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ORIGINAL RESEARCH

Establishment and Validation of a Predictive Nomogram Model for Osteoporosis in Postmenopausal Women with Type 2 Diabetes Mellitus: A Retrospective Study

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Aim: To investigate the correlation between blood biomarkers and blood glucose fluctuations with the risk of osteoporosis (OP) in postmenopausal women with type 2 diabetes mellitus (T2DM), and to construct a predictive nomogram for OP.

Methods: Based on bone mineral density (BMD) results from dual-energy X-ray absorptiometry (DXA), participants were divided into OP (BMD T-value ≤ −2.5 SD) and Non-OP (BMD T-value > −2.5 SD) groups. Logistic analysis were used to explore the potential risk factors, following by the construction of a nomogram to predict the risk of OP. The discrimination and calibration of the nomogram were evaluated using concordance index (C-index), area under curve (AUC), and calibration curves.

Results: We finally included 381 participants, with 147 in the OP group. Correlation analysis revealed a significant positive correlation between age and SII, and a negative correlation between BMI and CV. SII and CV demonstrated a positive dose-response relationship with OP, while FT3 exhibited a negative relationship. Multivariate logistic analysis showed that age (OR=1.088, 95% CI 1.052–1.125, P<0.001), BMI (OR=0.772, 95% CI 0.702–0.848, P<0.001), SII (OR=1.004, 95% CI 1.003–1.005, P<0.001), FT3 (OR=0.529, 95% CI 0.280–0.998, P=0.049), and CV (OR=1.051, 95% CI 1.007–1.097, P=0.022) were independent risk factors. The subgroup analysis showed the correlation between SII and OP occurred primarily in individuals aged ≥60 years. A predictive nomogram model was constructed based on age, BMI, SII, FT3, and CV, with a C-index of 0.842 (range 0.801–0.883). Decision Curve Analysis (DCA) demonstrated good clinical fit of the model.

Conclusion: SII can predict the OP occurrence in women aged ≥60 years, while FT3 is applicable for predicting OP in women aged ≥70 years and those with a BMI <24 kg/m². The predictive nomogram demonstrated great predictive value in postmenopausal women with T2DM.

Keywords: type 2 diabetes mellitus, osteoporosis, postmenopausal women, systemic immune-inflammation index, free triiodothyronine, nomogram

Introduction

Osteoporosis (OP) is a chronic systemic bone disease characterized by decreased bone mass and microarchitecture deterioration of bone tissue, which may lead to increased bone fragility and susceptibility to fracture, particularly in women and men over the age of 55 and 65 years, respectively. OP represents a clear and growing public health concern. The National OP Foundation predicted that approximately 10.2 million Americans have

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OP and an additional 43.4 million have decreased bone mass, and the number of adults with OP and decreased bone mass is expected to increase to 71 million by 2030.[1,2] Previous studies have shown that both diabetes mellitus and postmenopause are risk factors for OP, and perimenopausal women lose 20 mg of calcium per day compared to premenopausal women. Such small changes in mineral balance explains at least a two-to-three-fold increase in the risk of OP after ten years of menopause.[3–5] Aging and the lack of postmenopausal estrogen are believed to be the main reasons for the loss of bone mass and structural changes to bone among this population.[6,7] In addition, many studies have suggested that underlying diseases also play a role, with type 2 diabetes mellitus (T2DM) being one such disease, as patients with combined T2DM have a 12-fold greater lifetime risk of OP compared to those without T2DM.[8] T2DM-related metabolic abnormalities such as increases in adipose tissue and loss of body weight, hyperglycemic state and fluctuating blood glucose levels, formation of advanced glycation end products (AGEs), T2DM-related chronic kidney disease, and disturbances in calcium-parathyroid hormone (PTH)-vitamin D metabolism, are possible major mechanisms.[9] Therefore, early screening programs for postmenopausal women with T2DM who are at high risk of developing OP are urgently needed.

It has been demonstrated that systemic immune and chronic inflammatory states are closely related to OP, and that metabolic changes or tissue dysfunction due to endocrine and autoimmune diseases (eg, thyroid dysfunction, DM, rheumatoid arthritis, and multiple sclerosis) would lead to a chronic inflammatory state, which exacerbates the impact of immune cells on the metabolism and physiology of osteocytes. In addition to direct cell-to-cell contact or paracrine signaling interactions between lymphocytes and bone physiologically-related cells, neutrophils also play a role. In particular, neutrophils can be overactivated and enhance osteoclastogenesis and osteoblast apoptosis through the release of reactive oxygen species (ROS) as well as the RANKL signaling pathway during estrogen deficiency.[10,11] Therefore, the search for easily accessible biomarkers suggestive of the degree of systemic immune-inflammatory response is critical to improve the accuracy and reduce the difficulty in assessing OP risk.

The systemic immune-inflammatory index (SII) is a composite biomarker based on immune-inflammatory cells (neutrophils, lymphocytes, and platelets) that reflects the systemic immune and inflammatory status, with high SII levels indicating a high inflammatory state and a weak immune response.[12] Previous studies have shown that higher levels of SII in postmenopausal women tend to indicate a higher risk of OP.[12,13] However, few studies have addressed menopausal women with comorbid chronic metabolic diseases. We hypothesized that the SII plays a role in the risk of OP in postmenopausal women with T2DM and analyzed its predictive efficacy.

Based on the above theory and research background, this study aimed to identify potential biomarkers for OP risk in postmenopausal women with T2DM and construct a predictive nomogram accordingly to provide recommendations for its prevention and treatment.

Methods

Patients Selection

381 postmenopausal women with type 2 diabetes mellitus (T2DM) who were admitted to Hefei Hospital Affiliated to Anhui Medical University from January 2018 to December 2023 were included in this retrospective study. All patients completed dual-energy X-ray absorptiometry (DXA), and then were divided into two groups based on the bone mineral density (BMD) T-value, namely the osteoporosis (OP) group (147 participants, BMD T-value ≤ -2.5 SD) and the Non-OP group (234 participants, BMD T value > -2.5 SD). Figure 1 illustrates the detailed screening process.

Inclusion Criteria

1. All patients were postmenopausal women diagnosed with T2DM according to the World Health Organization (1999) diagnostic criteria for diabetes mellitus (DM);[14]
2. Patients with complete clinical data and laboratory results.

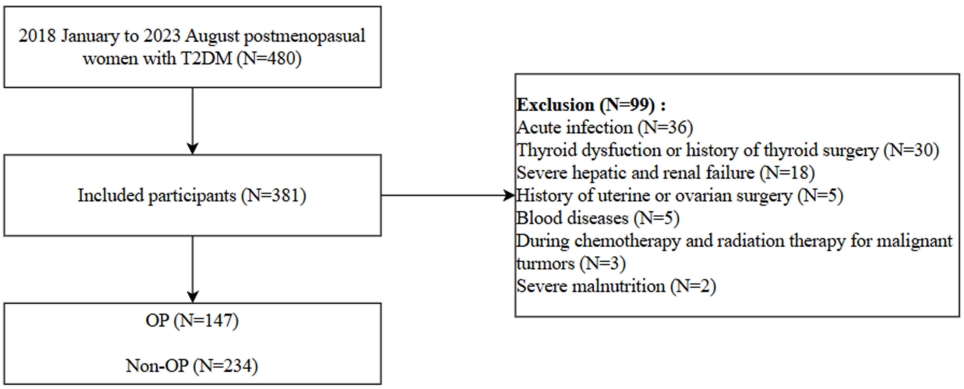

Figure 1 Study design flowchart.

Exclusion Criteria

1. Patients with other types of DM, including type 1 DM and gestational diabetes;
2. Previous diagnosis of OP and treatment with anti-OP therapy;
3. Previous use of drugs or hormonal preparations that affect bone metabolism and induce OP development;
4. Combination with DM-related acute complications;
5. Being in the acute stage of infection;
6. Combination with severe systemic diseases such as chronic infectious diseases, organ failure (including heart, liver, and kidney insufficiency), hematologic diseases, or autoimmune rheumatoid diseases;
7. Abnormal thyroid function or a history of thyroid-related surgery;
8. Previous history of reproductive surgery such as hysterectomy or oophorectomy;
9. Patients with malignant tumors;
10. Severe malnutrition or impaired consciousness.

Medical History and Data Collection

Clinical data of the patients were retrospectively collected through an electronic medical record system including age, duration of DM, years since menopause, history of hypertension, family history of DM, history of insulin use, history of diabetic retinopathy, history of cerebrovascular disease, history of bone fracture or previous fracture-related surgery, as well as height and weight. Results of fasting blood tests within 24 h of study inclusion were collected including white blood cell (WBC), red blood cell (RBC), platelet, neutrophil, lymphocyte, and monocyte counts; hemoglobin (Hb) levels; red blood cell distribution width-CV; red blood cell distribution width-SD; and platelet distribution width. Fasting blood biochemical indices were collected, including blood calcium, creatinine, uric acid, albumin, alkaline phosphatase, lipid-related markers (Triglyceride (TG), Total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL)), and glucose (fasting blood glucose). Other indicators included glycosylated hemoglobin, C-peptide (fasting), and thyroid-related hormones (FT3, FT4, and Thyrotropin (TSH)). Moreover, the results of ambulatory glucose testing were collected including the CV of glucose levels.

The Systemic Immune-Inflammatory Index

The systemic immune-inflammatory index (SII) was calculated based on blood cell counts and blood biochemistry test results: SII[15] = neutrophil count ($\times 10^9$/L) * platelet count ($\times 10^9$/L) / lymphocyte count ($\times 10^9$/L).

Statistical Analysis

SPSS 26.0 (IBM, USA) and R v.4.3.0 (R Foundation for Statistical Computing, Austria) were used for statistical analysis and plotting. The *Kolmogorov–Smirnov* test was performed to determine whether a variable was normally distributed and *Levene*'s test was performed to determine the homogeneity of variance. Continuous data were expressed as means and

standard deviations if the variable followed a normal distribution, or as median (interquartile range) in cases of non-normally distributed variables. Independent samples *t*-test or *Mann–Whitney U*-test was performed for continuous variables between groups, and χ^2-test was performed for categorical variables. Correlations between variables were assessed using *Pearson* or *Spearman* correlation coefficients. Restricted cubic spline (RCS) curves were used to illustrate the dose-response relationship between age, BMI, SII, FT3, CV, and the onset of OP in postmenopausal patients with T2DM. Stratification factors were used for subgroup analysis, including age (<60 years; 60–70 years; ≥70 years), BMI (<24 kg/m^2; ≥24 kg/m^2), history of fracture or fracture-related surgeries, and history of insulin use. Considering the skewed distribution of SII, its logE transformation was performed for subgroup analyses. Variables with $P < 0.05$ in the univariate analysis were included in the multivariate logistic regression analysis to determine the independent risk factors for OP onset in postmenopausal patients with T2DM. A predictive nomogram was constructed by including the above risk factors, and the nomogram model including the above risk factors was plotted using the R software. Moreover, model discrimination was assessed using the ROC curve and C-index, and model calibration was assessed using the *Hosmer–Lemeshow* test and calibration curves (Bootstrap method with 1000 self-samples for internal validation). Decision curve analysis (DCA) was performed using the rmda package within the R environment to assess clinical efficacy of the model. A P-value < 0.05 was considered to be statistically significant.

Results

Demographic Characteristics

A total of 381 postmenopausal women with T2DM were included in this study, comprising 147 participants in the OP group and 234 in the Non-OP group. The proportions of patients in the OP and Non-OP groups were 38.58% and 61.42%, respectively. Significant differences (P<0.05) between the two groups were identified for age, diabetes duration, menopause duration, insulin use history/cases, fracture history, BMI, lymphocytes, SII, RDW-SD, TG, TC, LDL-C, FT3, and CV, while the other variables showed no statistical significance (P>0.05). Table 1 presents detailed clinical characteristics of the participants. In addition, we generated a heat map to visualize correlations between different variables, which revealed a significant positive correlation between age and SII (r [95% CI]=0.139 (0.039–0.236), P=0.007), and a significant negative correlation between BMI and SII (r [95% CI]=0.139 (0.039–0.236), P=0.007). Correlation between BMI and CV (r [95% CI] = –0.255 (–0.347 to –0.159)) was significant (P<0.001). More details can be inspected in Figure 2 (the figure displays correlation coefficients as numerical values).

Table 1 Comparison of Clinical Characteristics Between OP and Non-OP Patients

Variables	Total (n = 381)	Non-OP (n = 234)	OP (n = 147)	*t/(Z)/[x2]*	*P*
Age (*years; M, IQR*)	63.00 (56.00, 70.00)	59.50 (54.25, 67.00)	68.00 (61.00, 73.00)	−7.29	<0.001
Diabetes duration (*years; M, IQR*)	10.00 (4.00, 14.00)	7.00 (3.00, 12.00)	10.00 (6.00, 17.00)	−4.60	<0.001
Menopause duration (*years; M, IQR*)	10.00 (4.00, 17.00)	7.00 (2.00, 13.00)	15.00 (10.00, 22.00)	−7.52	<0.001
Hypertension(%)	220 (57.74)	142 (60.68)	78 (53.06)	2.15	0.143
Family history of diabetes/case(%)	197 (51.71)	117 (50.00)	80 (54.42)	0.71	0.400
Insulin use history /case(%)	177 (46.46)	98 (41.88)	79 (53.74)	5.11	0.024
Diabetic retinopathy/case(%)	100 (26.25)	63 (26.92)	37 (25.17)	0.14	0.705
Cerebrovascular diseases history(%)	175 (45.93)	99 (42.31)	76 (51.70)	3.21	0.073
Fracture history(%)	69 (18.11)	33 (14.10)	36 (24.49)	6.57	0.010
BMI (*kg/m2; M, IQR*)	24.14 (22.31, 26.64)	24.99 (23.03, 27.18)	23.23 (21.24, 24.97)	−6.13	<0.001
WBC (×*109/L; M, IQR*)	5.71 (4.82, 6.88)	5.68 (4.79, 7.01)	5.82 (4.90, 6.65)	−0.17	0.861
RBC (×*109/L; x*±s)	4.23 ± 0.42	4.26 ± 0.42	4.18 ± 0.43	1.75	0.080
HGB (*g/L; M, IQR*)	125.00 (118.00, 132.00)	126.00 (119.25, 133.00)	124.93 (116.50, 130.50)	−1.86	0.062
PLT (×*109/L; M, IQR*)	189.00 (159.00, 226.00)	188.00 (158.25, 222.00)	192.00 (159.50, 232.00)	−0.61	0.545
Neutrophils (×*109/L; M, IQR*)	3.49 (2.73, 4.20)	3.35 (2.57, 4.25)	3.58 (2.93, 4.15)	−1.56	0.119

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 381)	Non-OP (n = 234)	OP (n = 147)	*t/(Z)/[x2]*	*P*
Lymphocytes (×*109/L; M, IQR*)	1.77 (1.41, 2.18)	1.88 (1.56, 2.30)	1.49 (1.19, 1.90)	−6.07	<0.001
Monocytes (×*109/L; M, IQR*)	0.33 (0.30, 0.40)	0.33 (0.30, 0.40)	0.32 (0.29, 0.40)	−0.59	0.557
SII (*M, IQR*)	378.21 (257.31, 513.29)	327.95 (245.00, 440.59)	471.61 (337.82, 629.42)	−6.26	<0.001
RDW-CV (*%; M, IQR*)	12.90 (12.50, 13.30)	12.85 (12.40, 13.30)	12.90 (12.60, 13.30)	−1.52	0.129
RDW-SD (*fL; x±s*)	41.56 ± 2.37	41.31 ± 2.31	41.97 ± 2.42	−2.66	0.008
PDW (*fL; M, IQR*)	16.30 (16.10, 16.50)	16.30 (16.10, 16.60)	16.30 (16.10, 16.50)	−0.06	0.952
Ca (*mmol/L; M, IQR*)	2.32 (2.25, 2.39)	2.32 (2.25, 2.41)	2.32 (2.25, 2.39)	−0.80	0.426
CR (*μmol/L; M, IQR*)	53.10 (46.30, 61.00)	52.20 (46.00, 59.38)	54.00 (46.70, 62.55)	−1.38	0.167
UA (*μmol/L; M, IQR*)	285.40 (245.00, 339.00)	288.95 (246.22, 338.80)	279.20 (240.60, 338.90)	−0.74	0.460
ALB (*g/L; M, IQR*)	40.90 (38.40, 44.00)	40.85 (38.80, 44.40)	41.00 (38.25, 43.75)	−0.54	0.592
ALP (*U/L; M, IQR*)	84.00 (68.80, 99.40)	81.10 (68.48, 97.35)	86.00 (69.65, 101.10)	−1.36	0.174
TG (*mmol/L; M, IQR*)	1.57 (1.10, 2.35)	1.66 (1.17, 2.39)	1.40 (0.99, 2.08)	−2.67	0.008
TC (*mmol/L; M, IQR*)	4.52 (3.83, 5.26)	4.63 (4.04, 5.34)	4.23 (3.68, 5.04)	−3.26	0.001
HDL-C (*mmol/L; M, IQR*)	1.24 (1.05, 1.46)	1.23 (1.05, 1.46)	1.25 (1.06, 1.45)	−0.30	0.762
LDL-C (*mmol/L; M, IQR*)	2.58 (2.06, 3.19)	2.67 (2.16, 3.27)	2.53 (1.94, 2.96)	−2.53	0.011
VLDL-C (*mmol/L; M, IQR*)	0.31 (0.22, 0.47)	0.33 (0.23, 0.48)	0.28 (0.20, 0.42)	−2.69	0.007
FPG (*mmol/L; M, IQR*)	8.14 (6.56, 10.27)	8.34 (6.62, 10.79)	7.79 (6.47, 9.31)	−1.71	0.088
HbA1c (*%; M, IQR*)	8.60 (7.30, 10.10)	8.90 (7.30, 10.40)	8.20 (7.20, 10.05)	−1.30	0.194
C-Peptide (*pmol/L; M, IQR*)	1.49 (0.94, 2.15)	1.56 (0.95, 2.21)	1.47 (0.93, 2.00)	−0.74	0.460
FT3 (*pg/mL; M, IQR*)	2.72 (2.43, 2.99)	2.82 (2.48, 3.09)	2.60 (2.38, 2.87)	−3.72	<0.001
FT4 (*pg/mL; M, IQR*)	0.89 (0.81, 0.97)	0.88 (0.81, 0.97)	0.89 (0.82, 0.96)	−0.49	0.627
TSH (*μU/mL; M, IQR*)	2.19 (1.45, 3.18)	2.14 (1.39, 2.97)	2.35 (1.59, 3.49)	−1.54	0.123
CV (*%; M, IQR*)	22.85 (18.87, 26.40)	22.08 (18.13, 24.60)	23.50 (20.05, 28.61)	−4.07	<0.001

Abbreviations: OP, osteoporosis; BMI, body mass index; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; RDW-CV, red blood cell distribution width-CV; RDW-SD, red blood cell distribution width-SD; SII, systemic immune-inflammatory index; CR, creatinine, UA, uric acid; ALB, albumin; ALP, alkaline phosphatase; TG, Triglyceride; TC, Total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FPG, fasting blood glucose; HBA1c, glycosylated hemoglobin A1c; FT3, FT4, and Thyrotropin (TSH), thyroid-related hormones; CV, coefficient of variation.

Multiple Logistic Regression Analysis of OP in Postmenopausal Women

Those with significant differences (P<0.05) between two groups were included of logistic regression. Considering the significant positive associations of age with durations of menopause and diabetes and negative asssociation of SII with lymphocytes, multivariate logistic regression analysis did not included these variables. After analysis, the following variables were found to be statistically significant: age (OR=1.088, 95% CI 1.052–1.125, P<0.001), BMI (OR=0.772, 95% CI 0.702–0.848, P<0.001), SII (OR=1.004, 95% CI 1.003–1.005, P<0.001), FT3 (OR=0.529, 95% CI 0.280–0.998, P=0.049) and CV (OR=1.051, 95% CI 1.007–1.097, P=0.022), as shown in Table 2.

Association Between SII, FT3, and CV with OP Occurrence

When analyzed as continuous variables, SII (P for nonlinear = 0.017) and CV (P for nonlinear = 0.556) demonstrated positive dose-response relationships with OP, while FT3 (P for nonlinear = 0.888) exhibited a negative dose-response relationship with OP, as illustrated in Figure 3. FT3 (P for nonlinear = 0.888) exhibited a negative dose-response relationship with OP, as illustrated in Figure 3.

Subgroup Analysis

Subgroup analyses were conducted to assess whether the predictive value of SII, FT3, and CV remained consistent across different demographic characteristics or comorbidities. The results showed that after adjusting for multiple factors, the association between SII and OP primarily occurred in individuals aged ≥60 years. In Model 1, the association between FT3 and OP primarily occurred in individuals aged ≥60 years; the association occurred in individuals with no history of fractures or fracture-related surgeries, aged ≥70 years, or with a BMI < 24 kg/m². In Model 2 and Model 3, the

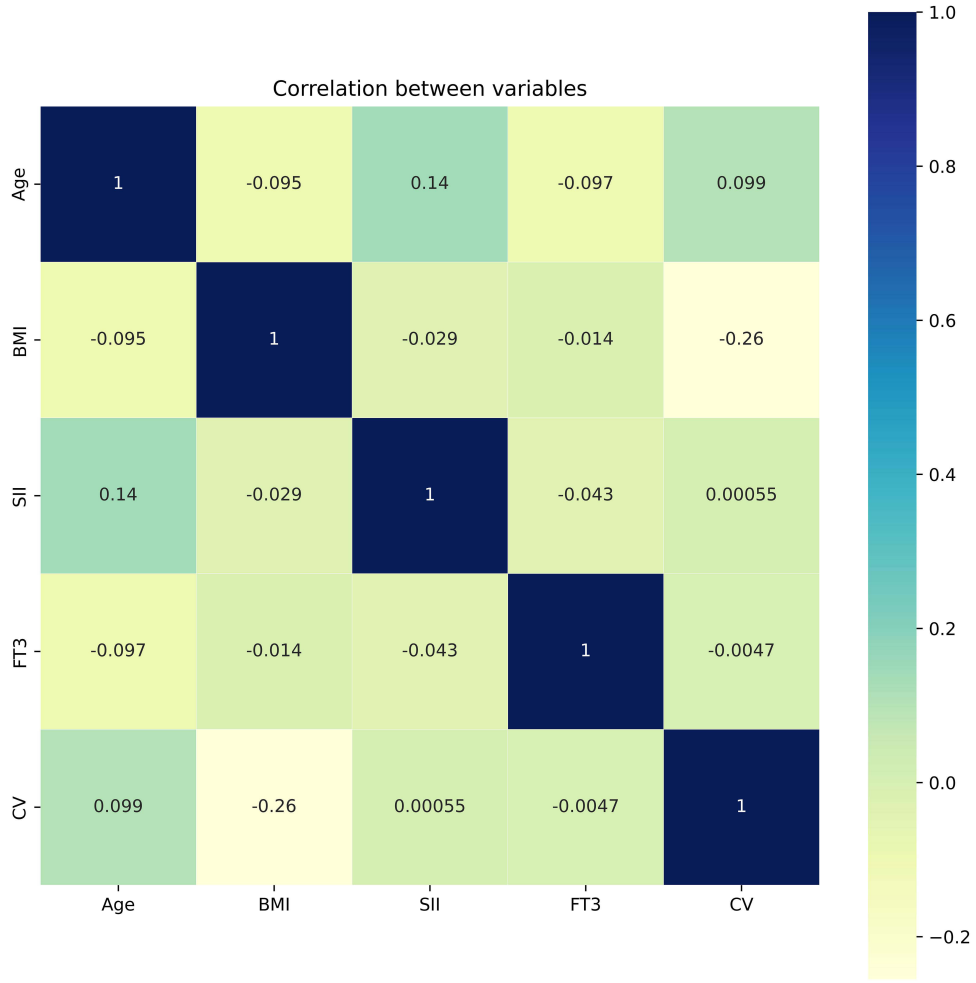

Figure 2 Correlations between different variables.

association occurred in individuals aged ≥70 years or with a BMI < 24 kg/m². In Model 1, the association between CV and OP occurred in individuals aged <70 years. In Model 2 and Model 3, the association occurred in individuals aged < 60 years, with no prior use of insulin-related medications, with no history of fractures or fracture-related surgeries, or with a BMI < 24 kg/m² (Table S1).

Establishment and Validation of Nomogram for Predicting OP Occurrence in Postmenopausal Women

A predictive nomogram for OP risk in postmenopausal women with T2DM was constructed based on the results of multivariate logistic regression analysis. The nomogram included age, BMI, SII, FT3, and CV. By using the nomogram,

Table 2 Multivariate Logistic Regression Analysis Results of Risk Factors for OP in Postmenopausal Women with T2DM

Parameters	β	SE	Z	P	OR (95% CI)
Age	0.084	0.017	4.893	<0.001	1.088 (1.052 ~ 1.125)
BMI	−0.259	0.048	−5.356	<0.001	0.772 (0.702 ~ 0.848)
SII	0.004	0.001	5.723	<0.001	1.004 (1.003 ~ 1.005)
FT3	−0.637	0.324	−1.965	0.049	0.529 (0.280 ~ 0.998)
CV	0.050	0.022	2.296	0.022	1.051 (1.007 ~ 1.097)

Abbreviations: BMI, body mass index; SII, systemic immune-inflammatory index; FT3, FT4, and Thyrotropin (TSH), thyroid-related hormones; CV, coefficient of variation.

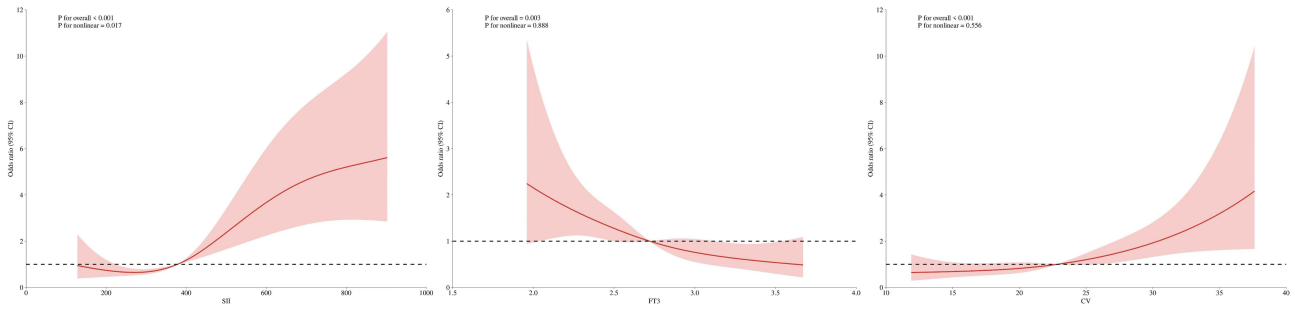

Figure 3 Dose-response relationship of SII, FT3, and CV with OP occurrence in postmenopausal women.

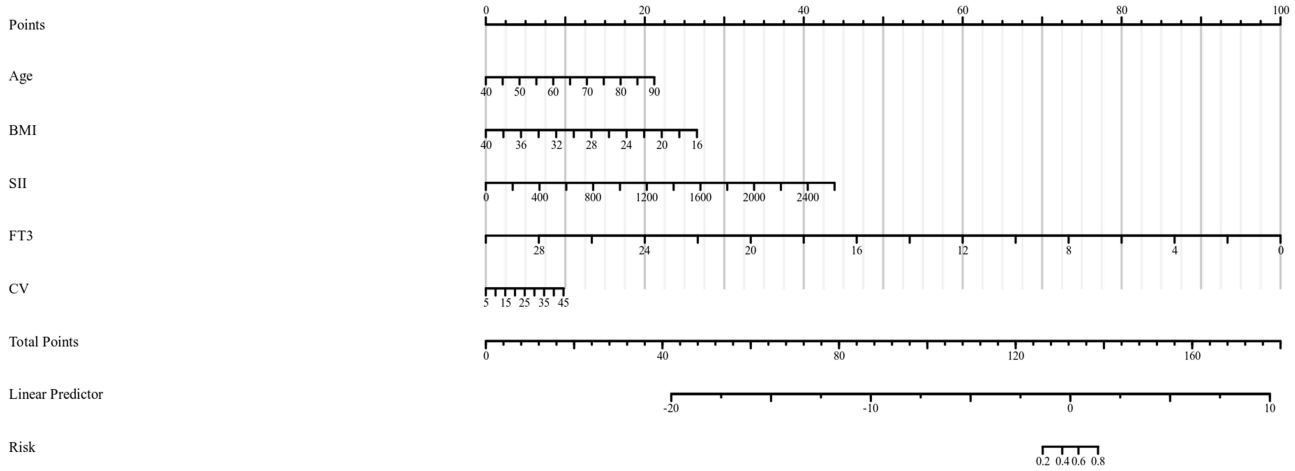

Figure 4 Nomogram of OP risk in postmenopausal women.

individual scores for each variable can be obtained, summed, and then mapped to the Total Points axis to determine the risk of OP in postmenopausal women with T2DM. Using the nomogram, individual scores for each variable can be obtained, summed, and then mapped to the Total Points axis to determine the corresponding probability of OP risk, as illustrated in Figure 4. The ROC curve demonstrated that the Area Under Curve (AUC) (95% CI) values for the predictive nomogram for age, BMI, SII, FT3, and CV were 0.722 (0.670–0.773), 0.686 (0.632–0.741), 0.690 (0.634–-0.747), 0.613 (0.556–0.671), and 0.624 (0.565–0.682), respectively. The optimal cut-off values of age, BMI, SII, FT3 and CV were 60.500, 24.976, 382.123, 2.815, and 23.135, respectively. Internal validation was performed using the Bootstraping method, with a C-index of 0.842 (95% CI: 0.801–0.883). The calibration curve showed that both the actual curve and the bias-corrected curve closely approximated the ideal curve (*Hosmer–Lemeshow:* $\chi 2$ = 10.234, P = 0.2490), indicating excellent agreement between the model's predicted probabilities and the actual observed probabilities. DCA demonstrated the model's predicted probabilities and the actual observed probabilities. DCA also demonstrated the model's favorable clinical utility, with a higher net clinical benefit compared to other variables (Figure S1).

Discussion

The participants included in this study were postmenopausal patients with T2DM. There were a total of 381 participants with a mean age of 63.00 years, of which the percentage of OP patients was 38.58 (147 patients). Compared with the Non-OP group, higher age, SII, and CV, as well as a lower BMI and FT3 were observed for the OP group. Multivariate logistic regression showed that age, SII, and CV were risk factors for developing postmenopausal OP in patients with T2DM, while BMI and FT3 were protective factors.

Osteogenesis and metabolic processes are subject to precise regulation by the immune system, and the core regulatory mechanisms may involve age-related oxidative stress and low-level activation of the immune system. Oxidative stress

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accumulates with increasing age, and low-level activation of the immune system occurs in the meantime. These factors would synergistically affect the physiological dynamics of the bone tissue. Measurement of the number of immune cells in the blood may be used as an indicator of systemic inflammation, which corresponds to changes in the metabolic status of the bone.[16–18] Such immune cell count data are often readily available and contribute to a better understanding of bone pathology.[19] SII is a composite index based on blood neutrophils, lymphocytes, and platelets, and has shown powerful diagnostic and predictive capacity in infections and immune disorders.[20,21] Previous studies have shown that the SII is strongly associated with OP in both female and male populations.[22] A prospective study including 238 postmenopausal women found that a high SII was a significant predictor of OP and could even be used to identify risks of OP fracture.[23] In a complex physiological state combining dysglycemia and postmenopausal endocrine hormone dysregulation, postmenopausal women with T2DM have an activated inflammatory microenvironment and relatively low systemic immune function.[24,25] In addition, a variety of inflammatory cells are found in the bone marrow cavity. For example, dysfunctional lymphocytes may elicit a cascade reaction of inflammatory factors and chemokines, leading to aggregation of neutrophils and macrophages.[11,26–28] Estrogen has been shown to affect neutrophil function and activity, whereas neutrophils may disrupt the dynamic homeostasis of bone through the expression of pro-resorptive mediators such as interleukin-6 (IL-6), thereby inhibiting bone formation and inducing bone resorption. Therefore, there is a potential link between blood neutrophils, lymphocytes, platelets, and OP.[10–13,29] The SII is a composite biomarker based on the above cell types and may reflect the overall immune and inflammatory status of the individual. The complex interactions between pro-inflammatory and anti-inflammatory cytokines in postmenopausal women with DM and OP create a challenging microenvironment, which serves as a reference for the subsequent exploration of more accurate biomarkers based on the above principles to assess the onset of OP.

The Asia Pacific Consortium on OP (APCO) suggested that low BMI is a common risk factor for OP, and several prediction models based on it can adequately characterize the risk of OP.[30–32] A cross-sectional study including 1,061 postmenopausal T2DM patients in China showed that low BMI was a predictor of OP in postmenopausal patients with T2DM, especially OP of the hip,[33] which was consistent with our findings. Higher BMI may help to maintain the body's bone mass. However, to our knowledge, there are no studies supporting the increase of BMI for the prevention of OP, given that elevated BMI is an important risk factor for cardiovascular events. Moreover, being overweight increases the burden on weight-bearing joints and the risk of degenerative joint disease.[34] An expansion of bone marrow adipose tissue (BMAT) is considered a typical feature of skeletal aging and increased fracture risk. However, metabolic disturbances involving the endocrine system, such as postmenopausal hormone deficiency, obesity, and DM, may accelerate the deleterious changes in bone homeostasis as well as lead to early onset of OP and damage to bone microstructure, ultimately resulting in changes in the BMAT. The possible mechanisms include DNA damage, ROS production, and skeletal aging.[35]

Glycated hemoglobin (HbA1c) has long been the gold standard for glycemic control and shown to be associated with various chronic complications of DM, such as diabetic retinopathy, diabetic nephropathy, and diabetic peripheral neuropathy.[36,37] A single-center retrospective study found that HbA1c > 7.5% was a contributing factor to changes in the BMD,[38] which suggested a role of blood glucose changes in the development of OP. Glucose fluctuation, as a special indicator independent of HbA1c, reflects the blood glucose changes of an individual within a certain period of time, including mean amplitude of glucose excursion (MAGE), CV, and time in range (TIR) derived from continuous glucose monitoring (CGM). In this study, CV—one of the above indicators—was found to be an independent risk factor for the development of OP in the study population, and high levels of CV reflected a greater risk of OP onset, which was consistent with previous studies.[39]

An increasing amount of evidence suggests that changes in thyroid function can affect bone metabolism. Nevertheless, previous studies are controversial in terms of the specific role of thyroid-related hormones. Some studies have suggested that serum TSH levels within the normal range are positively correlated with BMD, and high TSH levels within the normal range (> 2.5 mIu/L) could reduce the risk of OP in postmenopausal women.[40] Nevertheless, some scholars believe that the effects on bone metabolism cannot be illustrated by a single specific hormone, as the dynamic stability of thyroid hormones is regulated by the hypothalamic–pituitary–thyroid axis, in which FT3, FT4, and TSH interact with each other in vivo. Therefore, the use of composite indices (including the thyrotropic index and the

thyrotropic hormone resistance index) provides comprehensive and systematic observations of the hypothalamic–pituitary–thyroid axis.[41,42] However, both FT3 and FT4 originate from physiologic changes in TSH induced in the early stages of OP.[43] However, many studies disagree on the relationship between thyroid-related hormones and OP. In a prospective, observational, cross-sectional, controlled study involving 120 postmenopausal women, no statistically significant correlation was found between thyroid hormone levels and BMD, and there was no evidence that changes in TSH values in postmenopausal women with normal thyroid function resulted in differences in the BMD and fracture risk.[44,45] Understanding the effects of thyroid hormones on bone metabolism remains a great challenge. Our study showed that high levels of FT3 within the normal range played a protective role in the onset of OP in postmenopausal patients with T2DM; only a few previous analyses have been based on this population. The role of chronic hyperglycemia in the association between thyroid hormones and risk of OP and the specific mechanisms involved remain unclear.

This study had certain limitations: First, this was a retrospective study with a small sample size, a single sampling site, and a short sampling time adopting a single-center approach, we continuously enrolled the population throughout the study period without performing sample size estimation. These factors may lead to certain bias. A multicenter, prospective study with a larger sample size is planned to further confirm the feasibility and accuracy of the above indicators in the prediction of outcomes and to identify additional potential risk factors. Second, the SII based on blood tests changes dynamically during the onset and development of OP, and the association between fluctuations in blood biomarkers during various phases of the onset and development of the disease and OP should be analyzed in the future. Third, considering the role of glucose fluctuations in OP, we plan to extend the duration of ambulatory glucose testing and explore the clinical efficacy of the above factors and the prediction model at a TIR > 70% to further segment the study population to provide individualized treatment plans.

Conclusion

SII, age, and CV are risk factors for OP in postmenopausal women with T2DM, while BMI and FT3 represent protective factors. The nomogram constructed based on these factors demonstrated favorable efficacy in predicting the risk of OP onset in postmenopausal patients with T2DM.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author Yong-Hong Cao upon reasonable request.

Ethics Statement

This research protocol was reviewed and approved by the Ethics Committee of Hefei Hospital Affiliated to Anhui Medical University, with the ethical approval number 2019-SR-084. All participants provided informed consent to participate and for the publication of clinical data from the study. Consent was obtained prior to the enrollment of this study and all data were analyzed anonymously. This study complies with the Declaration of Helsinki.

Author Contributions

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

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Disclosure

The authors have no conflicts of interest to disclose.

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