smoking, drinking, and tea consumption), and dietary habits (pork, beef, mutton, chicken, duck,

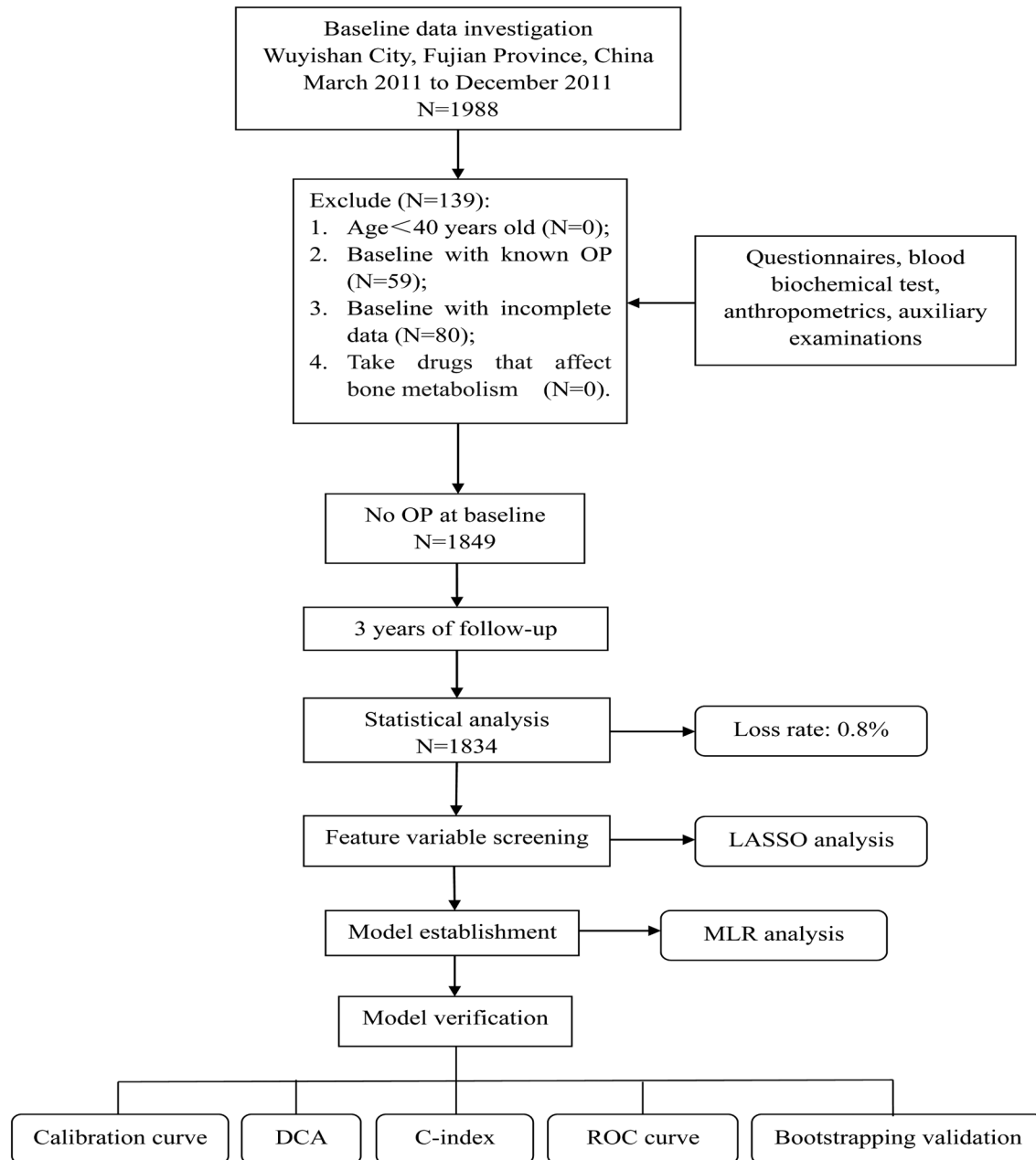


Figure 1

Flow diagram of study design. OP, osteoporosis; LASSO, least absolute shrinkage and selection operator; MLR, multiple logistic regression; DCA, decision curve analysis; ROC, receiver operating characteristic.

goose, seafood, dairy products, soy products). Exercise intensity was divided into three levels: light exercises (such as walking), moderate exercises (such as jogging, playing ping pong, and practicing tai chi), and strenuous exercises (such as playing basketball, swimming, and running), each having to last for more than 10 min. Past medical history had been clearly diagnosed by specialists from second-level and above hospitals. Smoking was divided into no (including never smoked or ex-smokers) and yes

(current smokers); alcohol consumption was categorized as no (including never drank or previous drinkers) and yes (currently drinking). Tea consumption history was divided into three parts: frequent (more than three times a week), occasionally (one to three times a week), and never. Blood samples with fasting for more than 8 h were extracted to detect for hemoglobin A_{1c} (HbA_{1c}), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), triglycerides (TG), alanine

aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and uric acid (UA). All subjects underwent oral glucose tolerance testing (OGTT), and fasting plasma glucose (FPG) and postprandial plasma glucose (2hPG) were measured at fasting and 2 h after a glucose load. The glucose oxidase method was utilized to determine blood glucose. An automatic biochemical analyzer (Modular E170, Roche) was used to detect blood lipids, and liver and kidney functionalities. HbA1c was determined by high-performance liquid chromatography (automated glycohemoglobin analyzer, Bio-Rad).

The height, weight, waist circumference (WC), hip circumference (HC), neck circumference (NC), pulse, and blood pressure (BP) were measured by uniformly trained investigators. The subjects wore thin shirts and stood upright on the bottom plate of a stadiometer to measure their height and weight. WC was measured at the thinnest part of the waist (the horizontal circumference of the waist through the umbilical point), and NC was measured at the thinnest part of the middle of the neck. HC was measured at the most convex part of the pubic symphysis and gluteus maximums. BMI was then calculated by weight (kg)/height (m^2), and the waist-to-height ratio (WHtR) was calculated by WC (cm)/height (cm). The waist-to-hip ratio (WHR) was calculated by WC (cm)/hip(cm), and BP and pulse were measured after the subjects rested for 10 min. An electronic sphygmomanometer (Omron) was used to measure BP and pulse three times, and the average value was taken as the data analysis. Calcaneus quantitative ultrasound (QUS) was used to measure bone mineral density (BMD) by the Achilles Express ultrasonic bone densitometer (GE Lunar Corp., Madison, WI, USA). The SI-derived T-score was the parameter we used to assess BMD. T-score could be obtained directly from the Achilles Express ultrasonic bone densitometer. And, we used the standard provided by the manufacturer as a reference to evaluate the T-score. The manufacturer's standards were based on a database of young, healthy Chinese individuals in the same study area as the reference. The QUS instrument was calibrated daily according to the manufacturer's recommendations before measurement. Data collection and analysis were performed by two collaborators (Yaqian Mao and Lizhen Xu); divergences were resolved through discussion.

Diagnostic and classification criteria

According to the diagnostic criteria from the World Health Organization (WHO) (17), the definition of osteopenia is $-2.5 < \text{T-score} < -1$, and the definition for OP is T-score

≤ -2.5 . In our study, according to the diagnostic criteria from the American Diabetes Association (ADA) in 2003 (18), the definition of diabetes is $\text{FPG} \geq 7.0 \text{ mmol/L}$ and/or $2\text{hPG} \geq 11.1 \text{ mmol/L}$; the definition for IFG is $6.1 \text{ mmol/L} \leq \text{FPG} < 7.0 \text{ mmol/L}$, and $2 \text{ hPG} < 7.8 \text{ mmol/L}$; the definition for IGT is $\text{FPG} < 7.0 \text{ mmol/L}$, and $2 \text{ hPG} \geq 7.8 \text{ mmol/L}$ or $< 11.1 \text{ mmol/L}$; prediabetes including IFG and IGT. The definition for centric obesity is defined as (19, 20, 21): male WC $\geq 90 \text{ cm}$, male WHR ≥ 0.9 , WHtR ≥ 0.5 . We defined NC $\geq 35 \text{ cm}$ as centric obesity.

Statistical analysis

R software (version 4.0.2; <https://www.r-project.org>) and IBM SPSS software (version 25.0 for windows, SPSS Inc.) were implemented for data analysis. Missing data were filled in by multiple interpolations (22). Categorical variables were shown as a percentage. Baseline data analysis was used by chi-square test, and the value of $P < 0.05$ (two-sided) was considered statistically significant. In the construction of the predictive model, we used the least absolute shrinkage and selection operator (LASSO) regression analysis to screen out characteristic variables with nonzero coefficients. The glmnet package in the R software was used to run LASSO. LASSO regression analysis causes the regression coefficients of some variables to approach zero by imposing constraints on the model parameters, thereby minimizing prediction errors. It uses the control parameter lambda for variable screening and complexity adjustments and is particularly suitable for high-dimensional data analysis and risk factor screening (23, 24). Then, MLR analysis was adopted to analyze the characteristic variables with nonzero coefficients. These characteristic variables in the MLR model were represented by a regressive coefficient (β), odds ratio (OR) with 95% CI, and P -value. The rms package in R software was used to run LR. LR is the most adopted technique in ML (25), which often analyzes the risk factors of disease and builds risk prediction models.

We verified the model performance, accuracy, and practicality through C-index, receiver operating characteristic (ROC) curve, decision curve analysis (DCA), and calibration charts. Bootstrapping validation (1000 Bootstrap Resamples) calculated a relatively corrected C-index (26), and we used the ROCR package of R language to perform the ROC. The area under the ROC curve (AUC) can adequately distinguish performances across the risk spectrum (27). We used the rms package to draw the calibration curve, which was plotted to assess the calibration of the OP nomogram (28). Also, the R language rmda package

was applied for the clinical decision curve analysis. DCA is a novel method for evaluating predictive models, which can be used to evaluate the clinical utility of the model (29).

Results

Patient characteristics of the study cohort

This was a 3-year retrospective cohort study. The detailed research process is shown in Fig. 1. A total of 1834 baseline non-OP male patients completed this follow-up with a completion rate of 1834/1849 (99.2%). All patients have completed the relevant examinations. A total of 187 patients developed OP after 3 years (10.2%), aged 41–79 years. Supplementary Table 1 (see section on [supplementary materials](#) given at the end of this article) for the BMD value (T-score) of 1834 male patients who completed the 3-year follow-up. We defined these 187 male patients who developed OP as the OP group and 1647 male patients who had not developed OP as the non-OP group. The comparison of characteristic variables between OP group and non-OP group are shown in Table 1.

Feature selection

The variables in our study included demographic characteristics, anthropometric characteristics, blood biochemical indicators, auxiliary examinations, co-morbidities, and lifestyles. We selected 10 characteristic variables with nonzero coefficients from 44 variables through the LASSO regression model, including age, neck circumference, waist-to-height ratio, BMI, TG, IFG, dyslipidemia, osteopenia, smoking history, and strenuous exercises (see Fig. 2 for details).

Development of individualized prediction nomogram

We employed the feature variables selected from the LASSO regression model to construct the prediction model. The predictive model construction will use the multiple LR method (see Table 2 for details), and the predictive model constructed by the aforementioned predictors was represented by a nomogram (see Fig. 3 for details).

Model validation and clinical use

The area under the ROC curve (AUC) of the risk nomogram was 0.882 (95% CI, 0.858–0.907) (Fig. 4A), which suggested

that the model had adequate predictive capabilities and performance. The C-index for the prediction model in the cohort was 0.882 (95% CI, 0.858–0.907) and was 0.870 by bootstrapping validation, indicating that the model had good refinement. Figure 4B shows the clinical DCA for the risk nomogram. The DCA shows that if the threshold probability of the DCA is >1 and <100%, using this risk nomogram to predict the 3-year risk for OP was beneficial in clinical work. Figure 4C shows the calibration curve for the risk nomogram, which exhibited good consistency in this cohort.

Discussion

OP is often considered a health problem for females, but its effects on males are often overlooked. In order to prevent and evaluate OP, various OP risk assessment tools have gradually appeared and developed. Taking the fracture risk assessment tool (FRAX) as an example, which is currently the most widely used standard for evaluating bone health. FRAX was released by the WHO Collaborating Center in Sheffield, UK, in 2008 to assess the individualized probability of hip and major osteoporotic fractures in 10 years (30). FRAX is a questionnaire-based scoring tool, and its reference indicators include clinical risk factors and femoral neck BMD (30). Due to regional differences, lack of appropriate cohort data, and design flaws, some studies have found that FRAX has limitations in clinical use (31, 32, 33, 34). The study of Harvey *et al.* (35) showed that the accuracy of using FRAX to predict fracture risk in men may be lower than in women. At present, the risk factors for OP in male patients are still unclear, and targeted and personalized assessment tools are insufficient. Based on the data from the epidemiological surveys, we constructed a nomogram of the 3-year incidence risk of OP for Chinese adult males to provide a quantitative forecasting tool for the early identification of OP high-risk groups. Our research found that age, BMI, NC, WHtR, TG, IFG, dyslipidemia, osteopenia, smoking history, and strenuous exercise were risk factors for OP in males.

The risk factors related to OP occurrence in our study were similar to most previous studies. However, the difference is the statistical analysis method used. Most previous studies (36, 37, 38) usually used single-factor analysis to initially screen risk factors and then implemented multi-factor stepwise regression to obtain significant variables. In this study, we implemented new statistical methods to identify OP risk factors and explained the issues from multiple perspectives while exploring

Table 1 Comparison of characteristic variables between OP group and non-OP group. Categorical variables were shown as percentage.

Variables	Non-OP <i>n</i> = 1647	OP <i>n</i> = 187	P-value	Variables	Non-OP <i>n</i> = 1647	OP <i>n</i> = 187	P-value
Age (years)			0.002	ALP (U/L)			0.050
<50	593 (36.00)	49 (26.20)		<100	1387 (84.21)	147 (78.61)	
50–70	976 (59.26)	120 (64.17)		≥100	260 (15.79)	40 (21.39)	
≥70	78 (4.74)	18 (9.63)		UA (μmol/L)			0.737
SBP (mmHg)			0.606	≤420	1016 (61.69)	113 (60.43)	
<140	1043 (63.33)	122 (65.24)		>420	631 (38.31)	74 (39.57)	
≥140	604 (36.67)	65 (34.76)		Hypertension			0.854
DBP (mmHg)			0.895	No	1383 (83.97)	158 (84.49)	
<90	1341 (81.42)	153 (81.42)		Yes	264 (16.03)	29 (15.51)	
≥90	306 (18.58)	34 (18.58)		Diabetes			0.035
Pulse (b.p.m.)			0.092	No	1393 (84.58)	169 (90.37)	
<60	97 (5.89)	4 (5.89)		Yes	254 (15.42)	18 (9.63)	
60–100	1501 (91.14)	176 (91.14)		Prediabetes			0.105
≥100	49 (2.98)	7 (2.98)		No	1292 (78.45)	137 (73.26)	
BMI (kg/m ²)			<0.001	Yes	355 (21.55)	50 (26.74)	
<18.5	25 (1.52)	9 (5.89)		IFG			0.301
18.5–24	716 (43.47)	100 (91.14)		No	1500 (91.07)	166 (88.77)	
24–28	709 (43.05)	58 (2.98)		Yes	147 (8.93)	21 (11.23)	
≥28	197 (11.96)	20 (30.42)		IGF			0.266
WC (cm)			0.108	No	1439 (87.37)	158 (84.49)	
<80	404 (24.53)	59 (24.53)		Yes	208 (12.63)	29 (15.51)	
80–90	724 (43.96)	76 (43.96)		Dyslipidemia			0.181
≥90	519 (31.51)	52 (31.51)		No	545 (33.09)	71 (37.97)	
HC (cm)			0.089	Yes	1102 (66.91)	116 (62.03)	
<90	318 (19.31)	48 (19.31)		Overweight			0.018
90–100	1032 (62.66)	112 (62.66)		No	971 (58.96)	127 (67.91)	
≥100	297 (18.03)	27 (18.03)		Yes	676 (41.04)	60 (32.09)	
NC (cm)			0.013	Obesity			0.335
<35	513 (31.15)	75 (31.15)		No	1449 (87.98)	169 (90.37)	
≥35	1134 (68.85)	112 (68.85)		Yes	198 (12.02)	18 (9.63)	
WHR			0.513	Abdominal obesity			0.242
<0.9	760 (46.14)	91 (48.66)		No	1277 (77.53)	152 (81.28)	
≥0.9	887 (53.86)	96 (51.34)		Yes	370 (22.47)	35 (18.72)	
WHtR			0.005	Osteopenia			<0.001
<0.5	505 (30.66)	76 (40.64)		No	1405 (85.31)	34 (18.18)	
≥0.5	1142 (69.34)	111 (59.36)		Yes	242 (14.69)	153 (81.82)	
FPG (mmol/L)			0.119	Fracture			0.845
<6.1	1255 (76.20)	152 (81.28)		No	148 (8.99)	16 (8.56)	
≥6.1	392 (23.80)	35 (18.72)		Yes	1499 (91.01)	171 (91.44)	
2hPG (mmol/L)			0.672	Smoking history			0.005
<7.8	1022 (62.05)	119 (63.64)		No	739 (44.87)	64 (34.22)	
≥7.8	625 (37.95)	68 (36.36)		Yes	908 (55.13)	123 (65.78)	
HbA _{1c} (%)			0.117	Drinking history			0.566
<6.0	1323 (80.33)	161 (86.10)		No	952 (57.80)	104 (55.61)	
6.0–6.5	168 (10.20)	16 (8.56)		Yes	695 (42.20)	83 (44.39)	
≥6.5	156 (9.47)	10 (5.35)		Tea drinking history			0.083
HDL (mmol/L)			0.228	Never	393 (23.86)	52 (27.81)	
≥1.0	1399 (84.94)	165 (88.24)		Occasionally	516 (31.33)	44 (23.53)	
<1.0	248 (15.06)	22 (11.76)		Often	738 (44.81)	91 (48.66)	
LDL (mmol/L)			0.849	Pork, beef, mutton			0.308
<3.4	1219 (74.01)	142 (75.94)		No	14 (0.85)	3 (1.60)	
3.4–4.1	293 (17.79)	31 (16.58)		Yes	1633 (99.15)	184 (98.40)	
≥4.1	135 (8.20)	14 (7.49)		Chicken, duck, goose			0.916

(Continued)

Table 1 Continued.

Variables	Non-OP <i>n</i> = 1647	OP <i>n</i> = 187	<i>P</i> -value	Variables	Non-OP <i>n</i> = 1647	OP <i>n</i> = 187	<i>P</i> -value
TC (mmol/L)			0.903	No	109 (6.62)	12 (6.42)	
<5.2	907 (55.07)	106 (56.68)		Yes	1538 (93.38)	175 (93.58)	0.006
5.2–6.2	514 (31.21)	57 (30.48)		Seafood			
≥6.2	226 (13.72)	24 (12.83)		No	92 (5.59)	20 (10.70)	
TG (mmol/L)			0.093	Yes	1555 (94.41)	167 (89.30)	0.082
<1.7	913 (55.43)	116 (62.03)		Dairy products			
1.7–2.3	278 (16.88)	33 (17.65)		No	788 (47.84)	102 (54.55)	
≥2.3	456 (27.69)	38 (20.32)		Yes	859 (52.16)	85 (45.45)	0.008
ALT (mmol/L)			0.498	Soy products			
≤25	1141 (69.28)	135 (72.19)		No	352 (21.37)	56 (29.95)	
25–50	432 (26.23)	42 (22.46)		Yes	1295 (78.63)	131 (70.05)	0.013
>50	74 (4.49)	10 (5.35)		Strenuous exercises			
AST (mmol/L)			0.156	No	1509 (91.62)	181 (96.79)	
≤20	684 (41.53)	76 (40.64)		Yes	138 (8.38)	6 (3.21)	0.192
20–40	871 (52.88)	94 (50.27)		Moderate exercises			
>40	92 (5.59)	17 (9.09)		No	1525 (92.59)	178 (95.19)	
GGT (mmol/L)			0.344	Yes	122 (7.41)	9 (4.81)	0.354
≤30	735 (44.63)	92 (49.20)		Light exercises			
30–60	551 (33.45)	53 (28.34)		No	781 (47.42)	82 (43.85)	
>60	361 (21.92)	42 (22.46)		Yes	866 (52.58)	105 (56.15)	

P < 0.05 (two-sided) was considered statistically significant.

2hpg, 2 h plasma glucose; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HC, hip circumference; HDL, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGF, impaired glucose tolerance; LDL, low-density lipoprotein cholesterol; NC, neck circumference; Non-OP, non-osteoporosis; OP, osteoporosis; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

the risk factors for chronic diseases. The disadvantage inherent to this traditional variable selection is that the variance in the model is generally higher, and flexibility is poor. While exploring disease risk factors, there are generally multiple independent variables. If all variables are used, model overfitting is likely to occur. Meanwhile, the multicollinearity problem must be considered. A major breakthrough in regression analysis in recent years is the introduction of regularized regression, namely the LASSO regression (23, 39, 40). The most prominent advantage of LASSO regression is that by applying penalized regression to all variable coefficients, the relatively unimportant independent variable coefficients become zero and are thus excluded from modeling (23). In addition, LASSO regression is suitable for any data type and for reducing high-dimensional data (23). LASSO regression can perform variable screening and complexity adjustments while fitting a generalized linear model. Different from previous studies, our study used LASSO regression to screen OP risk factors and used the traditional LR regression method to build the model (23). The research results showed that the model constructed with the variables screened by the LASSO regression has good accuracy and predictive ability.

Currently, most studies (37, 38, 41, 42) on OP risk factors were cross-sectional surveys. The cross-sectional

survey can only be used as a preliminary screening tool to assess the current OP risk but cannot predict OP risk in the future. In addition, most studies have proven that QUS is useful for predicting fracture risk in women (43, 44, 45). However, there are still few prospective data on QUS and OP risk in men. At present, the largest study today in men is MrOS study, a multi-center prospective study of risk factors for fracture in 5995 older men (46, 47). In order to explore the risk factors for OP in Chinese male patients, we conducted this survey. This study is a retrospective cohort study based on 3-year follow-up data. The analysis is explained subsequently.

Age, osteopenia, and OP

There is no doubt that age is a definitive risk factor for OP. Our research indicated that as age increased, OP risk gradually increased alongside it, which was consistent with most previous studies (37, 38). The bone loss caused by age is related to the following factors (48). First, as age increases, the level of sex hormones in the body decreases; however, sex hormones are key to maintaining bone mass. Secondly, as age increases, skeletal muscle mass decreases and muscle fat accumulates, leading to decreases in muscle strength and muscle functions, which promotes bone loss

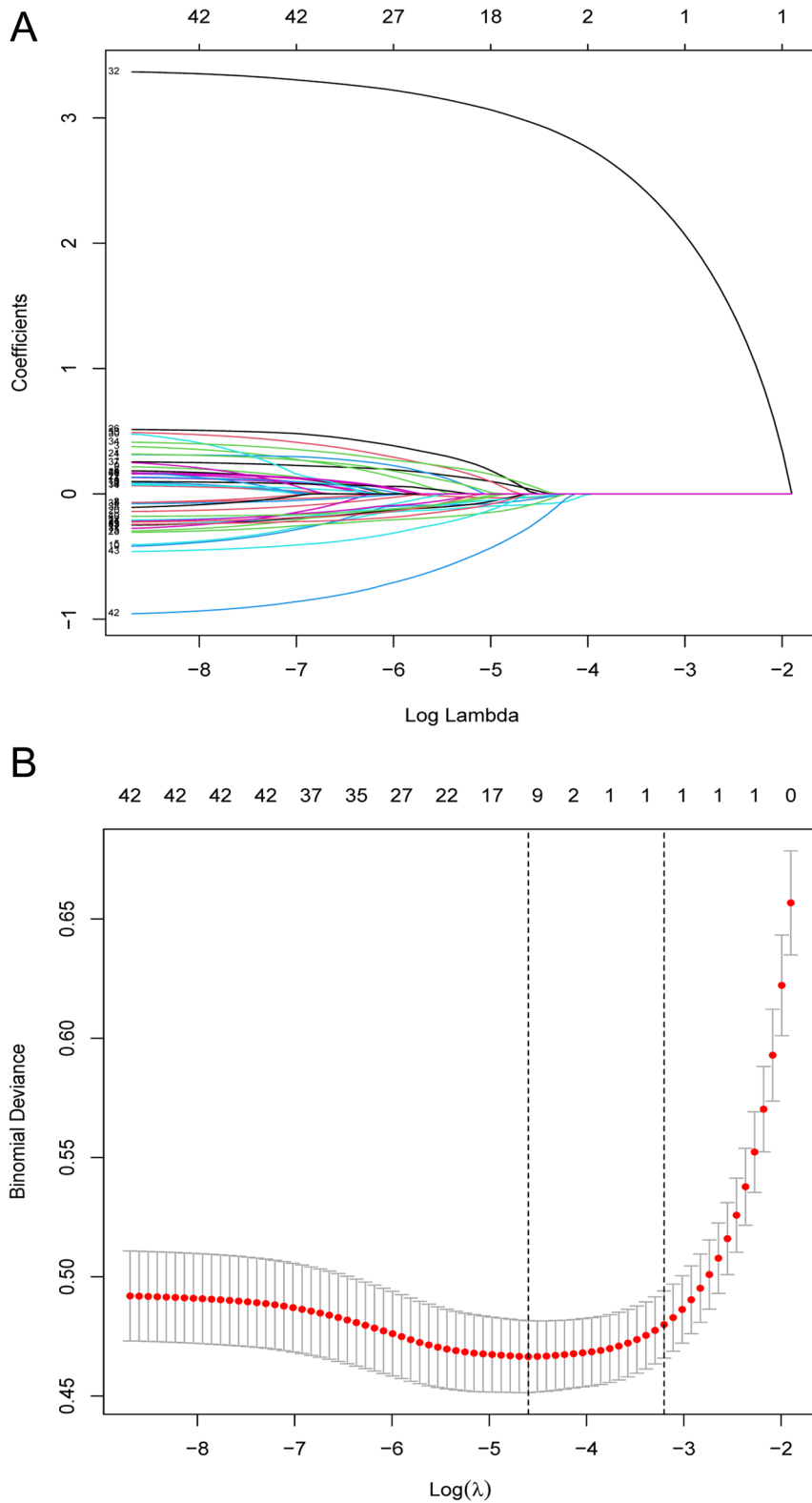


Figure 2

Characteristic variables selection using the least absolute shrinkage and selection operator (LASSO) logistic regression model. (A) The partial likelihood deviance (binomial deviance) curve was plotted vs log (lambda). Optimal parameter (lambda) selection in the LASSO logistic regression model used cross-validation, and dotted vertical lines were drawn via minimum criteria and the 1 s.e. of the minimum criteria. (B) LASSO coefficient profiles of the 44 features. A coefficient profile plot was produced against the log (lambda) sequence, where optimal lambda resulted in ten features with nonzero coefficients.

and decreasing bone density. Osteopenia is an early state of OP, and our study found that patients with osteopenia have a significantly increased risk of developing OP after 3

years. Therefore, active treatment and intervention while diagnosed with osteopenia before OP can occur reduce OP risk after 3 years.

Table 2 The predictors for the 3-year incidence risk of OP in Chinese male patients.

Intercept and variable	Prediction model		
	β	Odds ratio (95% CI)	P-value
Intercept	-3.279	0.038 (0.012–0.109)	<0.001
Age (years)		Reference	
≤50			
50–70	0.151	1.163 (0.776–1.757)	0.4692
>70	0.465	1.591 (0.751–3.305)	0.2177
NC (cm)		Reference	
<35			
≥35	-0.041	0.960 (0.601–1.535)	0.8626
WHTR		Reference	
<0.5			
≥0.5	-0.061	0.941 (0.570–1.549)	0.8100
BMI (kg/m ²)		Reference	
<18.5			
18.5–24	-0.330	0.719 (0.269–1.997)	0.5153
24–28	-0.742	0.476 (0.158–1.482)	0.1913
≥28	-0.468	0.627 (0.187–2.143)	0.4501
TG (mmol/L)		Reference	
<1.7			
1.7–2.3	-0.083	0.921 (0.549–1.524)	0.7511
≥2.3	-0.246	0.782 (0.471–1.286)	0.3370
IFG: yes vs no	0.593	1.810 (0.979–3.255)	0.0521
Dyslipidemia: yes vs no	-0.295	0.744 (0.492–1.126)	0.1614
Osteopenia: yes vs no	3.299	27.094 (18.266–41.272)	<0.001
Smoking history: yes vs no	0.371	1.450 (1.000–2.116)	0.0519
Strenuous exercises: yes vs no	-0.998	0.369 (0.135–0.852)	0.0312

IFG, impaired fasting glucose; NC, neck circumference; OP, osteoporosis; TG, triglyceride; WHTR, waist-to-height ratio.

BMI, central obesity, and OP

Previous studies (49) have shown that for both men and postmenopausal women, BMI, fat mass, and lean mass are conducive to increasing BMD. The study of Yang *et al.* (37) found that central obesity, BMI, and the prevalence of male OP were closely related. The studies from Wu *et al.* (50) and Lloyd *et al.* (42) also support this view, indicating that there is a strong negative correlation between BMI and OP. The above findings are consistent with our research. The protective effect of high BMI against OP is considered to be related to weight gain. The greater the body weight, the greater the mechanical load on the bones, which contributes to an increase in bone mass (51). On the contrary, the study of Zhao *et al.* (52) showed that increased fat mass may not benefit bone mass. Now, more and more studies have confirmed that higher fat mass may be an independent risk factor for OP and osteoporotic fractures.

TG, dyslipidemia, and OP

The relationship between blood lipids and OP has always been controversial. Hsu *et al.* (41) discovered that after adjusting for body weight, fat mass, and other confounding factors, a significant negative correlation exists between body bone mineral content (BMC) and TC, TG, and LDL. Another study from Poli *et al.* (53) found that after adjusting for BMI and age, postmenopausal women with high plasma LDL levels have a higher risk for osteopenia. On the contrary, a cohort study (54) conducted in Italy showed that both female and male body and buttocks BMD

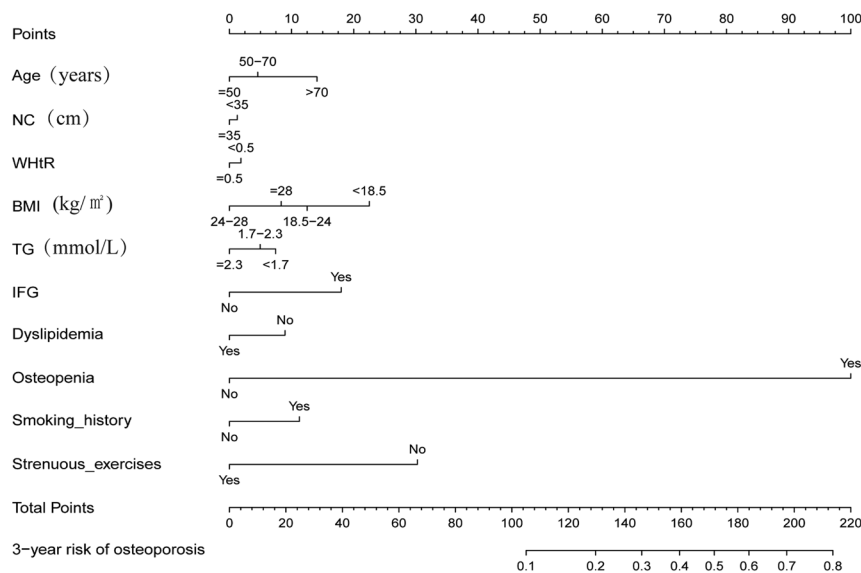


Figure 3

Nomogram prediction for the 3-year risk of osteoporosis. Predictors contained in the prediction nomogram included age, NC, WHTR, BMI, TG, IFG, dyslipidemia, osteopenia, smoking history, strenuous exercises. NC, neck circumference; WHTR, waist-to-height ratio; TG, triglyceride; IFG, impaired fasting glucose.

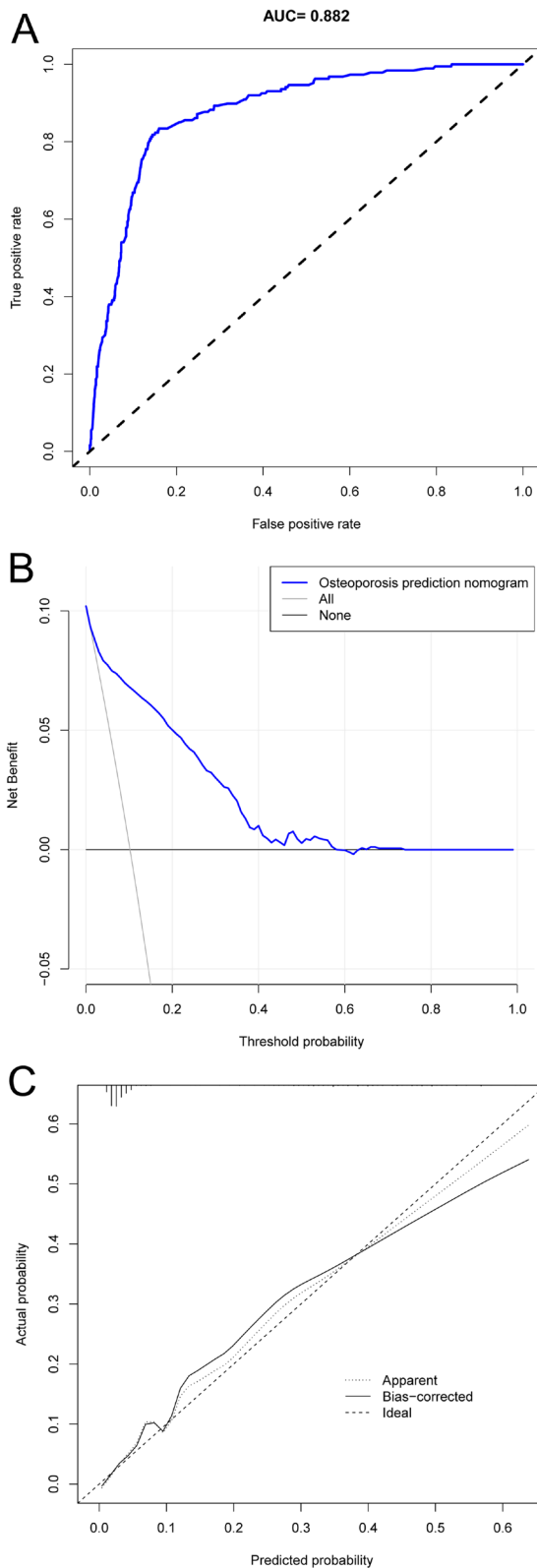


Figure 4

Receiver operating characteristic curve, clinical decision curve analysis, and calibration curves. (A) ROC curve of the predictive OP risk nomogram. The y-axis represents the TPR of the risk prediction, the x-axis represents the FPR of the risk prediction. The blue line represents the performance of the nomogram. (B) DCA curve of the predictive OP risk nomogram. The y-axis represents the net benefit. The thick solid line represents the assumption that no patients have OP, the thin solid line represents the assumption that all patients have OP, the blue line represents the OP risk nomogram. (C) Calibration curve of the predictive OP risk nomogram. The y-axis represents actual diagnosed cases of OP, the x-axis represents the predicted risk of OP. The diagonal dotted line represents a perfect prediction by an ideal model, the solid line represents the predictive power of the actual model, with the results indicating that a closer fit to the diagonal dotted line represents a better prediction. ROC, receiver operating characteristic; DCA, decision curve analysis; OP, osteoporosis; TPR, true positive rate; FPR, false positive rate.

were closely related to blood lipids. HDL-C was negatively correlated with BMD, while TG, TC, and LDL-C were positively correlated with BMD. The study of Loke *et al.* (55) found that in female patients, HDL-C and BMD were positively correlated, while in males, the opposite was true. In this study, we found that patients with dyslipidemia and high TG levels had a reduced risk for OP. It is worth noting that patients with abnormal blood lipid profiles are often accompanied by higher BMI levels. The positive effects of mechanical pressure may conceal the relationship between blood lipids and BMD (56). Therefore, when analyzing the relationship between blood lipid profiles and OP, BMI should be considered.

IFG and OP

At present, controversies abound regarding the relationship between T2DM and BMD. Some studies (57, 58, 59, 60) suggest that type 2 diabetes is associated with low BMD; a few report normal BMD; a few report increased BMD. Our study found that patients with impaired fasting blood glucose had an increased risk for OP. A study (61) from Japan reported that in elderly men in the community, there was a linear correlation between high blood sugar and increased fracture risk. Maddaloni *et al.* (62) found that serum osteocalcin levels negatively correlated with HbA_{1c}, indicating that poor blood glucose control would affect osteoblast functionality. A study from Parajuli *et al.* (63) also found that hyperglycemia can damage bones and mechanical load response. Therefore, actively controlling blood sugar has a positive effect on preventing OP.

Exercise, smoking, and OP

Multiple studies (64, 65, 66, 67) have confirmed that exercise is beneficial to health, including reducing falls and fractures. The meta-analysis from Zhao *et al.* (64) found that combined exercise intervention was effective in preventing bone density loss in postmenopausal women, and another from Xu *et al.* (65) showed that lifelong exercise for different ages was an effective way to maintain bone health in girls and women. The aforementioned studies (64, 65, 66, 67) were limited to female patients. The research from Wainstein *et al.* (68) found that regular physical activity might improve BMD in men. Another study from Korea (69) also found that appropriate exercise might decrease the risk for low BMD in elderly men, which is consistent with our study. Our research has found that weight-bearing exercise can prevent male OP to a certain extent. It should

be noted that for some patients, such as patients with diabetic peripheral neuropathy, exercise can increase the risk of falls. Therefore, doctors should formulate targeted health plans based on the risks to each patient individually. There is no doubt that smoking is harmful to the body. Most evidence (36, 37) suggests that smoking can reduce BMD in women and men, thereby increasing the risk of OP, which is consistent with our study.

Limitations

However, this paper still has the following shortcomings: First, QUS was used to measure bone density in this study, instead of DXA, the gold standard for diagnosing OP. But QUS has several advantages, such as portability, low cost, and ease of operation, making it more suitable for large epidemiological investigations. Secondly, the definition of OP and osteopenia in our study refers to the diagnostic criteria of WHO. Obviously, this will reduce the accuracy of diagnosis. Therefore, the BMD estimated by calcaneal QUS is suitable for the construction of predictive models rather than diagnostic models. In addition, patients diagnosed with OP by QUS of the calcaneus need to be further clarified by DXA in future research. Thirdly, model validation is achieved through bootstrapping validation in internal validation, which needs to be verified by external validation in future research.

Conclusion

Global research on OP primarily focuses on female patients, while there are few studies on male patients. Our study established a highly accurate nomogram to predict the 3-year incidence risk of OP in male patients. By assessing individual risks, clinicians can formulate effective interventions for patients and provide health education according to their lifestyles, diets, and exercise patterns.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-21-0330>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Gang Chen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Yaqian Mao, Gang Chen, Jixing Liang, Ting Xue, Lizhen Xu, Wei Lin, Junping Wen, Huibin Huang, Liantao Li. Acquisition, analysis, or interpretation of data: Yaqian Mao, Lizhen Xu, Ting Xue. Drafting of the manuscript: Yaqian Mao, Lizhen Xu, Ting Xue, Gang Chen. Critical revision of the manuscript for important intellectual content: Yaqian Mao, Wei Lin, Junping Wen, Gang Chen, Jixing Liang, Huibin Huang, Liantao Li. Statistical analysis: Yaqian Mao, Lizhen Xu, Ting Xue. Supervision: Gang Chen.

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