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Systemic immune-inflammation index to albumin (SII/ALB) ratio as a novel dual-dimensional powerful predictor for hip fractures in elderly females with diabetes: a postmenopausal longitudinal cohort study

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Abstract

Purpose Hip fracture is the most dangerous and potentially lethal fracture, described as "the last fracture of life" in older adults. Previous studies have shown that excessive immunoinflammatory response and nutrient deficiency may be involved. Nevertheless, a predictor for hip fracture risk that combines a thorough evaluation of immunoinflammatory with malnutritional conditions in postmenopausal women with type 2 diabetes mellitus (T2DM) remains scarce. This study explored the relationship between the SII/ALB ratio (SAR) and fragility fracture risk in postmenopausal older adults with T2DM.

Methods Between January 2014 and January 2021, a total of 509 postmenopausal female participants with T2DM were recruited from the Medical Record Database of the People's Hospital of Guangxi Zhuang Autonomous Region. Finally, 363 participants with an age median of 69.00 (64.00–75.00), were eligible for inclusion in this analysis. According to the statistical tertiles of the SAR, all participants were split into three groups: low-level (≤ 98.24, $n = 121$), moderate-level (98.24–157.25, $n = 121$), and high-level (≥ 157.25, $n = 121$). The participants were followed up for seven years, with a median follow-up time of 45.9 months (1389 person-years). The relationships between the SAR and a real-world fragility fracture event and an individualized future 10-year probability of major osteoporotic fracture (MOF) and hip fracture (HF) calculated by the fracture risk assessment tool (FRAX) were evaluated through Spearman's partial correlation analysis, restricted cubic spline (RCS) model, Cox proportional hazards regression model, and Kaplan-Meier survival analysis. Furthermore, some indicators such as geriatric nutritional risk index (GNRI), prognostic nutritional

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index (PNI), and SII were also calculated and compared to their diagnostic efficacy and the clinical application value through the receiver operating characteristic (ROC) curve analysis and the decision curve analysis (DCA), respectively.

Results Of the 363 participants, 69 suffered a real-world fragility fracture event (19%). Spearman's partial correlation analysis indicated that SAR was negatively related to femoral neck (FN) bone mineral density (BMD) (r = -0.108, P = 0.041) and total hip (TH) BMD (r = -0.118, P = 0.025), but not lumbar spine (LS) BMD (all Models P > 0.05); positively correlated with an individualized future 10-year probability of MOF (r = 0.136, P = 0.010) and HF (r = 0.139, P = 0.008) calculated by FRAX, especially in hip fracture risk. The RCS model demonstrated the relationship between the SAR and a fragility fracture endpoint event in a J-shaped dose-dependent manner (P for overall < 0.001, P for nonlinear = 0.866). Multivariate Cox regression analysis indicated that the SAR was positively associated with fragility fracture risk (P < 0.001). Kaplan-Meier survival analysis showed that patients with higher levels of SAR had a greater probability of fragility fracture risk (log-rank, P < 0.0001). The ROC curve demonstrated an optimal SAR cut-off value of 146.209 with an area under the curve (AUC) of 0.740, a sensitivity of 0.681, and a specificity of 0.701 (P < 0.001). According to the AUC values, the ROC curve analysis combined with the DCA illustrated that the diagnostic efficacy and the clinical application benefit ranked as follows: SAR > SII > PNI > GNRI, respectively.

Conclusion Our findings show the SAR is a novel dual-dimensional powerful predictor for fragility fracture risk, especially hip fracture, and as an effective tool for developing fragility fracture prevention strategies in postmenopausal females with T2DM. Consequently, monitoring SAR levels in usual clinical practice to focus on immunoinflammatory and nutritional status to identify individuals at high risk of hip fracture and implement timely fracture interventions is particularly essential.

Clinical trial number Not applicable.

Keywords Type 2 diabetes mellitus, Postmenopausal older women, Hip fracture, Systemic immune-inflammatory index to albumin ratio

Introduction

Aging drives the global prevalence of osteoporosis (OP) [1] and type 2 diabetes mellitus (T2DM) [2]. Osteoporosis affects 18.3% of adults (23.1% women, 11.7% men) worldwide [3], while China reports 19.2% prevalence in individuals aged ≥ 50, rising to 32% in those ≥ 65 (51.6% postmenopausal women, 10.7% men) [4]. Concurrently, global diabetes prevalence among adults aged 20–79 is projected to increase from 10.5% (2021) to 12.2% by 2045 [5], with one-third of Chinese elderly ≥ 60 affected by T2DM [6]. Fragility fractures, particularly in postmenopausal T2DM patients, are exacerbated by diabetes-related microvascular complications such as peripheral neuropathy that impair muscle strength and balance, elevating fall risk [7–9]. Addressing fracture prevention in this high-risk population is clinically imperative.

T2DM accelerates bone quality loss through glucolipotoxicity-induced inflammation, immune dysregulation, and malnutrition [10, 11]. Advanced glycosylation end products (AGEs) weaken collagen-mineral interactions, directly increasing fracture risk, while disrupting gut microbiota, epithelial integrity, and inflammatory pathways [12–16]. Age-related "inflammaging" amplifies proinflammatory cytokines IL-6, TNF-α, IL-1β, and coagulation markers D-dimer, further destabilizing bone homeostasis [17–26]. Hypoalbuminemia (serum albumin ≤ 35 g/L) independently predicts hip fractures [27, 28], underscoring the interplay between immunoinflammatory and nutritional deficits in fracture pathogenesis.

Existing immunoinflammatory/nutritional indices such as systemic immune-inflammation index (SII, platelet × neutrophil/lymphocyte counts) [29–32], prognostic nutritional index (PNI, serum albumin level + total lymphocyte count) [33–35], and geriatric nutritional risk index (GNRI, albumin + weight/ideal weight) [36–40] partially predict fracture risk in T2DM [36–40]. While SII reflects inflammatory severity [30, 31] and GNRI correlates inversely with fracture risk in dose-dependent patterns [40], these metrics lack integration of both immune and nutritional dimensions. PNI, though prognostic for hip fracture mortality [34], fails to independently predict fractures in comorbid conditions [35], highlighting the unmet need for a composite biomarker.

Hip fractures, termed "the last fracture of life in the elderly," demand predictors that synergistically evaluate immunoinflammatory and nutritional states in T2DM. This study introduces the systemic immune-inflammation index to albumin ratio (SAR: SII/ALB), a novel composite indicator dynamically linking inflammatory burden (SII) to nutritional reserve (albumin). SAR's diagnostic efficacy and clinical utility were compared with GNRI, PNI, and SII via ROC and decision curve analyses (DCA). As the first to integrate immune-nutritional crosstalk, SAR bridges a critical gap in fracture risk assessment, offering a cost-effective tool adaptable to primary healthcare settings for optimizing T2DM management in postmenopausal women.

Materials and methods

Study design and subjects

This current analysis was a retrospective longitudinal cohort study. The flowchart for the participant selection strategy is illustrated in Fig. 1. From January 2014 to January 2021, 509 postmenopausal female participants with T2DM were recruited from the Medical Record Database of the People's Hospital of Guangxi Zhuang Autonomous Region. All information regarding participants remained confidential during the survey and the analysis. The study complied with the Declaration of Helsinki guidelines and obtained approval from the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region (approval number: Ethics-KY-IIT-2023-60).

The inclusion criteria were defined as follows: (1) diagnosed T2DM per the diagnostic criteria of World Health Organization (WHO) in the 1999 edition [41]; (2) all subjects had comprehensive bone mineral density (BMD) data measured in the lumbar spine (L1 to L4), femoral neck, and total hip using dual-energy X-ray absorptiometry (DXA) (Hologic Inc, USA) and detailed lumbar and pelvic imaging data collected via digital radiography (DR). The criteria for exclusion included: (1) malignant tumors; (2) severe liver, kidney, cardiovascular dysfunction, acute infections statuses such as respiratory tract infections, urinary tract infections, and skin infections; (3) thyroid and parathyroid diseases; (4) hypophosphatemic rickets/osteomalacia; (5) anti-diabetic agents affecting bone turnover (e.g., increase bone turnover thiazolidinediones and sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors, and inhibit bone turnover glucagon-like peptide-1 receptor agonists (GLP-1RAs)), anti-osteoporosis therapies affecting bone turnover (e.g., inhibit bone resorption bisphosphonates and denosumab, increase bone formation teriparatide), and immunosuppressive regiments were excluded if used for > 3 months; (6) long-term bedridden status; and (7) incomplete data, lost to follow-up or a follow-up period of less than a year.

Finally, a total of 363 participants, with an age median of 69.00 (64.00–75.00), were eligible for inclusion in this analysis. According to the tertiles of the SAR, we divided subjects into three groups: low-level (≤ 98.24, $n = 121$), moderate-level (98.24–157.25, $n = 121$), and high-level (≥ 157.25, $n = 121$). All participants were followed up for seven years, with a median follow-up time of 45.9 months (1389 person-years). The relationships between the SAR and a real-world fragility fracture event and an individualized future 10-year probability of major osteoporotic fracture (MOF) and hip fracture (HF) calculated by the fracture risk assessment tool (FRAX) were evaluated.

Data collection

Basic demographic information, detailed physical examination anthropometric data, and essential serum biochemical parameters of all participants were gathered from the Medical Record System of People's Hospital of Guangxi Zhuang Autonomous Region. Complete blood cell (CBC) counts and blood biochemical indicator tests were conducted by the whole blood cell analyzer (Pentra120R, Horiba ABX, France) and the biochemical automated analyzer (P800, Roche, Germany), respectively. The lab instructions provided by the manufacturer were followed in accordance with the specific operating procedures (SOP). All participants were systematically followed up for seven years, with a median follow-up time of 45.9 months (1389 person-years) through medical record reviews, outpatient services, and telephone interviews by professionally trained interviewers to ensure a comprehensive assessment of fragility fracture endpoint events.

Definitions

The following related definitions were adopted in this analysis: (**1**) Fragility fracture (e.g., hip fracture, vertebral fracture, and other osteoporosis fracture) was defined as the endpoint event. (**2**) The individualized future 10-year probabilities of MOF and HF were estimated by the FRAX (https://frax.shef.ac.uk/FRAX/tool.aspx?lang=chs). Age, sex, weight (kg), height (cm), prior fracture, parent broken hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol use of three or more units per day, and FN BMD (g/cm^2) are among the twelve items that make up the FRAX questionnaire. FRAX is suitable for the population aged 40–90. Individuals aged < 40 are calculated as 40; however, those aged > 90 are considered as 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%. (**3**) SII = platelet × neutrophil/lymphocyte counts (10^9/l) [29]. (**4**) SAR = SII/ALB (g/l); in this current analysis, to stabilize the variance and make the raw ALB data more linear and closer to a normal distribution, the natural logarithm was applied, which made it simpler to evaluate the correlations. (**5**) PNI = 10×serum albumin level (g/dl) + 0.005×total lymphocyte count (per mm^3) [33]. (**6**) GNRI = [1.489 × ALB (g/l)] + 41.7 × [body weight (kg) / ideal body weight (kg)]; ideal body weight (men) = height (cm) – 100 - [height (cm) – 150] / 4; ideal body weight (women) = height (cm) – 100 - [height (cm) – 150] / 2.5.

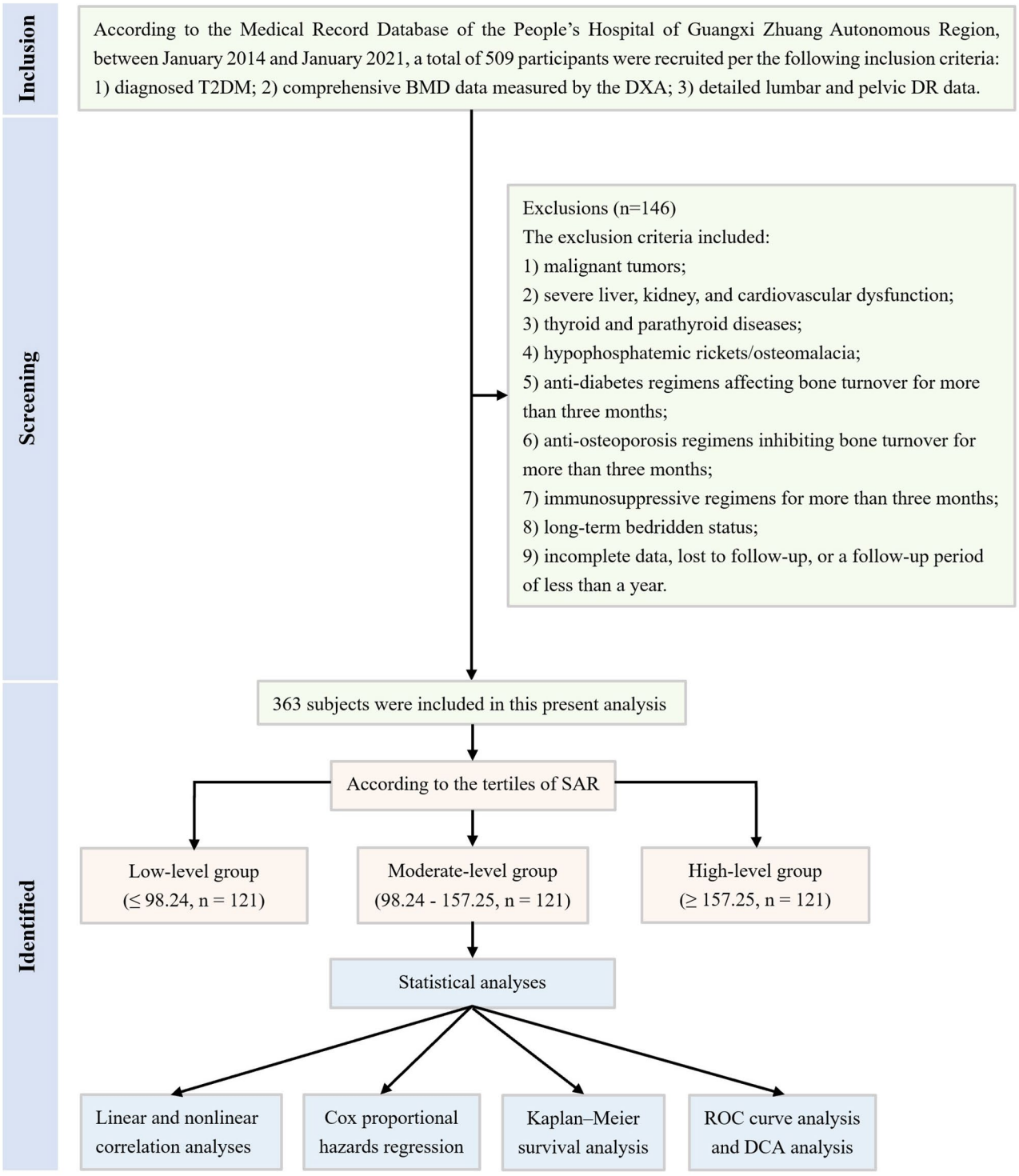

Fig. 1 The flowchart for the participant selection strategy. From January 2014 to January 2021, the data were sourced from the Medical Record Database of the People's Hospital of Guangxi Zhuang Autonomous Region. Finally, 363 postmenopausal females with T2DM were recruited in this present analysis. According to the SAR, all participants were split into three groups: low-level (≤ 98.24, $n = 121$), moderate-level (98.24–157.25, $n = 121$), and high-level (≥ 157.25, $n = 121$). The relationships between the SAR and a real-world fragility fracture event and a future individual 10-year probability of MOF and HF calculated by the FRAX were evaluated through Spearman's partial correlation analysis, RCS model, Cox proportional hazards regression model, and Kaplan-Meier survival analysis. Furthermore, the diagnostic efficacy comparisons of the SAR with the GNRI, PNI, and SII were conducted through the ROC curve analysis and DCA

If the patient's weight exceeded their ideal weight, set the ratio of weight to ideal weight to 1 [36].

Statistical analysis

Statistical analyses were conducted through the SPSS 26.0 software package (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as the means ± SD for normal distribution and medians (interquartile range, IQR) for nonnormal distribution. Classification variables were expressed as frequencies. The Mann−Whitney U and Pearson's chi-squared tests were used to compare groups. Spearman's partial correlation analysis and Restricted cubic spline (RCS) model were performed for the linear and nonlinear correlation analyses, respectively. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. The trend test was conducted using the one-way analysis of variance (ANOVA). The cumulative occurrence and survival rates were calculated through the Kaplan–Meier analysis and the log-rank test assessed the differences between the groups. The diagnostic efficacy and clinical application value assessment were performed through the ROC curve analysis and DCA methods. A post-hoc power analysis was performed using the G*Power 3.1.9.2 version software. All statistical charts were drawn using the R language version 4.2.2 software package (R Foundation for Statistical Computing, Vienna, Austria). A statistically significant difference was considered as P value < 0.05 level.

Results

Baseline characteristics data

The baseline characteristics data of the subjects are shown in Table 1. Among the three groups, age, hypertension, 25-hydroxy vitamin D (25(OH) D), white blood cell count (WBC), neutrophil counts, platelet counts, lymphocyte counts, ALB, fracture, FN-BMD, FRAX MOF, FRAX HF, SII, GNRI, and PNI were significantly different (all $P < 0.05$). However, duration of diabetes, diabetic peripheral neuropathy (DPN), peripheral vascular disease (PVD), BMI, fasting blood glucose (FBG), glycosylated haemoglobin (HbA1c), haemoglobin (Hb), 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), creatinine (Cr), uric acid (UA), serum Ca, osteoporosis, fracture history, LS-BMD, and TH-BMD were not significantly different (all $P > 0.05$). Notably, baseline characteristics data showed that variable indicators, including the CBC- related to inflammatory load, ALB, 25(OH) D, fragility fracture events, and FN-BMD, but not LS-BMD, were significantly different among the three SAR groups, suggesting an association between SAR and hip fractures.

Linear and nonlinear correlation analyses

The linear correlations between SAR with BMDs and the individualized 10-year probability of MOF and HF calculated by FRAX, conducted by Spearman's partial correlation analysis, are displayed in Table 2; Fig. 2. The results of Spearman's partial correlation analysis were exhibited as follows: (**A**) a linear correlation between SAR and LS-BMD in Model I (r = -0.090, $p = 0.088$), Model II (r = -0.068, $p = 0.198$), and Model III (r = -0.013, $p = 0.815$); (**B**) a linear correlation between SAR and FN-BMD in Model I (r = -0.151, $p = 0.004$), Model II (r = -0.108, $p = 0.041$), and Model III ($r = 0.030$, $p = 0.579$); (**C**) a linear correlation between SAR and TH-BMD in Model I (r = -0.163, $p = 0.002$), Model II (r = -0.118, $p = 0.025$), and Model III (r = -0.025, $p = 0.652$); (**D**) a linear correlation between SAR and MOF in Model I ($r = 0.177$, $p < 0.001$), Model II ($r = 0.136$, $p = 0.010$), and Model III ($r = 0.065$, $p = 0.236$); and (**E**) a linear correlation between SAR and HF in Model I ($r = 0.174$, $p < 0.001$), Model II ($r = 0.139$, $p = 0.008$), and Model III ($r = 0.070$, $p = 0.201$). To recap, after adjusting confounding factors for age and duration of diabetes in Model II, Spearman's partial correlation analysis indicated that SAR was negatively related to hip BMD including FN-BMD (r = -0.108, $P = 0.041$) and TH-BMD (r = -0.118, $P = 0.025$); positively correlated with an individualized future 10-year probability of MOF ($r = 0.136$, $P = 0.010$) and HF ($r = 0.139$, $P = 0.008$) calculated by FRAX, respectively. Spearman's partial correlation analysis indicated that a decrease in hip bone mass and an increase in the probability of fragility fracture was linearly associated with an increase in SAR, especially evident in the hip-BMD.

Moreover, the RCS model performed the nonlinear correlation analysis. The result is presented in Fig. 3. After adjusting for confounding factors, the data were fitted by a restricted cubic spline Cox proportional hazards regression model, and the model was constructed with 4 knots at the 5th, 35th, 65th, and 95th percentiles of the SAR (reference was the 5th percentile). The solid lines indicate hazard ratios (HRs), and the shadow shapes indicate 95% confidence intervals (CIs). The RCS model demonstrated a J-shaped dose-dependent association between the SAR and a fragility fracture endpoint event (P for overall < 0.001, P for nonlinear = 0.866). RSC analysis showed that the risk of fragility fractures progressively increased with increased SAR and vice versa.

As mentioned above, both Spearman's partial correlation analysis and the RCS model illustrate that SAR may possess a potential prognostic value for hip fragility fracture risk in postmenopausal elderly individuals with T2DM.

Table 1 Baseline characteristics data

Characteristics	All Participants ($n=363$)	Low-level SAR (≤ 98.24, $n=121$)	Moderate-level SAR (98.24–157.25, $n=121$)	High-level SAR (≥ 157.25, $n=121$)	*P*-values
Age, years	69.00 (64.00,75.00)	67.00 (62.00,74.00)	69.00 (64.00–75.00)	72.00 (66.00–77.00)	0.005*
Duration of diabetes, years	10.00 (3.00–16.00)	8.00 (2.00–15.00)	10.00 (3.00–17.00)	10.00 (4.00–17.00)	0.516
Hypertension, n (%)					0.002*
No	133 (36.64%)	58 (47.93%)	43 (35.54%)	32 (26.45%)	
Yes	230 (63.36%)	63 (52.07%)	78 (64.46%)	89 (73.55%)	
DPN, n (%)					0.781
No	135 (37.19%)	47 (38.84%)	46 (38.02%)	42 (34.71%)	
Yes	228 (62.81%)	74 (61.16%)	75 (61.98%)	79 (65.29%)	
PVD, n (%)					0.878
No	34 (9.37%)	12 (9.92%)	12 (9.92%)	10 (8.26%)	
Yes	329 (90.63%)	109 (90.08%)	109 (90.08%)	111 (91.74%)	
BMI, kg/m^2	24.39 (22.31–26.93)	24.22 (22.37–26.91)	24.61 (22.51–26.63)	24.56 (22.07–27.28)	0.965
FBG, mmol/L	7.28 (5.67–9.55)	6.80 (5.42–9.11)	7.34 (5.83–9.60)	7.48 (5.92–10.21)	0.302
HbA1c, %	8.20 (6.90-10.35)	8.00 (6.60–10.70)	8.20 (7.00-10.30)	8.60 (7.00-10.30)	0.766
Hb, g/L	125.00 (116.00-134.00)	128.00 (118.00-134.00)	125.00 (118.00-134.00)	125.00 (111.00-135.00)	0.185
TSH, μIU/mL	1.69 (1.11–2.61)	1.72 (1.14–2.60)	1.78 (1.18–2.70)	1.61 (1.03–2.34)	0.495
FT3, pmol/L	4.52 (4.10–4.92)	4.52 (4.12–4.95)	4.55 (4.09–4.95)	4.48 (4.11–4.89)	0.847
FT4, pmol/L	11.15 (9.94–13.01)	10.87 (9.97–12.55)	11.15 (9.75–12.88)	11.75 (10.09–13.55)	0.105
TC, mmol/L	4.84 (3.99–5.68)	4.84 (4.01–5.73)	5.00 (4.05–5.71)	4.77 (3.90–5.54)	0.672
TG, mmol/L	1.42 (1.06–2.08)	1.42 (1.04–1.99)	1.55 (1.15–2.45)	1.34 (1.01–1.99)	0.167
HDL-C, mmol/L	1.17 (1.01–1.38)	1.16 (0.99–1.37)	1.20 (1.01–1.39)	1.15 (1.01–1.38)	0.877
LDL-C, mmol/L	2.90 (2.27–3.54)	2.92 (2.22–3.61)	2.98 (2.28–3.62)	2.84 (2.26–3.46)	0.763
Cr, μmol/L	64.00 (54.00-78.50)	63.00 (53.00–72.00)	63.00 (55.00–76.00)	65.00 (55.00–91.00)	0.179
UA, μmol/L	317.00 (269.50–391.00)	316.00 (267.00-394.00)	319.00 (264.00-390.00)	317.00 (272.00-385.00)	0.976
Ca, mmol/L	2.28 (2.20–2.36)	2.28 (2.20–2.36)	2.29 (2.23–2.38)	2.27 (2.18–2.35)	0.099
25(OH) D, nmol/L	55.59 (39.96–68.75)	58.44 (45.88–72.87)	53.88 (42.19–67.54)	50.96 (31.89–66.57)	0.006*
WBC, 10^9/L	6.94 (5.71–8.11)	6.15 (5.29–7.01)	6.61 (5.70–7.85)	7.90 (6.96–9.32)	< 0.001*
Neutrophil, 10^9/L	3.97 (3.14–4.97)	3.10 (2.55–3.72)	3.76 (3.30–4.57)	5.20 (4.44–6.18)	< 0.001*
Platelet, 10^9/L	237.00 (199.00-280.00)	198.00 (167.00-233.00)	241.00 (206.00-281.00)	273.00 (240.00-318.00)	< 0.001*
Lymphocyte, 10^9/L	2.11 (1.67–2.52)	2.39 (1.92–2.90)	2.16 (1.64–2.52)	1.78 (1.48–2.18)	< 0.001*
ALB, g/L	38.50 (35.80–41.20)	39.20 (37.10–41.70)	39.20 (36.20–40.90)	37.20 (33.90–40.70)	< 0.001*
Osteoporosis, n (%)					0.727
No	115 (31.68%)	40 (33.06%)	35 (28.93%)	40 (33.06%)	
Yes	248 (68.32%)	81 (66.94%)	86 (71.07%)	81 (66.94%)	
Fracture history, n (%)					0.600
No	263 (72.45%)	91 (75.21%)	88 (72.73%)	84 (69.42%)	
Yes	100 (27.55%)	30 (24.79%)	33 (27.27%)	37 (30.58%)	
Fracture, n (%)					< 0.001*
No	294 (80.99%)	110 (90.91%)	105 (86.78%)	79 (65.29%)	
Yes	69 (19.01%)	11 (9.09%)	16 (13.22%)	42 (34.71%)	
LS-BMD, g/cm^2	0.75 (0.66–0.85)	0.73 (0.66–0.83)	0.78 (0.68–0.86)	0.73 (0.64–0.85)	0.081
FN-BMD, g/cm^2	0.56 (0.49–0.63)	0.59 (0.51–0.65)	0.56 (0.50–0.63)	0.55 (0.47–0.61)	0.018*
TH-BMD, g/cm^2	0.71 ± 0.13	0.72 ± 0.12	0.71 ± 0.13	0.69 ± 0.14	0.061
FRAX MOF, %	6.10 (4.10–9.50)	5.60 (3.70–8.20)	6.10 (4.30–9.20)	7.70 (4.40–11.00)	0.016*
FRAX HF, %	2.30 (1.10–4.30)	2.00 (0.80–3.60)	2.30 (1.20-4.00)	2.90 (1.20–5.80)	0.011*
SII	442.00 (304.38-658.38)	264.54 (218.91-301.26)	442.00 (397.32–502.50)	743.33 (659.13-903.77)	< 0.001*
GNRI	98.61 (93.73–102.60)	99.32 (96.35-103.34)	99.03 (95.16-102.45)	96.35 (90.54-102.13)	0.001*
PNI	49.20 (45.35-53.00)	51.45 (47.60–55.10)	49.43 (45.90-52.95)	46.90 (42.30–50.70)	< 0.001*

Notes: Mean ± standard deviation (SD) and median (Inter Quartile Range, IQR) for continuous variables. Percentage (%) for categorical variables. *$P < 0.05$

Abbreviations: SAR, systemic immune-inflammatory index to ALB (SII/ALB) ratio; SII, systemic immune-inflammatory index; ALB, albumin; DPN, diabetic peripheral neuropathy; PVD, peripheral vascular disease; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; Hb, haemoglobin; 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; WBC, white blood cell counts; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; TH, total hip; FRAX, fracture risk assessment tool; MOF, major osteoporotic fracture; HF, hip fracture; GNRI, geriatric nutrition risk index; PNI, prognostic nutritional index

Table 2 The linear correlations between the SAR with BMDs and an individualized 10-year probability of MOF and HF were estimated through Spearman's partial correlation analysis

	LS - BMD		FN - BMD		TH - BMD		MOF		HF	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Model I	-0.090	0.088	-0.151	0.004*	-0.163	0.002*	0.177	<0.001*	0.174	<0.001*
Model II	-0.068	0.198	-0.108	0.041*	-0.118	0.025*	0.136	0.010*	0.139	0.008*
Model III	-0.013	0.815	0.030	0.579	-0.025	0.652	0.065	0.236	0.070	0.201

Notes: Model I: adjusted for none. Model II: adjusted for age and duration of diabetes. Model III: adjusted for age, duration of diabetes, hypertension, DPN, PVD, BMI, FBG, HbA1c, Hb, TSH, FT3, FT4, TC, TG, HDL-C, LDL-C, Cr, UA, Ca, 25(OH) D, WBC, Neut, Plt, Lym, ALB, osteoporosis, fracture history. * $P < 0.05$

Abbreviations: SAR, systemic immune-inflammatory index to ALB (SII/ALB) ratio; SII, systemic immune-inflammatory index; ALB, albumin; BMD, bone mineral density; MOF, major osteoporotic fracture; HF, hip fracture; LS, lumbar spine; FN, femoral neck; TH, total hip; DPN, diabetic peripheral neuropathy; PVD, peripheral vascular disease; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; Hb, hemoglobin; TSH, thyrotropin; FT3, free triiodothyronine; FT4, free thyroxine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Cr, creatinine; UA, uric acid; Ca, calcium; 25(OH) D, 25-hydroxyvitamin D; WBC, white blood cell; Neut, neutrophils; Plt, platelets; Lym, lymphocyte; ALB, albumin

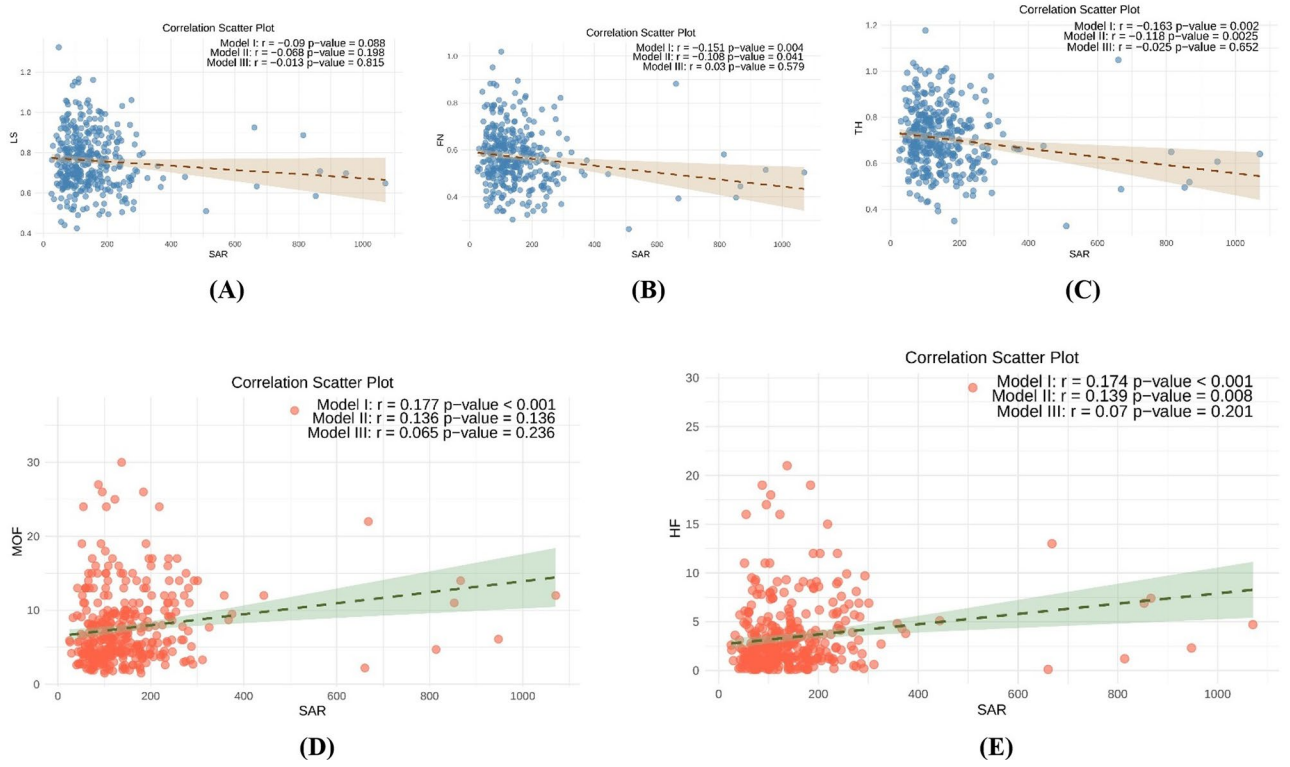

Fig. 2 The linear correlation analysis for SAR with BMDs and an individualized future 10-year probability of MOF and HF calculated by FRAX using Spearman's partial correlation analysis. (**A**) a linear correlation between SAR and LS-BMD in Model I (r = -0.090, p = 0.088), Model II (r = -0.068, p = 0.198), and Model III (r = -0.013, p = 0.815); (**B**) a linear correlation between SAR and FN-BMD in Model I (r = -0.151, p = 0.004), Model II (r = -0.108, p = 0.041), and Model III (r = 0.030, p = 0.579); (**C**) a linear correlation between SAR and TH-BMD in Model I (r = -0.163, p = 0.002), Model II (r = -0.118, p = 0.025), and Model III (r = -0.025, p = 0.652); (**D**) a linear correlation between SAR and MOF in Model I (r = 0.177, p <0.001), Model II (r = 0.136, p = 0.010), and Model III (r = 0.065, p = 0.236); and (**E**) a linear correlation between SAR and HF in Model I (r = 0.174, p <0.001), Model II (r = 0.139, p = 0.008), and Model III (r = 0.070, p = 0.201)

Cox proportional hazards regression analyses

The relationships of the SAR with fragility fracture endpoint events evaluated by Cox proportional hazards regression analyses are exhibited in Table 3. The risk factor variables for fragility fracture endpoint events were identified using univariate Cox regression analysis. In the multivariate Cox regression analysis, variables with a P value less than 0.1 in the univariate Cox regression analysis were included. Compared with the low-level SAR group, the high-level SAR group in Model I (HR = 4.526, 95% CI = 2.329–8.795, $P < 0.001$), Model II (HR = 3.696, 95% CI = 1.892–7.220, $P < 0.001$), and Model III (HR = 2.823, 95% CI = 1.370–5.814, $P = 0.005$) were positively correlated with fragility fracture endpoint events (all P values for trend < 0.01). Notably, after adjusting for the confounders of age, duration of diabetes, hypertension, DPN, PVD, BMI, FBG, HbA1c, Hb, TSH, FT3, FT4, TC, TG, HDL-C, LDL-C, Cr, UA, Ca, 25(OH) D, osteoporosis, and fracture history in Modell III (HR = 1.003, 95% CI = 1.002–1.005, $P < 0.001$), in all

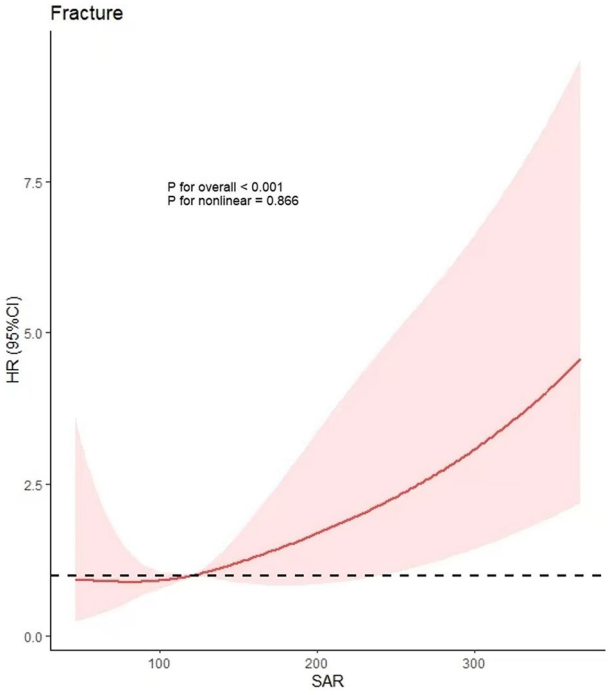

Fig. 3 The nonlinear correlation analysis for SAR with a fragility fracture probability through the RCS model. After adjusting for confounding factors, the data were fitted by a restricted cubic spline Cox proportional hazards regression model, and the model was constructed with 4 knots at the 5th, 35th, 65th, and 95th percentiles of the SAR (reference was the 5th percentile). The solid lines indicate HRs, and the shadow shapes indicate 95% CIs. The RCS model demonstrated a J-shaped dose-dependent association between the SAR and a fragility fracture endpoint event (P for overall < 0.001, P for nonlinear = 0.866). RSC analysis showed that the risk of fragility fractures progressively increased with increased SAR and vice versa

participants, the association between the SAR and fragility fractures remained strongly associated. Multivariate Cox regression analysis demonstrated that the SAR was a valuable predictor for a real-world fragility fracture endpoint event.

Kaplan–Meier survival analysis

The survival probabilities from fragility fractures for each group are shown in Fig. 4. At the end of the follow-up, the remaining participants at risk of being censored in each group who had not yet experienced a fragility fracture were as follows: low-level group (17%, $n = 20$), moderate-level group (12%, $n = 14$), and high-level group (7%, $n = 8$) (log-rank test, $P < 0.0001$), suggesting that the survival probability from a fragility fracture decreases with increasing SAR levels. Similarly, after follow-up with a median time of 45.9 months (1389 person-years), out of 363 participants, 69 experienced a fragility fracture event (19%) with a low-level SAR (15.94%, $n = 11$), moderate-level SAR (23.19%, $n = 16$), or high-level SAR (60.87%, $n = 42$) (log-rank test, $P < 0.0001$), revealing the cumulative incidences of fragility fractures increase as elevating SAR levels. Therefore, the Kaplan-Meier survival curves demonstrate that the higher the SAR, the higher the risk of fragility fractures.

Diagnostic efficacy evaluation

The diagnostic value of the SAR for predicting fragility fracture events, as evaluated through ROC curve analysis, is illustrated in Fig. 5. According to the Jordon index, the ROC curve identified an optimal SAR cut-off value of 146.209 with an area under the curve (AUC) of 0.740, a sensitivity of 0.681, and a specificity of 0.701 ($P < 0.001$). Clearly, SAR serves as a valuable prognostic indicator for fragility fractures in postmenopausal adults with T2DM. Additionally, a post-hoc power analysis was performed using G*Power 3.1.9.2 software, with 363 participants, 19% fracture incidence, and two tails $\alpha = 0.05$, the study achieved 95.70% power to detect a HR ≥ 2.0 for SAR. To objectively assess SAR's diagnostic value, comparisons with established indicators known for their diagnostic accuracy in fragility fractures, such as the GNRI, PNI, and SII, were performed within the same clinical cohort using ROC analysis. The results are presented in Fig. 6. Based on the AUC values, the diagnostic efficacy of these indicators was ranked as follows: SAR (0.740) > SII

Table 3 Multivariate Cox regression analyses for evaluating the association between SAR and fragility fractures

SAR	Case/total	HR (95% CI)					
		Model I	*P* - values	Model II	*P* - values	Model III	*P* - values
All participants	69/363	1.004 (1.003–1.004)	< 0.001*	1.003 (1.002–1.004)	< 0.001*	1.003 (1.002–1.005)	< 0.001*
Low-level (≤ 98.24)	11/121	Ref		Ref		Ref	
Moderate-level (98.24–157.25)	16/121	1.518 (0.704–3.270)	0.287	1.516 (0.703–3.267)	0.288	1.299 (0.587–2.875)	0.518
High-level (≥ 157.25)	42/121	4.526 (2.329–8.795)	< 0.001*	3.696 (1.892–7.220)	< 0.001*	2.823 (1.370–5.814)	0.005*
P for trend			< 0.001*		< 0.001*		0.005*

Notes: Model I: adjusted for none. Model II: adjusted for age and duration of diabetes; Model III: adjusted for age and duration of diabetes, hypertension, DPN, PVD, BMI, FBG, HbA1c, Hb, TSH, FT3, FT4, TC, TG, HDL-C, LDL-C, Cr, UA, Ca, 25(OH) D, osteoporosis, fracture history. * $P < 0.05$

Abbreviations: SAR, systemic immune-inflammatory index to ALB (SII/ALB) ratio; SII, systemic immune-inflammatory index; ALB, albumin; HR, hazard ratio; CI, confidence interval; DPN, diabetic peripheral neuropathy; PVD, peripheral vascular disease; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; Hb, hemoglobin; TSH, thyrotropin; FT3, free triiodothyronine; FT4, free thyroxine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Cr, creatinine; UA, uric acid; Ca, calcium; 25(OH) D, 25-hydroxyvitamin D

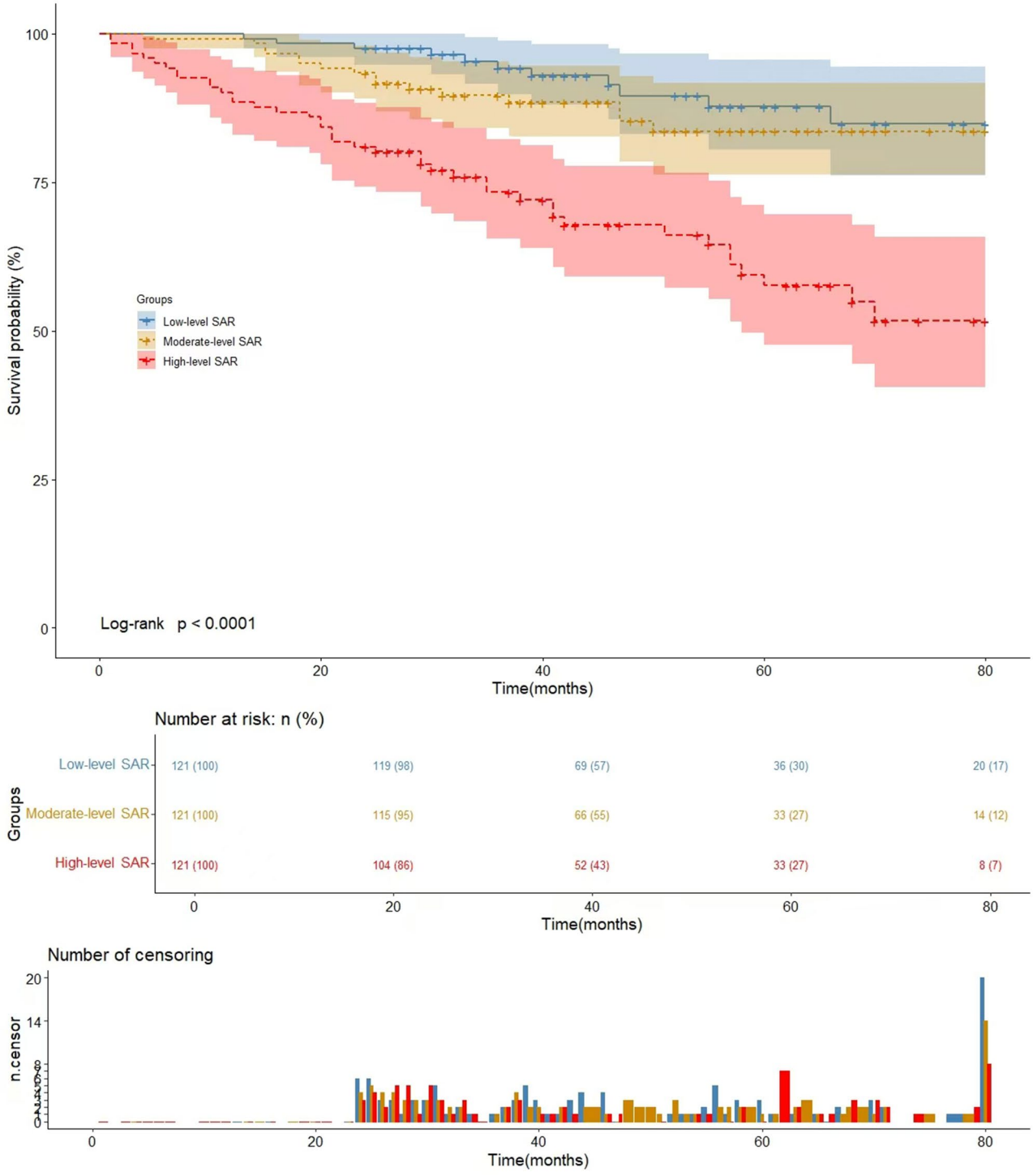

Fig. 4 Kaplan–Meier survival probability analysis for SAR with a fragility fracture. At the end of the follow-up, the remaining participants at risk of being censored in each group who had not yet experienced a fragility fracture were as follows: low-level group (17%, $n = 20$), moderate-level group (12%, $n = 14$), and high-level group (7%, $n = 8$) (log-rank test, $P < 0.0001$), suggesting that the survival probability from a fragility fracture decreases with increasing SAR levels

(0.732) > PNI (0.683) > GNRI (0.634). Furthermore, DCA was utilized to compare the net benefits of these metrics at a specific threshold probability in accurate clinical decision-making. At a threshold probability of 40%, the clinical application value (net benefit) of these indicators was ranked in the following order: SAR > SII > PNI > GNRI (Fig. 7). Both ROC curve analysis and DCA confirm that SAR possesses significant diagnostic value for fragility

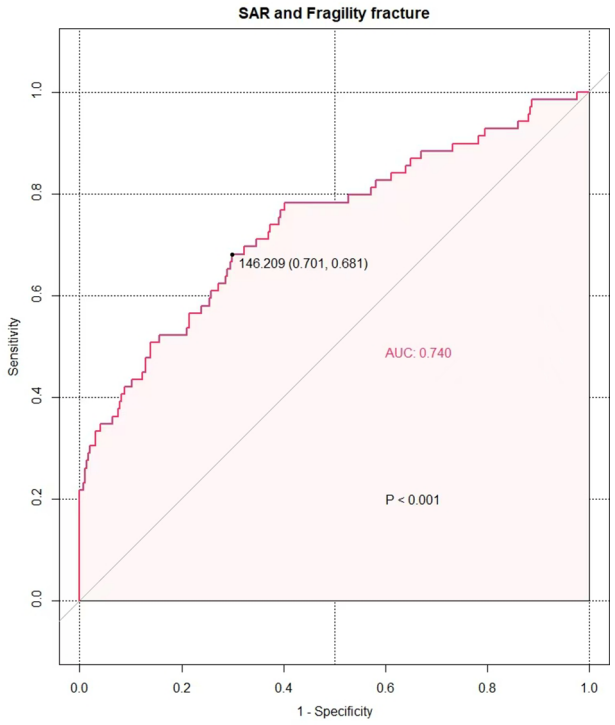

Fig. 5 ROC analysis for the diagnostic efficacy of SAR for predicting a fragility fracture event. According to the Jordon index, the ROC curve identified an optimal SAR cut-off value of 146.209 with an AUC of 0.740, a sensitivity of 0.681, and a specificity of 0.701 ($P < 0.001$)

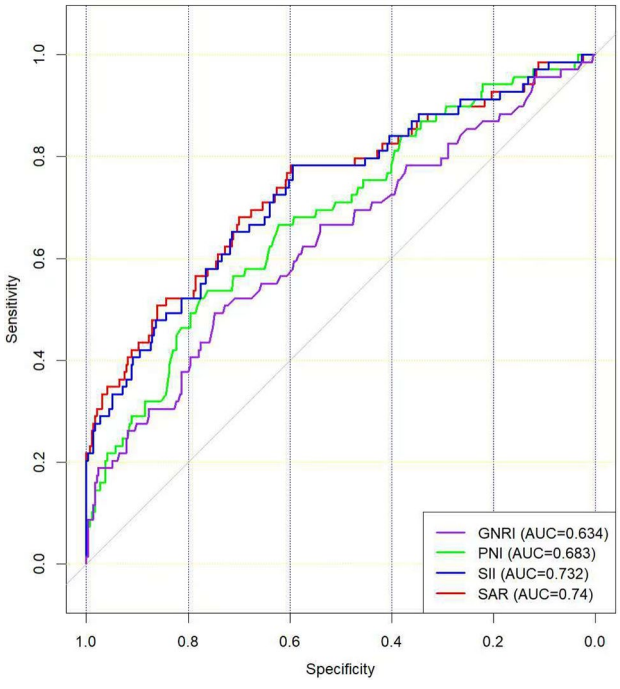

Fig. 6 Comparisons of diagnostic efficacy of SAR for fragility fractures with established indicators known, such as GNRI, PNI, and SII, were performed within the same clinical cohort using ROC analysis. According to the AUC values, the diagnostic efficacy of these indicators was ranked as follows: SAR (0.740) > SII (0.732) > PNI (0.683) > GNRI (0.634)

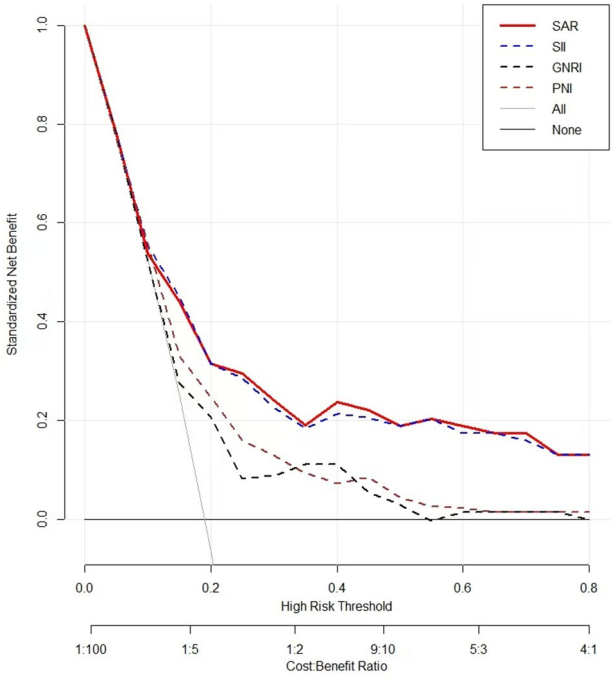

Fig. 7 Comparison of the net benefits of identified indicators at a specific fragility fracture threshold probability for accurate clinical decision-making using DCA. At a fragility fracture threshold probability of 40%, the clinical application value (net benefit) of these indicators was ranked in the following order: SAR > SII > PNI > GNRI

fracture endpoint events and merits consideration for clinical practice.

Discussion

In this present study, we have acquired the following significant findings for the first time based on elderly postmenopausal adults with T2DM. Firstly, SAR is negatively related to FN- BMD and TH- BMD but not LS- BMD. Secondly, SAR is positively associated with an individual's future 10-year probability of MOF and HF, as calculated by FRAX, especially in hip fracture risk. Thirdly, SAR is correlated with fragility fractures in a J-shaped dose-dependent manner. Fourthly, the formula for SAR proposed in this study accurately reflects the pathogenesis of immunoinflammation and malnutrition conditions related to fragility fractures in elderly postmenopausal females with T2DM. Fifthly, compared to other traditional and fragility fracture-related predictors, SAR has optimal diagnostic performance and clinical benefit, which is worthwhile in clinical practice, especially in most primary hospitals.

With the aging of society, fragility fracture adverse clinical events in elderly patients with T2DM have become a significant menace to the quality of life and even survival, particularly evident in postmenopausal females [42]. Pathophysiologically, disrupted immune homeostasis, oxidative stress, and overactivated inflammatory

cytokines play a key role in impaired bone quality, characterized by degraded bone matrix properties, bone mineralization, and trabecular bone microstructure further deteriorated by T2DM [10, 11]. Additionally, some research has even reported that malnutrition-induced physical frailty in older adults with T2DM may outweigh other pathologic factors as a significant cause contributing to fall-induced fragility fractures [43, 44]. Well-known metrics such as SII, GNRI, and PNI reflect only one side of the immune-inflammatory and nutritional coin and do not capture the full spectrum of pathologic factors contributing to the risk of fragility fractures in elderly female patients with T2DM, which was the original intent of the current study.

Hip fractures are the deadliest fractures in older postmenopausal women. One study found that under the inflammatory loading conditions, hip fracture was strongly associated with decreased hip bone density in older white women [45]. This is consistent with the current study's finding that inflammation raises SAR levels, which in turn leads to lower FN-BMD and TH-BMD, and with the probability of HF (by FRAX), as well as the decreased survival probability from fragility fractures in the high-level SAR group found by the Kaplan-Meier survival analysis. Another study showed that low ALB level was associated with decreased BMD and increased fractures in the hip [27, 28]. Malnutrition, sarcopenia, and frailty are common nutrition-related issues that coexist in older individuals with hip fractures [46]. It has been proposed that as dietary protein intake increases, BMD, bone trabecular and cortical microarchitecture, and bone strength positively correlate with total protein intake, improving fitness and reducing fracture risk [47]. This is consistent with our findings that SAR was decreased by increasing nutrient enrichment and that lower levels of SAR were positively associated with a reduced probability of fragility fracture. In nondiabetic patients, high protein intake significantly increased LS-BMD only in non-elderly women, with limited effects on FN-BMD and TH-BMD [48], in partial agreement with our current findings. Our present study found that improved nutrition-induced lower SAR levels were significantly related to increased hip BMD, although it was not associated with LS-BMD. The likely reason is that the Inflammatory load in type 2 diabetes attenuates nutrition-induced enhancement of LS-BMD. One study reported that physical fitness enhancement after physical activity in nondiabetic older postmenopausal women had little effect on LS-BMD, FN-BMD, and TH-BMD [49]. Another study showed that older women with T2DM had higher BMD, better bone characteristics, and an increased risk of fracture due to weakness from nutritional deficiencies caused by inappropriate diabetic dietary management as well as hypoglycemic events due to inappropriate diabetes therapies, including insulin and falls due to chronic neurovascular complications, as compared to women without diabetes [50]. As seen in the two studies above, the most important means of increasing fitness, besides physical activity, is increased nutrition. Increased nutrition is beneficial in preventing fall-induced fracture risk. This is generally consistent with our results that the smaller the SAR value due to increased nutrition, the lower the risk of fragility fracture.

Bone mineral mass in adults, established by peak bone mass and bone loss over the rest of life, is mainly determined by genetic factors (about 60–80%), while acquired environmental factors, such as dietary intake, contribute about 20–40% of the total. Pathological factors, including glucotoxicity, lipotoxicity, accumulation of AGEs, oxidative stress, impaired immune homeostasis, and inflammation-related interleukins, cytokines, adipokines under the T2DM conditions, as well as postmenopausal estrogen withdrawal induce alterations in bone metabolism and skeletal characteristics, including BMD, trabecular bone microstructure, bone matrix properties, and bone mineralization levels, as well as a high risk of recurrent falls or a combination of these factors, can potentially be related to nutritional status contributing to the bone quality [12, 17, 18, 51]. Despite reduced bone turnover and even better-than-normal BMD, T2DM, characterized by long-term chronic systemic low-grade inflammation, increases the risk of fragility fracture, which appears to be a problem of bone quality rather than quantity [52, 53]. Our research has shown that, as demonstrated by SAR, improving bone quality to reduce fragility fracture risk lies primarily in two measures: reducing inflammation and increasing nutrition.

Limitations

There are still some limitations to our current study. First, long-term insulin use may be present in patients, and insulin-induced hypoglycemic events, especially hypoglycemia-related falls that may lead to fragility fractures, have not been investigated in detail. Additionally, while this study focused on immunoinflammatory and nutritional biomarkers, external factors such as falls due to hypoglycemia, neuropathy-related imbalance, or environmental hazards also contribute to fragility fractures. Future studies should integrate these external causes with SAR levels to refine risk stratification and prevention strategies. Second, although patients with long-term use of antidiabetic prescription and standardized anti-osteoporosis regimens affecting bone turnovers such as thiazolidinediones, SGLT-2 inhibitors, GLP-1RAs, bisphosphonates, estrogen receptor agonists, raloxifene, teriparatide injection, and denosumab injection have been included in the exclusion criteria, those with short-term use of these agents have not been screened

individually. Third, dietary habits, nutrient intake, outdoor activity, body fat distribution, and physical fitness were not assessed in detail. Fourth, this current study is a small sample retrospective cohort study. Future large-scale, multicentre, randomized, double-blind, and controlled prospective cohort studies still need to confirm the findings.

Conclusions

Our findings show the SAR is a novel dual-dimensional powerful predictor for fragility fracture risk, especially hip fracture, and as an effective tool for developing fragility fracture prevention strategies in postmenopausal females with T2DM. Consequently, monitoring SAR levels in usual clinical practice to focus on immunoinflammatory and nutritional status to identify individuals at high risk of hip fracture and implement timely fracture interventions is particularly essential.

Abbreviations

ALB	Albumin
SAR	SII/ALB ratio
T2DM	Type 2 diabetes mellitus
MOF	Major osteoporotic fracture
HF	Hip fracture
FRAX	Fracture risk assessment tool
RCS	Restricted cubic spline
GNRI	Geriatric nutritional risk index
PNI	Prognostic nutritional index
ROC	Receiver operating characteristic
DCA	Decision curve analysis
WHO	World Health Organization
BMD	Bone mineral density
DXA	Dual-energy X-ray absorptiometry
DR	Digital radiography
SGLT-2	Sodium-glucose cotransporter protein-2
GLP-1RAs	Glucagon-like peptide-1 receptor agonists
FN	Femoral neck
TH	Total hip
LS	Lumbar spine
OP	Osteoporosis
AGEs	Advanced glycosylation end products
Ln	Natural logarithm
CBC	Complete blood count
SOP	Specific operating procedures
IQR	Interquartile range
ANOVA	Analysis of variance
WBC	White blood cell count
BMI	Body mass index
DPN	Diabetic peripheral neuropathy
PVD	Peripheral vascular disease
FBG	Fasting blood glucose
HbA1c	Glycated haemoglobin
Hb	Haemoglobin
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	Ualcium
25(OH) D	25-hydroxy vitamin D
HRs	Uazard ratios
CIs	Confidence intervals
AUC	Area under the curve

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Author contributions

Wensheng Lu designed this study and drafted the English version of this paper. Jie Lu, Fenglian Wei, Jingxia Sun, and Jiangmei Pan completed the data collection and the partial statistical analysis. Zhenwei Zhai and Haolun Wang drew all the graphs for this analysis through the R language software package. Jingxia Sun and Shishan Huang retrieved the medical records of all the participants. Qiu Wang, Wenxin Chu, Jinming Yu, and Jianhao Huang took part in the partial follow-up of the participants. Xubin Wu completed the supervision and management of part of the study.

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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

Ethical approval

Written informed consent was acquired from each patient who consented to participate in the study. All information regarding participants remained confidential during the survey and the analysis. The study complied with the Declaration of Helsinki guidelines and obtained approval from the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region (approval number: Ethics-KY-IIT-2023-60).

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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