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Systemic immune-inflammatory index predicts fragility fracture risk in postmenopausal anemic females with type 2 diabetes mellitus: evidence from a longitudinal cohort study

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Abstract

Background Chronic low-grade inflammation is related to bone metabolism in patients with type 2 diabetes mellitus (T2DM). However, credible data indicating the relationship between inflammation and fragility fracture risk in postmenopausal anemic females with T2DM are sparse. The current study sought to investigate the relationships between the systemic immune-inflammatory index (SII) and fragility fracture events, as well as the future 10-year fragility fracture probability evaluated using the fracture risk assessment tool (FRAX) in postmenopausal females with T2DM.

Methods According to the tertiles of SII, 423 postmenopausal females with T2DM were divided into three groups: low-level (≤ 381.32, $n = 141$), moderate-level (381.32–629.46, $n = 141$), and high-level (≥ 629.46, $n = 141$). All participants were followed up for 7 years with a median of 46.8 months (1651 person-years). The association between SII and fragility fracture risk was assessed.

Results Of 423 subjects, 75 experienced a fragility fracture event. Spearman partial correlation analysis revealed that SII was negatively related to bone mineral density (BMD) and was positively associated with the future 10-year probability of major osteoporotic fracture (MOF) and hip fracture (HF). Restricted cubic spline (RCS) analysis revealed a positive correlation between SII and fragility fracture risk in an approximately inverted J-shaped dose–response pattern (P for overall < 0.0001). Multivariate Cox regression analysis demonstrated that patients with a high SII presented a greater risk of fragility fractures ($P = 0.011$). Stratified analysis revealed that fragility fractures in the high-level SII were predominantly associated with anemia with an increase of 4.15 times ($P = 0.01$). Kaplan–Meier analysis indicated a greater cumulative incidence of fragility fractures in patients with a high SII (log-rank, all $P = 0.0012$). Receiver operating characteristic (ROC) analysis indicated an optimal SII cut-off value of 537.34, with an area under the curve (AUC) of 0.646, a sensitivity of 60%, and a specificity of 64.1% ($P < 0.001$).

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Conclusion The SII revealed a significant positive association with a real-world fragility fracture event and a future 10-year fragility fracture probability in postmenopausal females with T2DM, particularly evident in individuals with anemia. Therefore, monitoring the SII and hemoglobin in postmenopausal older women with T2DM is helpful in routine clinical practice to identify individuals at high risk for fragility fractures and to promptly execute appropriate fracture intervention procedures.

Keywords Systemic immune-inflammatory index (SII), Fragility fracture, Type 2 diabetes mellitus (T2DM), Postmenopausal females, Anemia

Introduction

At present, diabetes has become a severe social public health issue in China and other regions worldwide [1]. With rapid aging and decreasing physical activity outdoors, the prevalence of type 2 diabetes mellitus (T2DM) has climbed to 12.8% in China [2]. Elderly diabetic patients are more prone to anemia, sarcopenia, frailty, bone loss, and osteoporosis caused by glucolipotoxicity and inappropriate glucose control measures such as dietary restriction, which in turn leads to fall-related fragility fracture adverse events in clinical practice [3]. Moreover, malnutrition in elderly individuals increases the risk of brittle fracture [4]. According to a recent meta-analysis, the prevalence of fragility fractures among elderly people in China is 18.9% [5]. Compared with nondiabetic patients, diabetic patients, especially elderly postmenopausal females with rapid withdrawal of estrogen-induced bone mass loss, have a greater risk of fragility fractures [6–9], which has caused heavy financial pressure on sufferers. Therefore, early identification of at-risk individuals using simple predictors and timely prevention strategies is urgently needed, particularly in primary care hospitals.

Over the past few decades, as the intricate connection between bone health and immune system function has gradually unfolded, a novel concept called "immunoporosis" has been introduced, which highlights the increasing significance of inflammation in osteoporosis, especially in postmenopausal women characterized by estrogen deficiency-mediated activation of osteoclasts and continual progression of chronic inflammation [10–14]. In addition, glucotoxicity caused by insulin dysfunction in T2DM patients and progressive functional recession of pancreatic beta cells with aging also result in a persistent activated inflammatory response, ultimately leading to immune imbalance, bone mass loss, and degenerative bone microarchitecture [15].

The systemic immune-inflammatory index (SII), a novel index calculated by the platelet count × neutrophil count/lymphocyte count and expressed as $\times 10^9$ cells/μl, can comprehensively reflect the body's inflammation and immune status [16]. Increasing evidence shows that the SII may be a valuable predictor of the risk and prognosis of cancer [17], adverse cardiovascular events [18], diabetic nephropathy (DN) [19], and diabetic retinopathy (DR) [20]. Recently, studies have demonstrated that the SII is positively associated with the severity of anemia and sarcopenia, especially among female participants [21, 22]. In addition, studies have shown that the SII is related to bone mineral density (BMD) and the incidence of osteoporosis. A cross-sectional study that included 4092 women revealed that the SII was negatively associated with the BMD of postmenopausal women but not premenopausal women, which indicated that an elevated SII may be a potential risk factor for osteoporosis in postmenopausal women [23]. Research-based on the National Health and Nutrition Examination Survey (NHANES) database shows that an increase in the SII is related to low BMD and an increased risk of osteoporosis [24]. The SII may be a simple inflammatory marker to predict the risk for low BMD, osteoporosis, and fragility fractures in postmenopausal women [25], especially in older women. Daily low-dose aspirin (a nonsteroidal anti-inflammatory drug) has been shown to reduce the risk of serious falls and fractures in the healthy older population [26].

Until now, there has been no credible evidence about the association between the SII and a real-world fragility fracture endpoint event or a future 10-year individualized probability of hip fracture (HF) and major osteoporotic fracture (MOF) calculated by fracture risk assessment tool (FRAX) through dual-energy X-ray absorptiometry (DXA) in postmenopausal anemic females with T2DM, which is the topic of interest in the present study.

Materials and methods

Study design

The present study was an ambispective longitudinal cohort study conducted between January 2014 and January 2021 from the Active Health Management Database of the People's Hospital of Guangxi Zhuang Autonomous Region. The median age in the study was 69 years (IQR, 64.00, 75.00). The inclusion criteria were as follows: (1) the diagnosis and classification of diabetes mellitus according to the 1999 WHO recommendation criteria [27] and (2) all postmenopausal female patients with

T2DM who received dual-energy X-ray absorptiometry (DXA) and complete anthropometry data including lumbar spine and pelvis digital X-ray data. The exclusion criteria were as follows: (1) malignant tumors, severe heart, liver, kidney diseases or infections; (2) thyroid or parathyroid diseases and immune system diseases; (3) other metabolic bone diseases (MBD) including hypophosphatemic osteomalacia, osteosclerosis and disease or hemodialysis -related secondary osteoporosis; (4) long-term use of antidiabetic prescription affecting the bone turnover, such as thiazolidinediones including rosiglitazone and pioglitazone, sodium-glucose co-transporter type 2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonist (GLP-1RA); long-term use of standardized anti-osteoporosis regimens affecting the bone turnover, including bisphosphonates, estrogen receptor agonists, raloxifene, teriparatide injection, and denosumab injection; (5) with the diagnosis of thalassemia; (6) long-term bedridden status and receiving long-term glucocorticoid or immunosuppressant therapeutic regimens; and (7) incomplete data, lost to follow-up, or a follow-up time of less than one year. A total of 509 postmenopausal patients with T2DM were recruited for this study. All participants were followed up for fragility fracture endpoints through outpatient check-ups, medical records, and telephone interviews every 6 months for 7 years, with a median of 46.8 months (1651 person-years). Finally, 423 subjects were eligible for inclusion in the present analysis. According to the SII tertiles, all subjects were classified into three groups: low-level ($\leq$381.32, n=141), moderate-level (381.32–629.46, n=141), and high-level ($\geq$629.46, n=141). The relationships between the SII and fragility fracture endpoint events and the individual next 10-year probability of HF and MOF calculated by FRAX were evaluated by Spearman partial correlation analysis, multivariate Cox regression analysis, RCS analysis, stratified analysis, Kaplan–Meier survival curve analysis, and ROC curve analysis. All patients agreed to participate in this study and signed a written informed consent and a nondisclosure agreement (NDA) to ensure privacy while analyzing the data. The study adhered to the Declaration of Helsinki guidelines and received approval from the Ethics Committee at the People's Hospital of Guangxi Zhuang Autonomous Region (approval number: Ethics-KY-IIT-2023–60).

Clinical data acquisition

The trained professionals collected biochemical indexes and follow-up data and anonymously analyzed the hospitalization data, which were used to obtain baseline characteristic data, including demographic, anthropometric, laboratory biochemical indicator, and medical records data, and to determine the fragility fracture endpoint event from the follow-up information obtained from outpatient check-ups, medical records, and telephone visits. The whole blood cell analyzer (Pentra120R, Horiba ABX, France) and biochemical automatic analyzer (P800, Roche, Germany) performed complete blood cell counts and blood biochemical indicators tests, respectively. The specific operating procedures (SOP) were followed according to the manufacturer-supplied lab manuals.

Definitions used in this study

Several related definitions in this study were as follows: (1) The endpoint event was defined as a fragility fracture. The location, time, and cause of the fragility fracture were confirmed through follow-up and medical imaging evidence, including radiation imaging, magnetic resonance imaging, computed tomography, and bone scanning. Fragility fractures refer to fractures in any part caused by minor or moderate trauma, and we excluded pathological fractures and fractures caused by severe trauma. If there were multiple fractures, the first fracture during the follow-up period was considered an endpoint event. (2) The SII, a bioindicator based on the complete blood count (CBC), is calculated as (platelet count$\times$neutrophil count/lymphocyte count), expressed as$\times 10^9$ cells/μl. (3) BMI was calculated by dividing weight by the square of height (kg/m^2). A single piece of breathable clothing and no shoes were dressed to measure height and weight. (4) DXA (Hologic Company, United States) was utilized to measure the lumbar spine, femur neck, and total hip BMD. The trained professionals controlled the instrument and rectified it daily according to quality-control standards. The BMD (g/cm^2) was synchronously and automatically converted into the T score through DXA. According to the criteria established by the WHO in 1994 [28], the T value is considered the gold standard, with a normal BMD T score of≥ -1.0 SD, $-1.0\sim-2.5$ SD indicating osteopenia, and≤ -2.5 SD demonstrating osteoporosis. Based on the formula [(the measured value of BMD—the peak BMD in ordinary young people of the same race and sex)/standard deviation (SD) of the peak BMD in ordinary young people of the same race and sex], the T score was calculated through DXA in the present study. The China Guidelines for Diagnosis and Treatment of Primary Osteoporosis (2022) recommended a peak BMD of 1.197 g/cm^2 in Chinese Han women aged 30–34 years and a peak BMD of 1.28 g/cm^2 in Chinese Han men aged 20–24 years. (5) The individual future 10-year probabilities of MOF and HF were calculated by FRAX (https://frax.shef.ac.uk/FRAX/tool.aspx?lang=chs). The FRAX includes a 12-item questionnaire consisting of age, sex, weight (kg), height (cm), previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis,

alcohol 3 or more units/day, and FN BMD (g/cm^2). FRAX is suitable for people aged 40–90 years. The age of individuals aged < 40 years is calculated as 40; however, those aged > 90 years are considered to be 90. According to the China Guidelines for Diagnosis and Treatment of Primary Osteoporosis (2022), the risk of fragility fractures is assessed by FRAX, with a low-risk probability of MOF < 10% and HF < 1.5%, moderate-risk probability of MOF 10%—20% and HF 1.5%—3.0%, high-risk probability of MOF 20%—30% and HF 3.0%—4.5%, and extremely high-risk probability of MOF ≥ 30% and HF ≥ 4.5%. (6) Elderly people were defined as adults aged over 65 years.

Statistical analysis

Normally distributed variables are displayed as the means (± SD), and nonnormally distributed variables are displayed as medians (interquartile ranges). Discontinuous classification variables are expressed as frequencies. The nonparametric Mann–Whitney U test was used to compare continuous variables with nonnormal intergroup distribution. The chi-square test was used for intergroup comparisons of categorical variables. Cox regression analysis was used to evaluate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between the SII and the risk of fragility fractures.

Univariate Cox regression analysis was initially used to identify the risk factors for endpoint events. Factors with $P < 0.1$ in the univariate analysis were included in the multivariate Cox regression analysis. We used tolerance and variance inflation factors to detect multicollinearity between variables. A tolerance less than 0.1 or a variance inflation factor greater than 10 indicates the existence of collinearity. Three multivariate regression models were built and used to adjust for potential confounding factors for the endpoint event gradually. Model I was adjusted for none. Model II was adjusted for the age and duration of diabetes with Model I. Model III was further adjusted for the age and duration of diabetes, hypertension, Hb, FT4, HDL-C, Cr, 25-hydroxyvitamin D [25(OH) D], ALB, and fracture history with Model II. The stratified analysis results for the subgroups are shown in forest plots generated with GraphPad Prism 9.3 (GraphPad Software, San Diego, CA). Kaplan–Meier survival curves were used to estimate the cumulative incidence of fragility fractures and the differences among the three groups were assessed using the log-rank test. The study sample size and power analysis were computed using PASS 11.0 (https://www.ncss.com/download/pass/updates/pass11/) to ensure that the minimum number of cases met a high testing power of over 90%. The statistical charts were drawn through the R language software package version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Data analyses were performed using GraphPad Prism 9.3 (GraphPad Software, San Diego, CA) and the SPSS 26.0 statistical software package (IBM Corp., Armonk, NY, USA). Statistical significance was set at the $P < 0.05$ level.

Results

Baseline characteristics

The flow chart in Fig. 1 illustrates the screening strategy for the subjects. This study included 509 postmenopausal patients with T2DM with complete BMD data who were hospitalized at the People's Hospital of Guangxi Zhuang Autonomous Region from January 2014 to January 2021. Finally, 423 participants with an average age of 69 years who met the inclusion criteria were recruited. The baseline characteristics of the participants are shown in Table 1. According to the tertiles of the SII, the subjects were divided into three groups: low-level (≤ 381.32, $n = 141$), moderate-level (381.32–629.46, $n = 141$), and high-level (≥ 629.46, $n = 141$). Among the three groups, age, hypertension, hemoglobin (Hb), creatinine (Cr), serum calcium (Ca), 25(OH) D, ALB, FN BMD, TH BMD, MOF, and HF were significantly different (all $P < 0.05$). Moreover, osteoporosis, DPN, PVD, fracture history, duration of diabetes, BMI, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), and LS BMD were not significantly different (all $P > 0.05$).

Spearman partial correlation analysis for the ability of the SII to predict endpoint events

The relationship between the SII and the risk for fragility fractures is shown in Table 2. The significant relationships between the SII and BMD and the next 10-year probability of MOF and HF calculated by the FRAX are also demonstrated as supplementary materials (S1-S7). Spearman partial correlation analysis indicated that the SII was negatively related to the BMD of the FN ($r = -0.101$, $P = 0.039$) and TH ($r = -0.127$, $P = 0.009$) and was positively associated with the future individual 10-year probability of major osteoporotic fracture (MOF, $r = 0.128$, $P = 0.008$) and hip fracture (HF, $r = 0.100$, $P = 0.041$) according to the FRAX. The above analyses suggested that the SII is a valuable predictor of the risk of fragility fractures.

RCS analyses for a dose–response correlation between the SII and fragile fracture risk

The results of the dose–response correlation analysis are presented in Fig. 2. After adjusting for confounding factors, hypertension, FT4, 25(OH) D, Hb, ALB, and Cr, a linear regression model was used to fit the data at 4

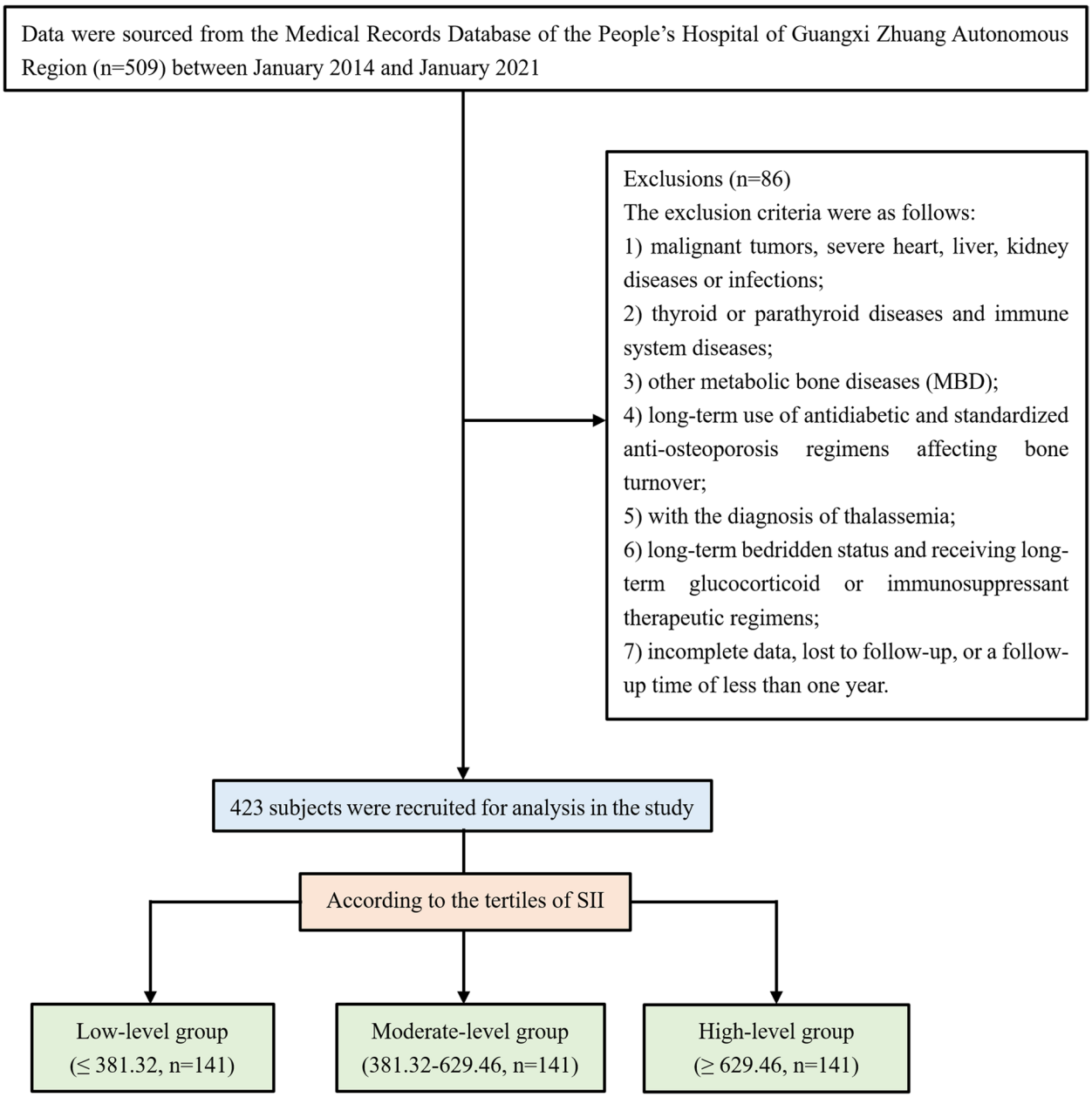

Fig. 1 The flow chart for selecting the subjects. The data ($n = 509$) were sourced from the Active Health Management Database of the Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region between January 2014 and January 2021. A total of 423 individuals were ultimately included in the present analysis. According to the tertiles of the SII, all subjects were divided into three groups: low-level group (≤ 381.32, $n = 141$), moderate-level group (381.32–629.46, $n = 141$), and high-level group (≥ 629.46, $n = 141$)

points in the 5th, 35th, 65th, and 95th percentiles of the SII (the reference value is the 5th percentile). The RCS model evaluates the relationship between the SII and a fragile fracture endpoint event in an inverse J-shaped dose-dependent correlation, which reveals that the SII is a biomarker of fragility fractures (P for overall < 0.0001). RSC analyses revealed that as the SII increased, the risk of fragility fractures gradually increased, and vice versa, which indicated that the SII plays a crucial role in predicting the risk of fragility fractures in elderly postmenopausal females with T2DM.

Cox proportional hazard models for risk factors for endpoint events

The assessment of the SII related to a fragile fracture endpoint event is depicted in Table 3. Univariate Cox

Table 1 Baseline characteristics of the subjects

Characteristics	All Participants (*n* = 423)	Low-level SII (≤ 381.32) (*n* = 141)	Moderate-level SII (381.32–629.46) (n = 141)	High-level SII (≥ 629.46) (*n* = 141)	*P* values
Age, years	69.00 (64.00,75.00)	67.00 (62.00,74.00)	70.00 (64.00,76.00)	72.00 (65.00,76.00)	0.012*
Osteoporosis, n (%)					0.740
No	129 (30.5)	46 (32.6)	43 (30.5)	40 (28.4)	
Yes	294 (69.5)	95 (67.4)	98 (69.5)	101 (71.6)	
Hypertension, n (%)					< 0.001*
No	146 (34.5)	68 (48.2)	45 (31.9)	33 (23.4)	
Yes	277 (65.5)	73 (51.8)	96 (68.1)	108 (76.6)	
DPN, n (%)					0.777
No	158 (37.4)	56 (39.7)	51 (36.2)	51 (36.2)	
Yes	265 (62.6)	85 (60.3)	90 (63.8)	90 (63.8)	
PVD, n (%)					0.973
No	41 (9.7)	13 (9.2)	14 (9.9)	14 (9.9)	
Yes	382 (90.3)	128 (90.8)	127 (90.1)	127 (90.1)	
Fracture history, n (%)					0.965
No	503 (77.9)	104 (73.8)	10 2(72.3)	103 (73.0)	
Yes	143 (22.1)	37 (26.2)	39 (27.7)	38 (27.0)	
Duration of diabetes, years	10.00 (3.00,16.00)	8.00 (2.00,16.00)	10.00 (3.00,16.50)	9.00 (3.00,15.00)	0.284
BMI, kg/m^2	24.24 (22.07,26.78)	24.22 (22.35,26.91)	24.61 (22.50,26.81)	23.83 (21.48,26.51)	0.252
FBG, mmol/L	7.27 (5.64,9.62)	6.80 (5.44,9.19)	7.59 (5.76,9.73)	7.28 (5.66,10.38)	0.315
HbA1c, %	8.20 (6.90,10.40)	8.00 (6.60,10.60)	8.40 (7.05,10.50)	8.50 (6.80,10.25)	0.541
Hb, g/L	125.00 (115.00,134.00)	126.00 (117.00,134.00)	126.00 (118.50,135.00)	122.00 (105.50,133.00)	< 0.001*
TSH, μIU/mL	1.68 (1.08,2.61)	1.72 (1.14,2.60)	1.68 (1.16,2.61)	1.62 (1.03,2.68)	0.902
FT3, pmol/L	4.50 (4.09,4.92)	4.52 (4.12,4.95)	4.56 (4.10,5.01)	4.37 (4.04,4.77)	0.066
FT4, pmol/L	11.25 (9.83,13.20)	10.88 (9.98,12.70)	11.26 (9.70,13.07)	11.69 (9.65,13.83)	0.293
TC, mmol/L	4.89 (4.00,5.75)	4.90 (4.04,5.77)	4.84 (4.00,5.70)	4.90 (3.89,5.78)	0.973
TG, mmol/L	1.42 (1.04,2.05)	1.42 (1.06,1.99)	1.46 (1.07,2.09)	1.38 (0.98,2.10)	0.814
HDL-C, mmol/L	1.17 (1.01,1.38)	1.16 (0.99,1.35)	1.21 (1.03,1.42)	1.14 (0.99,1.36)	0.191
LDL-C, mmol/L	2.92 (2.27,3.61)	2.94 (2.30,3.62)	2.92 (2.27,3.59)	2.88 (2.28,3.58)	0.982
Cr, μmol/L	65.00 (55.00,80.00)	63.00 (53.50,72.50)	64.00 (55.00,78.50)	68.00 (54.50,94.50)	0.034*
UA, μmol/L	317.00 (267.00,390.00)	316.00 (266.50,394.50)	321.00 (263.00,376.00)	317.00 (272.00,392.00)	0.976
Ca, mmol/L	2.27 (2.20,2.36)	2.28 (2.20,2.36)	2.29 (2.23,2.37)	2.26 (2.17,2.35)	0.034*
25(OH) D, nmol/L	54.42 ± 22.54	58.75 ± 22.97	55.44 ± 23.16	49.06 ± 20.46	0.001*
ALB, g/L	38.40 (35.30,41.00)	38.90 (36.70,41.55)	39.00 (36.15,41.00)	36.40 (32.40,40.00)	< 0.001*
SII	481.72 (337.92–721.26)	274.29 (226.13–337.90)	481.72 (424.43–526.97)	904.25 (722.28–1294.11)	< 0.001*
LS BMD, g/cm^2	0.744 (0.657,0.841)	0.733 (0.655,0.832)	0.770 (0.674,0.859)	0.732 (0.649,0.824)	0.138
FN BMD, g/cm^2	0.556 (0.494,0.631)	0.586 (0.510,0.655)	0.555 (0.504,0.625)	0.539 (0.458,0.613)	0.011*
TH BMD, g/cm^2	0.704 ± 0.130	0.722 ± 0.127	0.711 ± 0.129	0.679 ± 0.132	0.016*
FRAX MOF, %	6.10 (4.10,9.60)	5.60 (3.65,8.55)	6.20 (4.40,9.45)	7.20 (4.20,12.00)	0.025*
FRAX HF, %	2.30 (1.10,4.40)	1.90 (0.80,3.65)	2.40 (1.30,4.10)	2.80 (1.20,6.10)	0.009*

Mean ± standard deviation (SD) and median (interquartile range, IQR) for continuous variables. Percentages (%) for categorical variables

Abbreviations: *DPN* diabetic peripheral neuropathy, *PVD* peripheral vascular disease, *BMI* body mass index, *FBG* fasting blood glucose, *HbA1c* glycated hemoglobin, *Hb* hemoglobin, *TSH* thyroid stimulating hormone, *FT3* free triiodothyronine, *FT4* free thyroxine, *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *Cr* creatinine, *UA* uric acid, *Ca* calcium, *25(OH) D* 25-hydroxy vitamin D, *ALB* serum albumin, *BMD* bone mineral density, *SII* systemic immune-inflammatory index, *LS* lumbar spine, *FN* femoral neck, *TH* total hip, *FRAX* fracture risk assessment tool, *MOF* major fracture, *HF* hip fracture

* $P < 0.05$

Table 2 Pearson and partial correlation analyses for the relationship between the SII and BMD and the next 10-year probability of MOF and HF calculated by the FRAX in postmenopausal women with T2DM

	LS BMD		FN BMD		TH BMD		MOF		HF	
	r	p	r	p	r	p	r	p	r	p
Model I	−0.037	0.454	−0.133	0.006*	−0.136	0.005*	0.128	0.008*	0.144	0.003*
Model II	−0.066	0.175	−0.101	0.039*	−0.127	0.009*	0.093	0.056	0.100	0.041*
Model III	−0.027	0.577	−0.037	0.451	−0.052	0.283	0.036	0.462	0.041	0.404

Model I: adjusted for none. Model II: adjusted for age and hypertension. Model III: adjusted for age, hypertension, FT4, 25(OH) D, Hb, ALB, and Cr

Abbreviations: *SII* systemic immune-inflammatory index, *BMD* bone mineral density, *MOF* major osteoporotic fracture, *HF* hip fracture, *FRAX* fracture risk assessment tool, *T2DM* type 2 diabetes mellitus, *LS* lumbar spine, *FN* femoral neck, *TH* total hip, *FT4* free thyroxine, *25-(OH) D* 25-hydroxy vitamin D, *Hb* hemoglobin, *ALB* serum albumin, *Cr* creatinine

* $P < 0.05$

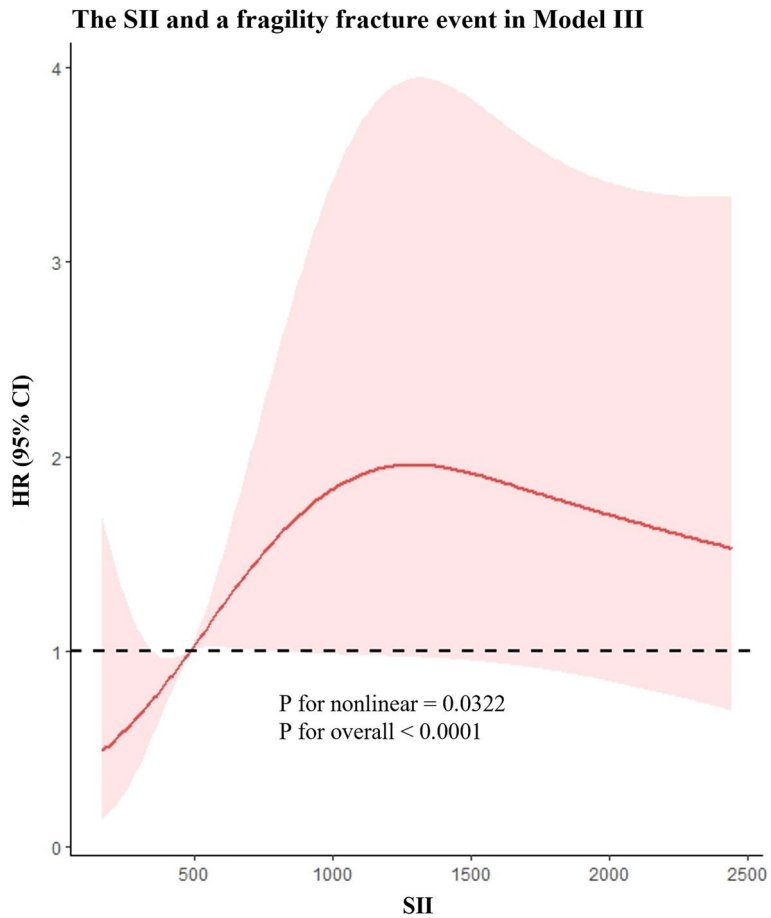

Fig. 2 The RCS model for the dose–response relationship between the SII and a real-world fragile fracture endpoint event in elderly postmenopausal women with T2DM. The adjustment factors included age, hypertension, FT4, 25(OH) D, Hb, ALB, and Cr. After adjusting for confounding factors, a linear regression model was used to fit the data at 4 points in the 5th, 35th, 65th, and 95th percentiles of the SII (the reference value is the 5th percentile). RCS analysis revealed an inverted J-shaped dose-dependent correlation between the SII and a real-world fragile fracture event (*P* for overall < 0.0001)

regression analysis was used to determine the risk factors for fragility fracture endpoints. Variables with a *P* value < 0.1 in the univariate Cox regression analysis were included in the multivariate Cox regression analysis. Compared with the low-level SII, the moderate-level SII in Model I (HR = 1.967, 95% CI = 1.022–3.785,

Table 3 Univariate and multivariate Cox regression analyses for evaluating the association between the SII and fragility fractures

SII	HR (95% CI)					
	Model I	*P*—values	Model II	*P*—values	Model III	*P*—values
All participants						
Low-level SII (≤ 381.32)	Ref		Ref		Ref	
Moderate-level SII (381.32–629.46)	1.967 (1.022–3.785)	0.043*	1.807 (0.938–3.483)	0.077	1.828 (0.942–3.546)	0.074
High-level SII (≥ 629.46)	3.016 (1.626–5.594)	< 0.001*	2.625 (1.402–4.917)	0.003*	2.397 (1.222–4.700)	0.011*
P for trend		< 0.001*		0.002*		0.009*

Model I: adjusted for none. Model II: adjusted for age and duration of diabetes; Model III: adjusted for age and duration of diabetes, hypertension, Hb, FT4, HDL-C, Cr, 25(OH) D, ALB, and fracture history. *P*-values indicate statistical differences between the Moderate- or High- and Low-level groups, respectively. P for trend indicates statistical differences between fracture endpoint events and gradient SII levels

Abbreviations: *SII* systemic immune-inflammatory index, *HR* hazard ratio, *CI* confidence interval, *Hb* hemoglobin, *FT4* free thyroxine, *HDL-C* high-density lipoprotein cholesterol, *Cr* creatinine, *25(OH) D* 25-hydroxyvitamin D, *ALB* albumin

* $P < 0.05$

$P = 0.043$), the high-level SII in Model II (HR = 2.625, 95% CI = 1.402–4.917, $P = 0.003$) and Model III (HR = 2.397, 95% CI = 1.222–4.700, $P = 0.011$) were positively correlated with the fragility fracture endpoint event (all P values for trend < 0.01), which indicated that the SII is a valuable predictor for a real-world fragility fracture endpoint event.

The forest plots for the subgroup stratified analysis

The influence of stratification factors on the SII in predicting fragility fractures in the whole study population is shown in the forest plots (Fig. 3). The stratified factors included BMI, hypertension, anemia, and DPN. The stratified subgroup analyses revealed that when HR = 1 in the low-level SII subgroup, the risk of fragility fractures increased significantly, with an increase of 2.708 times in the subgroup with a BMI < 24 (HR = 3.708, 95% CI = 1.210–11.359, $P = 0.022$, P for trend = 0.021), 1.439 times in the subgroup with hypertension (HR = 2.439, 95% CI = 1.171–5.079, P = 0.017, P for trend = 0.016), 4.15 times in the subgroup with anemia (HR = 5.150, 95% CI = 1.490–17.798, $P = 0.01$, P for trend = 0.008), and 2.439 times in the subgroup with DPN (HR = 3.439, 95% CI = 1.481–7.983, $P = 0.004$, P for trend = 0.004), respectively. The stratified factors were not confounding factors (all P values for interactions > 0.05), suggesting that

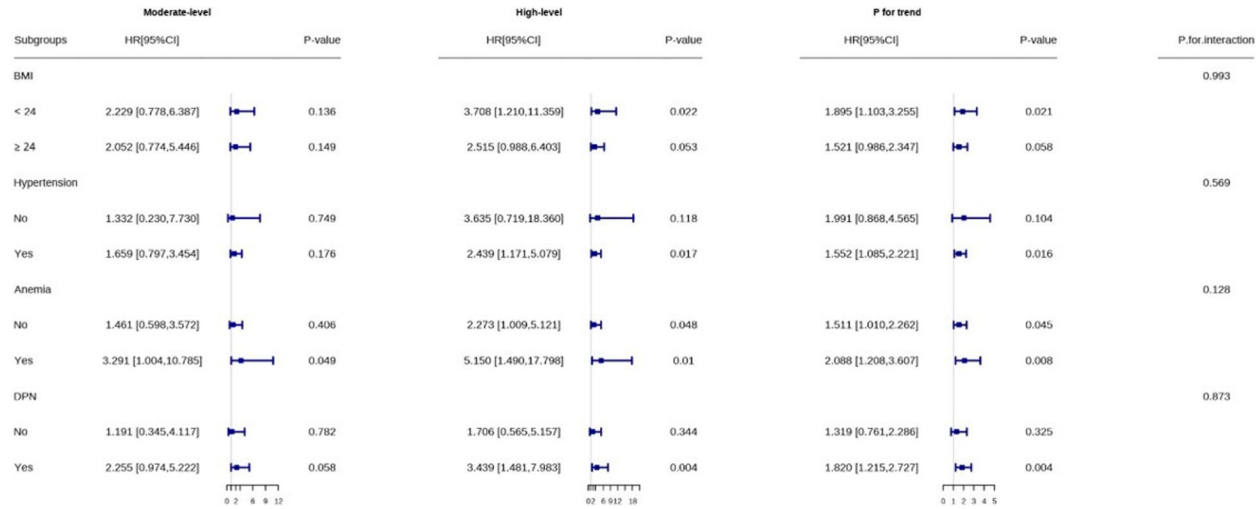

Fig. 3 Forest plots for the stratified analysis of the subgroups. A stratified analysis of the subgroups revealed that when HR = 1 in the low-level SII subgroup, the risk of fragility fractures increased significantly, with increases of 2.708 times in the BMI < 24 subgroup ($P = 0.022$, P for trend = 0.021), 1.439 times in the hypertension subgroup ($P = 0.017$, P for trend = 0.016), 4.15 times in the anemia subgroup ($P = 0.01$, P for trend = 0.008), and 2.439 times in the DPN subgroup ($P = 0.004$, P for trend = 0.004), which indicated that the SII was positively correlated with the risk of fragility fractures. Additionally, stratification by subgroup did not affect the ability of the SII to predict the risk of fragility fractures in the whole study population (all P values for interactions > 0.05), demonstrating that these stratification factors were not confounding factors

stratification factors did not affect the predictive value of the SII for the whole research population. In brief, the subgroup stratified analysis revealed a more significant positive association between the SII and fragility fracture events in postmenopausal females with T2DM, which was particularly evident in individuals with anemia.

Kaplan–Meier survival analysis for cumulative fracture incidence according to the SII

The incidence of fragility fracture endpoint events among all three groups is depicted in Fig. 4. Among the 423 patients, 75 experienced real-world fragile fracture endpoint events (17.73%), with low-level SII ($n=14$, 9.930%), moderate-level SII ($n=25$, 17.73%), and high-level SII ($n=36$, 25.53%), respectively. Survival curve analysis revealed a significant positive association between the SII and the cumulative incidence of fragility fractures (log-rank, all $P=0.0012$) (Fig. 5). Kaplan–Meier analysis verified again that fragility fracture endpoint events were more likely to occur in individuals with a higher SII.

ROC analysis for evaluating the diagnostic efficacy of the SII for fragility fractures

Although this study adopted a more accurate statistical tertile grouping of the SII, we still aimed to determine an ideal diagnostic cutoff value for the SII through the ROC curve to guide routine clinical practice. ROC curve analysis was conducted to assess the predictive value of the SII for fragility fracture risk in elderly postmenopausal females with T2DM (Fig. 6). The ROC curve revealed an ideal SII cutoff value of 537.34, with an AUC of 0.646, a sensitivity of 60%, and a specificity of 64.1% ($P<0.001$); the SII may serve as a potentially valuable predictor for real-world fragility fracture events in elderly postmenopausal females with T2DM.

Discussion

The present study revealed that the SII was negatively correlated with the BMD of the femoral neck and total hip and was positively correlated with fragility fracture events in an inverted J-shaped dose-dependent pattern (P for overall < 0.0001) and with the future 10-year probability of HF and MOF, as estimated by the FRAX. When the SII is converted from a continuous variable to a classified variable, the BMD of the femoral neck and total hip is the lowest, and the fracture probability increases. In addition, an increase in the SII is associated with an increased fracture risk. Finally, the subgroup analysis revealed that the associations between the SII and fragility fractures were more significant in the subgroups with anemia.

The SII is a promising inflammatory index that can comprehensively reflect immune and inflammatory states [29]. An elevated SII indicates an activated inflammatory response and a weak immune response [30]. Previous studies on the relationship between the SII and BMD or osteoporosis found a negative correlation between femoral neck bone mineral density and the SII in 413 postmenopausal women in China [31]. The SII is negatively correlated with the bone mineral density of postmenopausal women but not premenopausal women [23]. An increase in the SII may be a potential risk factor for osteoporosis in postmenopausal women [31]. Although a small-scale prospective cohort study of 238 patients revealed that the SII is a reliable predictor of postmenopausal osteoporosis diagnosis and fracture risk, these results call for further

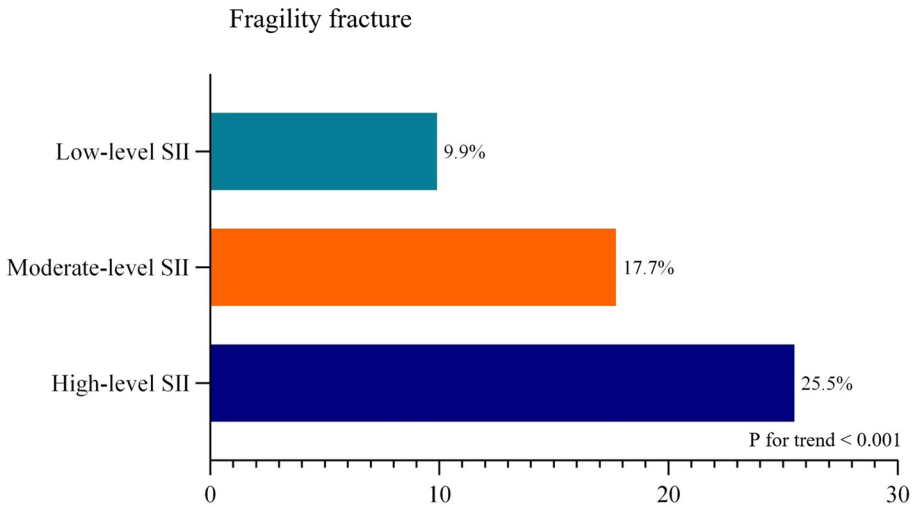

Fig. 4 The SII was used to determine the incidence of fragility fractures among the three groups. The incidences of fragile fractures were 9.9%, 17.7%, and 25.5% for low-level, moderate-level, and high-level SII, respectively, showing a positive dose–response relationship (P for trend < 0.001)

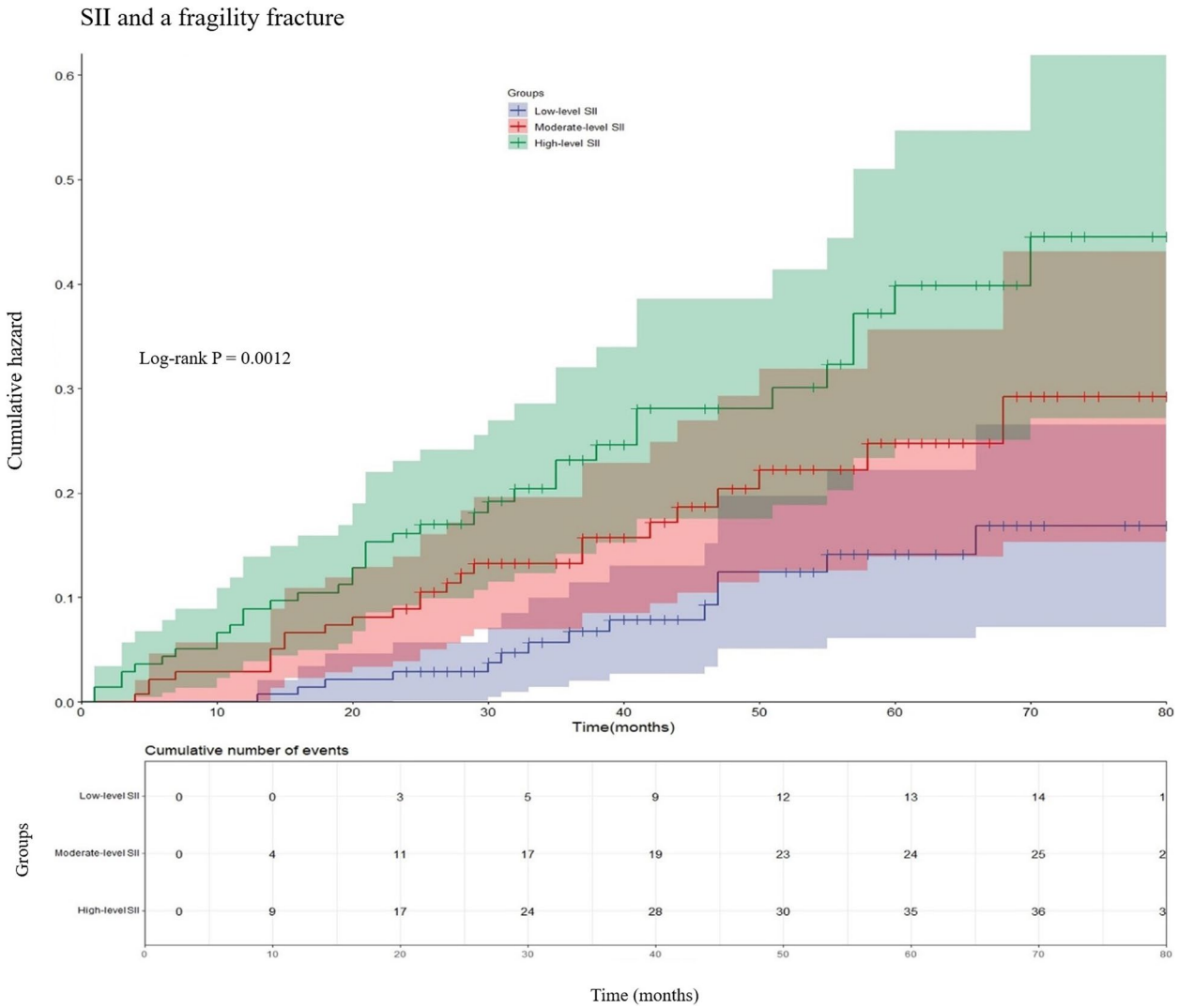

Fig. 5 Survival analysis for the cumulative incidence of fragility fractures stratified by the SII levels. The Kaplan–Meier survival analysis revealed a significant positive association between the SII and the cumulative incidence of fragility fractures (log-rank, $P = 0.0012$)

investigation and evaluation [25]. Compared with previous studies, this study has several advantages. To evaluate the relationship between the SII and bone metabolism more comprehensively, we first assessed the relationships between the SII and lumbar spine, femoral neck, and total hip BMD; analyzed the association between the SII and future 10-year individualized fracture probability estimated through the FRAX; and finally conducted survival analysis through follow-up to verify the role of the SII in bone metabolism in many ways, which is different from the findings of other previous studies. In addition, the present study conducted a subgroup analysis to evaluate the relationship between the SII and fracture risk in participants with distinct characteristics.

The main findings observed in the present study are that an increase in the SII is related to low bone mass and increased fragility fracture risk. On the one hand, an increase in the SII may indicate an increase in the inflammatory response or a weak immune status, leading to a decrease in bone mass. Moreover, other factors, such as decreased endogenous estrogen production after menopause, may lead to a decrease in bone mass, a mediated inflammatory state, and a disrupted immune balance. Bone health depends on the steady process between bone formation and absorption [32]. After women enter menopause, complex biological changes occur, including the activation of the inflammatory microenvironment and a decrease in immune system function [33]. The activation of the inflammatory microenvironment

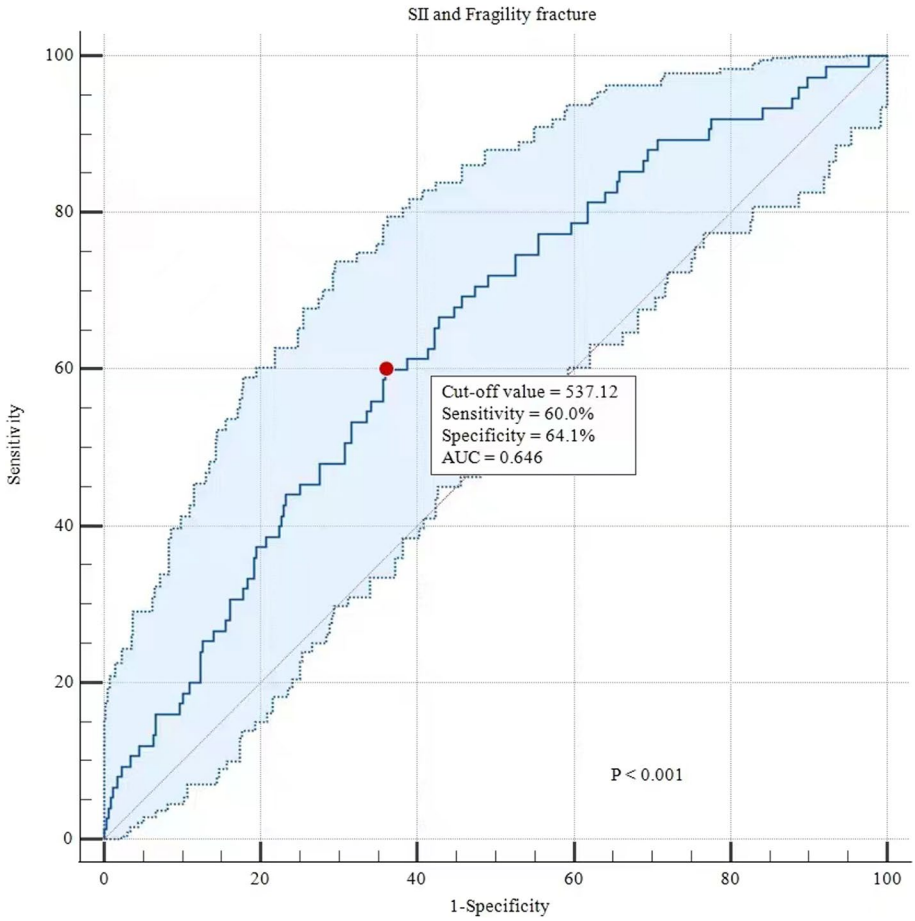

Fig. 6 ROC analysis of the optimal cutoff value for the SII. The SII had a predictive value for fragility fracture events, with an optimal cutoff value of 537.34, an area under the curve of 0.646, a sensitivity of 60.0%, and a specificity of 64.1% ($P < 0.001$)

and damage to the immune system significantly affect the microstructure of bone [34]. Moreover, there are many inflammatory cells in the bone marrow cavity. For example, dysfunctional lymphocytes can initiate a cascade of inflammatory cytokines and chemokines, leading to the aggregation of neutrophils and macrophages and destroying the dynamic balance of bone, thus inhibiting bone formation and inducing bone resorption [35]. Therefore, an imbalance in immune-related inflammation may lead to osteopenia, decreased BMD and bone strength, osteoporosis, and even fragility fractures.

The results of the subgroup analysis showed that the associations between the SII and low BMD and the risk of fragility fractures mainly occurred in the subgroups with anemia, a BMI < 24, DPN, and hypertension. Consistent with the findings of a previous study, the associations between the SII and the risk of low BMD and osteoporosis mainly occurred in postmenopausal women with a normal BMI. A meta-analysis showed that an elevated BMI is still a protective factor for most fragility fracture sites at the population level [36]. With aging, they become more susceptible to malnutrition due to deficiencies in micronutrients like vitamin D, vitamin K, and protein, which can lead to anemia and weight loss, which increase the risk of hip fractures caused by falls [37]. Skeletal homeostasis can be altered by a variety of pathological anemic situations. Osteoporotic fractures have been observed in thalassemia patients, and in murine thalassemia models, there is a net loss of bone [38, 39]. Given the increased fragility fracture rates in these patients, the pathological erythrocyte expansion that takes place within the bone marrow cavity may be primarily caused by the anemia. As was already mentioned, the body's normal response to anemia is an increase in erythropoietin. Thalassemia is an extreme example of chronic anemia caused by changes in the microenvironment of the bone marrow. various illness states, such as renal failure and refractory anemia of myelodysplastic syndrome (MDS), are described by anemic states deriving from various etiologies [40]. Additionally, a population study in China including 6003

patients showed that the SII is an independent risk factor for hypertension, and it can be used as an effective inflammatory cell index to predict the risk of hypertension [41]. A cross-sectional study of the Chinese population showed that a higher SII is independently related to an increased risk of DPN, and the SII may be a novel risk biomarker for DPN in the Chinese population [42], which can explain the difference between an increased SII and an increased risk of fragility fractures among different subgroups. However, due to the small sample size of this study, the findings need to be further verified in other studies with large sample sizes.

Notably, the high SII group in this study had lower 25(OH) vitamin D levels. Vitamin D plays a critical role in modulating immune function. Low vitamin D is significantly associated with the severity of inflammation [43]. However, the SII can comprehensively reflect the body's inflammation and immune status, which may explain the lower levels of 25(OH) vitamin D in the high SII group in this study. The control of the orderly retraction and shutdown of CD4+type 1 helper T (TH1) cell responses is one of the molecular mechanisms by which vitamin D modulates immunological inflammation and maintains the homeostasis of immune inflammation. Vitamin D-activating enzyme 25-hydroxyvitamin D3-1 alpha-hydroxylase (CYP27B1) and the vitamin D receptor are both intrinsically expressed by complement, which causes the TH1 responses to constrict. This allows T cells to respond to and activate in response to vitamin D. Next, pro-inflammatory interferon-γ+TH1 cells were switched to suppressive interleukin-10+cells by vitamin D. The transcriptional response to vitamin D is influenced by a combination of proteins, including c-JUN, signal transducer and activator of transcription 3 (STAT3), and the BTB and CNC homology 1 basic leucine zipper transcription factor 2 (BACH2), which are recruited by CD4+T cells and produce super-enhancers. The process was initiated by these alterations in the epigenetic landscape of CD4+T cells [44].

Limitations

There are still several limitations to this study. First, antidiabetic regimens and blood glucose control levels have not been fully investigated, but different glucose-lowering medicines and blood glucose levels may be associated with fragility fractures. Second, the correlation between chronic complications of diabetes and falls has not been attentively evaluated, but an increased risk of falls may be associated with fragility fractures. Third, the absence of information on bone turnover markers, daily recipes, outdoor activities, and quantitative assessments of nutritional status may have affected the conclusions. Fourth, the present data are limited by the small-scale retrospective nature of the study. Future well-designed, large-scale, multicenter, randomized double-blind, and healthy subjects control prospective longitudinal cohort studies are necessary to validate the current findings.

Conclusions

In conclusion, the SII revealed a significant positive association with a real-world fragility fracture event and a future 10-year fragility fracture probability in postmenopausal females with T2DM, particularly evident in individuals with anemia. Therefore, monitoring the SII and hemoglobin in postmenopausal older women with T2DM is helpful in routine clinical practice to identify individuals at high risk for fragility fractures and to promptly execute appropriate fracture intervention procedures.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01792-1.

Supplementary Material 1. S1.The relationship between SII and FN BMD in Model I.

Supplementary Material 2. S2.The relationship between SII and FN BMD in Model II.

Supplementary Material 3. S3. The relationship between SII and TH BMD in Model I.

Supplementary Material 4. S4. The relationship between SII and TH BMD in Model II.

Supplementary Material 5. S5. The relationship between SII and MOF in Model I.

Supplementary Material 6. S6. The relationship between SII and HF in Model I.

Supplementary Material 7. S7. The relationship between SII and HF in Model II.

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Authors' contributions

W.S.L. designed this study and drafted the English version of this paper. D.G.H., Q.H., and J.M.P. completed the data collection and drafted the Chinese version of the report. Z.W.Z. performed all the statistical analyses and drew the related graphs through the R language software package. J.X.S., Q.W., W.X.C., J.H.H., and J.M.Y. participated in the follow-up visits. X.Q.Q. completed the supervision and management of part of the study. W.S.L. is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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Data availability
All initial data from this study are available by e-mail to the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
All patients agreed to participate in this study and provided written informed consent. The principles of the Declaration of Helsinki were followed. The Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region approved the trial (approval number: Ethics-KY-IIT-2023–60). Clinical trial number: not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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