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Association of HDL and LDL levels with osteoporosis in rheumatoid arthritis: a retrospective cohort study

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Abstract

Objectives A correlation exists between lipids and osteoporosis (OP), as well as between lipids and rheumatoid arthritis (RA). However, lipids, the relationship between RA and OP is still unclear. This study mainly investigates the relationship between lipid levels and OP risk in RA patients.

Methods Retrospective collection of RA patient data from July 2017 to May 2022, encompassing baseline demographics, treatment regimens, laboratory results, and bone mineral density (BMD) measurements. Analyses, stratified by BMD subgroups, were conducted using propensity score matching (PSM) based on age, sex, and baseline duration, and binary logistic regression to examine the interplay between lipoprotein levels and other risk factors. The relationship between continuous variables and OP risk was assessed using restricted cubic spline (RCS), followed by a reanalysis of the correlation between varying lipoprotein levels and different factors, segmented according to RCS-determined cutoffs.

Results The study included 2673 RA patients. Binary logistic regression revealed significant associations between high-density lipoprotein (HDL), low-density lipoprotein (LDL), and RA–OP ($p < 0.01$). Specifically, HDL emerged as a protective factor against OP (OR = 0.40, 95% CI 0.250–0.629; $p < 0.001$), whereas LDL was identified as a risk factor (OR = 1.56, 95% CI 1.290–1.890; $p < 0.001$). Furthermore, HDL (RCS cutoff point 1.28 mmol/L) showed a negative, linear correlation with RA-related OP, while LDL (RCS cutoff point 2.63 mmol/L) demonstrated a positive, linear correlation.

Conclusions The levels of HDL and LDL may be indicators of OP occurrence in RA patients.

Keywords Rheumatoid arthritis, High-density lipoprotein, Low-density lipoprotein, Osteoporosis, Correlation

Introduction

Rheumatoid arthritis (RA) is the most prevalent autoimmune disorder encountered in clinical settings, affecting approximately 0.5–1% of the global population [1, 2]. It is often associated with multisystem involvement and a spectrum of comorbidities. Notably, osteoporosis (OP) is frequently observed as a secondary condition, particularly among postmenopausal women [3].

RA is recognized as a contributory factor for OP development [4]. RA progression is characterized by bone erosion and destruction, attributing to overall bone loss.

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Contributing to this phenomenon, autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are identified as risk elements for bone erosion and reduced bone mineral density in patients with RA [5]. Reports indicate that inflammatory responses during RA exacerbate bone resorption, leading to bone mineral loss and subsequent reduction in bone mineral density [6]. In addition, despite "targeted therapy," the risk of OP persists [7]. The therapeutic use of glucocorticoids in RA management induces calcium and phosphorus metabolism disorders, bone loss, and trabecular bone depletion, markedly elevating the risk of OP and fractures [8].

In addition, RA is acknowledged as a risk factor for cardiovascular disease. Presently, the emphasis concerning RA largely centers on lipids and cardiovascular disease risk, especially in patients with a history of cardiovascular events. However, the significance of lipids as prognostic indicators for other secondary conditions is often overlooked. In the context of RA, inflammatory mediators disrupt the functionality of adipose tissue, skeletal muscle, and other organs, leading to lipid irregularities, notably with high-density lipoprotein (HDL) and low-density lipoprotein (LDL) [9]. Dyslipidemia, a contributor to atherosclerosis, also plays a pivotal role in OP [10]. Elevated lipid levels result in lipid deposition within the bone marrow and the production of pro-inflammatory lipids that precipitate bone loss [11]. Notably, the processes of osteogenesis and adipogenesis within the bone marrow are interconnected. An upsurge in the differentiation of bone marrow stromal cells into adipocytes inhibits osteoblast differentiation, while lipid elevation can induce bone ischemia and hypoxia, reducing bone formation capacity [12]. Although patients with RA commonly exhibit abnormal lipid metabolism, the underlying mechanisms remain elusive [13]. However, similar to other dyslipidemia cases, increased lipid levels in the body can lead to extensive fat accumulation and the release of inflammatory mediators that curb bone resorption, promote osteoclast differentiation, and trigger bone loss [14]. Moreover, increased lipid levels can interfere with osteoblast differentiation and formation across various mesenchymal cell lines and bone marrow by disrupting osteoblast differentiation signaling pathways [15]. OP, a metabolic bone ailment, involves lipid metabolism [16]. The risk of OP in postmenopausal women escalates concurrently with declining estrogen levels, which modulate lipid metabolism, cholesterol accumulation, osteoclast activity, and function [17–19].

To date, few studies have delved into the interrelation between lipids, RA, and OP. Some research indicates an inverse correlation between LDL levels and OP risk, while others identify LDL as a risk factor not only for cardiovascular diseases but also for OP [20, 21]. In light of this, the study examines the interplay between RA, OP, and lipid metabolism to pioneer novel strategies for predicting and addressing OP in clinical settings.

Methods

Subjects

Data were retrospectively collected from cases admitted to the Department of Rheumatology and Immunology at the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (TCM) between July 2017 and May 2022, aligning with the RA classification criteria [22]. For patients with multiple admissions during this period, only laboratory results from their initial hospitalization were considered.

The inclusion criteria encompassed: (i) comprehensive medical records, clinical manifestations, laboratory findings, and BMD measurements; (ii) absence of lipid-metabolism-influencing medications in the past 3 months; (iii) no history of bone tumors or metastases. The exclusion criteria were as follows: (i) age below 16 years; (ii) idiopathic OP (Existence before the occurrence of RA disease, It is a relatively rare primary osteoporosis with unknown etiology. The usual age of onset is in adolescents aged 8–14,), or extreme lipid levels (Beyond 3 times the normal range); (iii) conditions such as tuberculosis, tumors, thyroid disorders; (iv) recent infections, liver or renal diseases within the past 3 months; (v) concurrent diabetes, hypertension, or coronary artery disease; (vi) prior lumbar spine or hip fractures with prosthetic implants; (vii) coexisting systemic lupus erythematosus, Sjögren's syndrome, or ankylosing spondylitis; (viii) history of JAK inhibitor use; (ix) prior use of lipid-lowering agents; and (x) history of ovariectomy. Meanwhile, cases with lost data will be excluded and re matched. Participants were randomly categorized into RA–OP and RA–non-OP groups based on their BMD outcomes. Group allocation followed WHO diagnostic criteria for OP: perimenopausal and postmenopausal women, as well as men aged 50 years or above with T-scores ≤ -2.5, and non-menopausal women along with men under 50 years with Z-scores ≤ -2.0 were placed in the RA–OP group. Meanwhile, for patients with a history of brittle fractures in the past, BMD ≤ -2.5 is divided into RA–OP group. If it is greater than −2.5, patients will be excluded from the analysis.

This study received approval from the Medical Ethics Committee of the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (KYW2022020) and waived the requirement for patient consent forms.

Data collection

Data were retrieved from the hospital's medical record system, assessing patients' general conditions through laboratory tests. Collected data included gender, age, body mass index(BMI), medical history, previous GC use (has it been used for ≥ 3 months), anti-osteoporosis drugs and anti-rheumatic drug treatment, collected joint pressure pain (TJC) and the number of swellings (SJC), the physician's overall disease score (MDGA), the patient's overall disease score(PGA) and overall health score (GH); The collected laboratory data included total cholesterol (TC), triglycerides (TG), HDL, LDL, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), calcium, ACPA, RF, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and BMD (lumbar spine, left hip/femoral neck and right hip/femoral neck).

Test methodologies, reagent catalog numbers, and brands were detailed as follows (179-2300, Kang Jian Medical) was measured by the Westergren method. RF (998-40391, FUJIFILM Wako Pure Chemical Corporation), TC (10376501, Siemens ADVIA 1800), TG (10335892, Siemens ADVIA 1800), HDL (06521559, Siemens ADVIA 1800), LDL (09796248, Siemens ADVIA 1800), ApoA1 (23061904-1, Siemens ADVIA 1800), ApoB (230041105-1, Siemens ADVIA 1800), and CRP (994-65391, FUJIFILM Wako Pure Chemical Corporation) were measured by immunoturbidimetry. ACPA (5031656190, Roche) was measured by chemiluminescence. BMD was quantified by DEXA (LUNAR BX-L, America) using dual energy X-ray bone densitometer.

Data analysis

A variety of disease activity indices for RA were measured, including disease activity calculation using the Disease Activity Score of 28 joints (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) [23–25], DAS28 using five variables: SJC, TJC, GH, ESR (DAS28ESR), CRP levels (DAS28CRP), SDAI using five variables: SJC, TJC, CRP, MDGA, PGA; CDAI using four variables: SJC, TJC, MDGA, PGA.

Statistical analysis

After categorization, propensity score matching (PSM) was applied to minimize data bias and the influence of confounding variables, focusing on age, gender, and disease duration for a more accurate comparison between groups. Concurrently, potential confounding factors due to medication were assessed and addressed, we first calculate the medication usage of the two groups of patients after grouping. If there are any differences, we will conduct additional analysis to further investigate whether there are confounding factors. Descriptive statistics, displayed as numbers (n) and percentages (%), were analyzed using the χ^2 test. Continuous variables adhering to normal distribution were presented as mean ± standard deviation. Non-normally distributed variables were represented using quartiles [M (P25–P75), and their statistical analysis was conducted via the t test or Mann–Whitney U. For BMD integration, the three lowest partial values for individual patients were selected and analyze the association between different parts of BMD in two groups of patients. Based on BMD outcomes, correlation analysis for grouped variables utilized Pearson's coefficient for normally distributed data and Spearman's coefficient for non-normally distributed data, with $0 < r < 1$ indicating positive correlation, and $-1 < r < 0$ denoting negative correlation. Subsequent to correlation analysis, binary logistic regression was employed to assess potential risk factors, considering osteoporosis as the dependent variable. Combining correlation analysis to understand the relationship between independent and dependent variables, identifying potential relationships between variables, and establishing effective predictive models. The interaction between the lipoprotein with the highest relative risk and other factors was examined, contrasting models with and without the interaction term. Interaction variables were categorized based on values being below normal, within normal range, or above normal. The choice of interaction variables was informed by prior research indicating possible interactions with study outcomes [26], and their relevance to baseline characteristics. Restricted cubic splines (RCS) were utilized to model the relationship between continuous variables and the risk of OP occurrence. Patients were further stratified based on hyperlipidemia guidelines (TC ≥ 6.22 mmol/L, LDL ≥ 4.14 mmol/L, HDL < 1.03 mmol/L, and TG ≥ 2.26 mmol/L) to investigate potential risk associations between hyperlipidemia and osteoporosis [27]. All statistical analyses were executed using SPSS 25.0, while PSM and graph generation were conducted using R4.2.0. A two-sided $p < 0.05$ was considered statistically significant.

Results

The initial cohort comprised 6134 patients with RA. After accounting for repeated admissions, complicating factors, and incomplete data, 2673 patients were finalized for the study through PSM (RA–OP and RA–non-OP at a 1:2 ratio) based on age, gender, and disease duration. This group included 891 RA–OP and 1782 RA–non-OP patients, classified according to BMD (Fig. 1). The demographic composition was 377 males and 2296 females, due to the late start of rheumatic and immune diseases in our province, with 36.8% having received antirheumatic drugs. However, no significant disparities were noted in

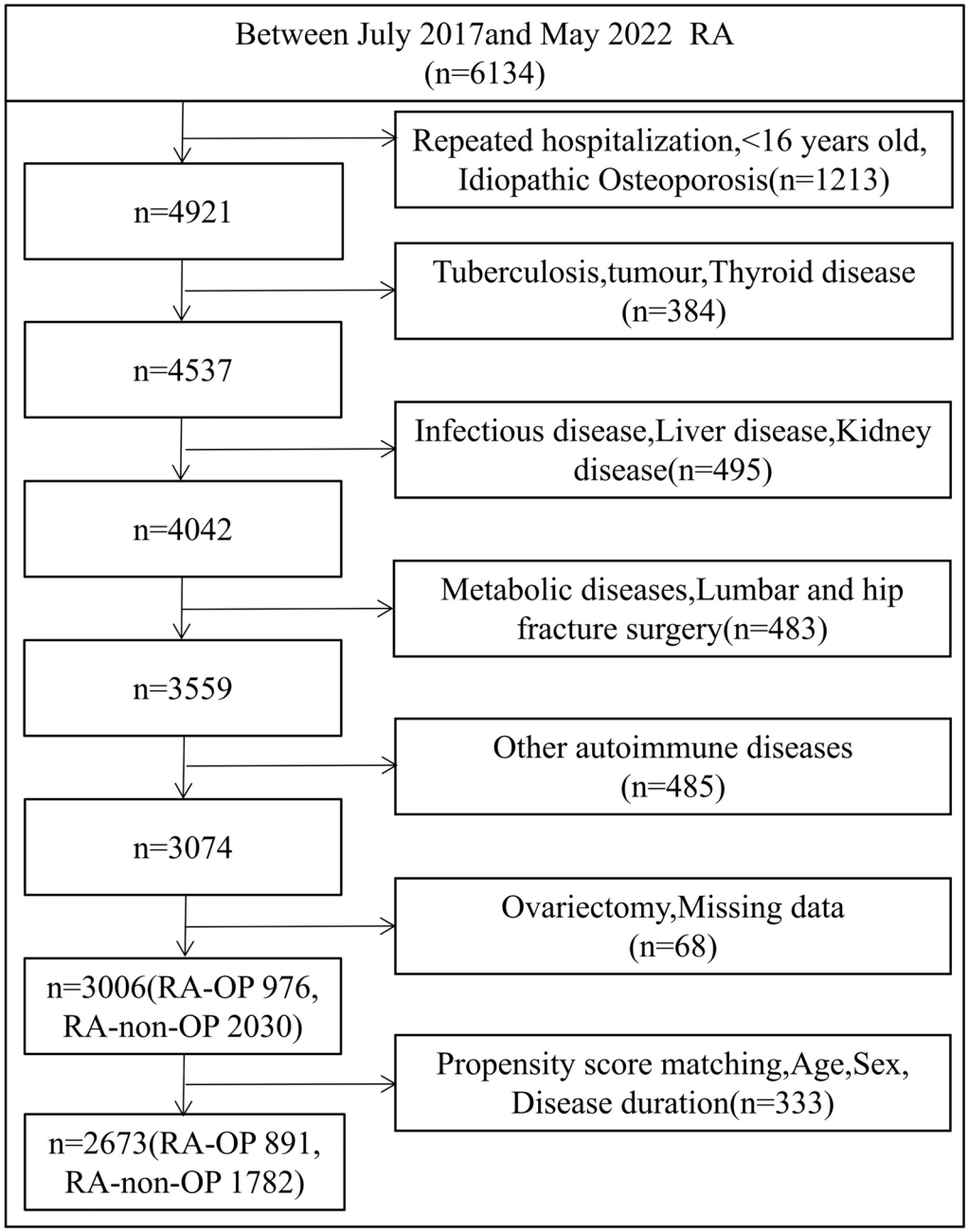

Fig. 1 Flow chart of included patients

the baseline analysis (smoking history, history of alcohol use, diuretic, beta-blocker, long-term glucocorticoid use, medication history) ($p > 0.05$). The RA–OP group exhibited elevated levels of ACPA, CDAI, DAS28 ESR, DAS28–CRP, LDL/HDL, and LDH, whereas the RA–non-OP group had lower BMI, CA, and HDL ($p < 0.01$) (Table 1).

In RA, the correlation analysis with OP revealed that age ($r = 0.170$), disease duration ($r = -0.114$), BMI ($r = 0.291$), CA ($r = 0.141$), DAS28 ESR ($r = -1.119$), DAS28 CRP ($r = -0.096$), SDAI ($r = -0.089$), CDAI ($r = -0.097$), TG ($r = 0.105$), HDL ($r = 0.104$), and LDL ($r = -1.101$) were significantly associated with OP ($p < 0.05$) (Table 2).

Regression analysis for RA–OP identified certain contributing factors, deliberately excluding interacting variables. Elevated LDL levels (OR = 1.56) were pinpointed as an independent risk factor for RA–OP ($p < 0.01$), while

Table 1 Select cohort characteristics and Comparison of basic data of two groups of patients

Variables	Total ($n=2673$)	RA–OP ($n=891$)	RA–non-OP ($n=1782$)	*P*
Sex (Man/Women)	377/2296	128/763	249/1533	0.783*
Age, years	60.6 (53.9, 67.0)	62.0 (54.3, 67.3)	59.5 (53.7, 66.8)	0.140#
BMI (kg-m^{-2})	22.3 (3.4)	21.3 (3.5)	23.1 (3.2)	< 0.001†
Disease duration (months)	60.0 (24.0, 120.0)	72.0 (24.0, 121.0)	60.0 (24.0, 120.0)	0.322#
RF (U/L)	91.1 (25.1, 167.1)	95.8 (28.5, 166.0)	89.0 (24.2, 167.7)	0.737#
ACPA(RU/mL)	174.6 (41.2, 400.0)	217.0 (55.6, 400.0)	159.6 (32.1, 400.0)	0.042#
CA(mmol/L)	2.3 (2.2, 2.4)	2.3 (2.2, 2.4)	2.4 (2.3, 2.4)	0.001#
SDAI	22.3 (18.0, 29.8)	23.0 (18.3, 30.7)	21.8 (17.2, 28.6)	0.023#
CDAI	20.0 (17.0, 25.0)	20.0 (17.0, 25.0)	19.0 (17.0, 24.0)	0.024#
DAS28 ESR	5.5 (4.7, 6.2)	5.6 (4.8, 6.3)	5.5 (4.6, 6.1)	0.019#
DAS28 CRP	4.9 (3.7, 5.8)	5.1 (3.8, 6.0)	4.7 (3.4, 5.7)	0.019#
Smoking history (≥ 3 months), *n* (%)	263 (9.8)	87 (9.7)	176 (9.9)	0.927*
History of alcohol (≥ 3 months), *n* (%)	209 (7.8)	66 (7.4)	143 (8.0)	0.575*
Diuretic, *n* (%)	80 (3.0)	23 (2.6)	57 (3.2)	0.377*
Beta-blocker, *n* (%)	53 (2.0)	17 (1.9)	36 (2.0)	0.844*
Long-term (≥ 3 months) Glucocorticoids, *n* (%)	605 (22.6)	211 (23.7)	394(22.1)	0.360*
Medication history				
csDMARDs, *n* (%)	985 (36.8)	315 (35.4)	670 (37.6)	0.257*
bDMARDs, *n* (%)	527 (19.7)	164 (18.4)	363 (20.4)	0.229*
Vitamin D, *n* (%)	490 (18.3)	164 (18.4)	326 (18.3)	0.127*
Other anti-osteoporosis drugs, *n* (%)	655 (24.5)	219 (24.6)	436 (24.5)	0.962*
Lipoproteins				
TC(mmol/L)	4.3 (3.7, 5.0)	4.4 (3.7, 5.0)	4.3 (3.6, 5.1)	0.617#
TG(mmol/L)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.2 (0.9, 1.7)	0.143#
HDL(mmol/L)	1.3 (1.0, 1.5)	1.2 (1.0, 1.4)	1.3 (1.1, 1.6)	< 0.001#
LDL(mmol/L)	2.6 (2.1, 3.3)	2.8 (2.2, 3.4)	2.5 (2.1, 3.2)	0.004#
LDL/HDL	2.3 (1.6, 2.7)	2.5 (1.8, 3.0)	2.1 (1.5, 2.5)	< 0.001#
ApoA1(g/L)	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	0.538#
ApoB(g/L)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.293#
BMD (g/cm^{-2})				
Lumbar spine	−1.6 (−2.6, −0.6)	−2.7 (−3.2, −2.1)	−1.0 (−1.6, −0.2)	< 0.001#
Left hip/femoral neck	−1.5 (−2.3, −0.7)	−2.5 (−3.0, −1.9)	−0.9 (−1.5, −0.2)	< 0.001#
Right hip/femoral neck	−1.5 (−2.3, −0.7)	−2.5 (−3.0, −1.9)	−1.0 (−1.5, −0.2)	< 0.001#

csDMARDs conventional synthetic DMARDs, *bDMARDs* biologic DMARDs, *BMI* body mass index, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibodies, *CA* calcium, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *DAS28* Disease Activity Score of 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TC* total cholesterol, *TG* triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ApoA1* apolipoprotein A1, *ApoB* apolipoprotein B, *BMD* bone mineral density

* Chi-square test was used for analysis of enumeration data

Mann–Whitney *U* test was used for analysis of data

† the independent-samples *t* test was used for analysis of data

increased HDL (OR = 0.40), CA (OR = 0.34), and BMI (OR = 0.84) served as protective factors against RA–OP ($p < 0.05$) (Fig. 2).

According to laboratory reference standards, in the study of observing whether there is interaction between different variables, we conducted interaction analysis at normal high-density lipoprotein levels (1.03–1.42 mmol/L). Significant correlations were observed in individuals aged < 60 years ($p = 0.002$), with a disease duration of 120–180 months ($p < 0.001$), BMI ranging from 18.5 to 23.9 kg/m^2 ($p = 0.014$) versus 24–27.9 kg/m^2 ($p = 0.029$), CA levels between 2.02 and 2.6 mmol/L ($p = 0.004$), and DAS28 ESR > 5.1 ($p = 0.038$). However, no significant correlations were detected in the interaction between HDL and other variables ($p > 0.05$) (Table 3).

Table 2 Correlation analysis of OP

Variables	*r*	*p*
Age	−0.170	< 0.001
Disease duration	−0.114	0.003
BMI	0.291	< 0.001
CA	0.141	< 0.001
RF	−0.054	0.166
ACPA	−0.065	0.092
DAS28 ESR	−1.119	0.002
DAS28 CRP	−0.096	0.013
SDAI	−0.089	0.021
CDAI	−0.097	0.012
TC	0.010	0.800
TG	0.105	0.006
HDL	0.104	0.007
LDL	−1.101	0.009
ApoA1	0.028	0.475
ApoB	0.040	0.298

BMI body mass index, *CA* calcium, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibodies, *DAS28* Disease Activity Score of 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *TC* total cholesterol, *TG* triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ApoA1* apolipoprotein A1, *ApoB* apolipoprotein B

To understand the impact of hyperlipidemia and non-hyperlipidemia on OP, we conducted additional grouping analysis and found that hyperlipidemia patients had differences in BMI CA, CDAI, and DAS28 ESR were higher than those in non hyperlipidemic patients ($p < 0.05$), and there was no significant difference in BMD at different sites between the two groups of patients ($p > 0.05$) (Table 4).

To evaluate the relationship between overweight patients and OP, we also conducted additional analysis. According to WHO recommendations, we defined BMI ≥ 24.0 as overweight. We found that in RA, overweight patients are relatively less likely to experience OP ($p < 0.05$), and overweight patients have higher levels of TG and ApoB than normal BMI patients ($p < 0.05$) (Table 5).

The RCS model was employed to delineate the relationship between each variable and the incidence of RA–OP. Regression spline curves indicated positive linear correlations for LDL (cutoff 2.63), SDAI (cutoff 22.30), CDAI (cutoff 20.00), DAS28 ESR (cutoff 5.48), and DAS28 CRP (cutoff 4.88). Conversely, HDL (cutoff 1.28), BMI (cutoff 22.00), and CA (cutoff 2.30) exhibited negative linear correlations, while ACPA (cutoff point = 174.55) demonstrated a biphasic linear relationship (Fig. 3).

Regarding the influence of lipids on RA–OP, HDL and LDL emerged as risk factors following a comprehensive statistical analysis comparing RA–OP with RA–non-OP, alongside correlation and binary logistic analyses of risk factors. The analysis utilized RCS cutoff points, revealing that compared to the HDL > 1.28 mmol/L group, the HDL ≤ 1.28 mmol/L group presented elevated levels of ACPA, SDAI, CDAI, DAS28 ESR, and DAS28 CRP ($p < 0.05$), while disease duration showed an inverse trend. Similarly, in comparison to the LDL ≤ 2.63 mmol/L group, the LDL > 2.63 mmol/L group exhibited higher BMI ($p < 0.05$), whereas BMD measurements at the lumbar spine and right hip/femoral neck demonstrated the opposite trend (Table 6).

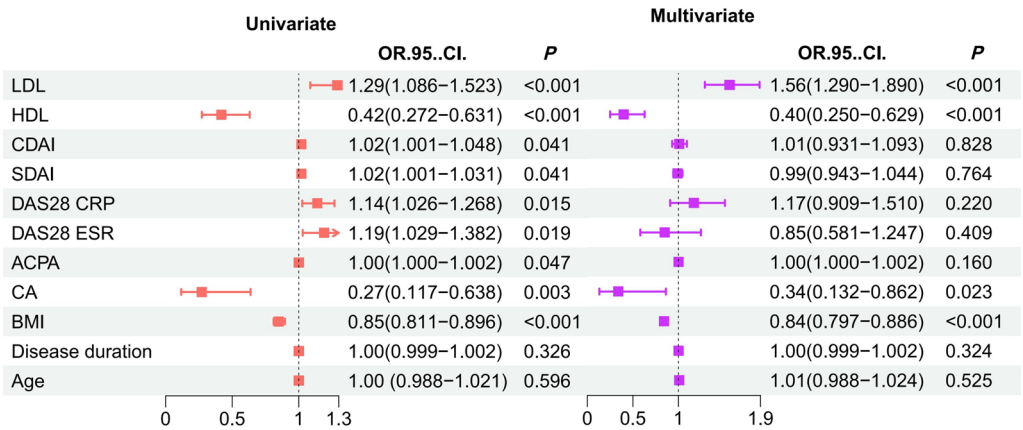

Fig. 2 Risk factors for the occurrence of RA–OP (logistic regression analysis for possible risk factor analysis and regression analysis for possible risk factor variables adjusted for confounding variables). *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *CDAI* Clinical Disease Activity Index, *SDAI* Simplified Disease Activity Index, *DAS28* Disease Activity Score of 28 joints, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ACPA* anti-citrullinated protein antibodies, *CA* calcium, *RF* rheumatoid factor, *BMI* body mass index

Table 3 Stratified association HDL by Age, Disease duration, BMI, CA, ACPA and DAS28 ESR

Clinical factors	HDL(mmol/L)			*P* for trend	*P* for interaction
	< 1.03 *n* = 681	1.03–1.42 *n* = 1163	> 1.42 *n* = 829		
Age (years)					
< 60, *n* = 1267	1	1.26 (0.68,2.32)	0.37 (0.18,0.78)	0.002	0.246
≥ 60, *n* = 1406	1	1.54 (0.86, 2.73)	0.70 (0.38, 1.29)	0.071	
Disease duration (months)					
< 60, *n* = 1203	1	2.18 (1.13, 4.20)	0.66 (0.31, 1.40)	0.168	0.754
60–120, *n* = 865	1	1.10 (0.45, 2.71)	0.63 (0.24, 1.65)	0.258	
> 120–180, *n* = 219	1	1.94 (0.68, 5.55)	0.13 (0.04, 0.48)	0.000	
> 180, *n* = 386	1	0.72 (0.22, 2.32)	1.29 (0.37, 4.47)	0.612	
BMI (kg-m^{-2})					
< 18.5, *n* = 347	1	7.62 (1.53, 37.86)	1.25 (0.31, 5.02)	0.882	0.402
18.5–23.9, *n* = 1498	1	1.61 (0.93, 2.81)	0.59 (0.32, 1.06)	0.014	
24–27.9, *n* = 677	1	0.70 (0.31, 1.58)	0.27 (0.10, 0.74)	0.029	
> 28, *n* = 151	1	0.65 (0.06, 6.66)	1.23 (0.11, 13.97)	0.634	
CA(mmol/L)					
< 2.02, *n* = 167	1	1.30 (0.17, 10.21)	0.61 (0.09, 4.23)	0.346	0.666
2.02–2.6, *n* = 2434	1	1.41 (0.91, 2.19)	0.54 (0.33, 0.88)	0.004	
> 2.6, *n* = 71	1	–	–	–	
ACPA(RU/mL)					
< 60, *n* = 841	1	1.24 (0.55, 2.81)	0.53 (0.22, 1.27)	0.106	0.953
≥ 60, *n* = 1833	1	1.51 (0.93, 2.44)	0.54 (0.31, 0.94)	0.010	
DAS28 ESR					
≤ 3.2, *n* = 36	1	–	–	–	0.368
> 3.2 to ≤ 5.1, *n* = 1032	1	2.63 (1.13, 6.12)	0.75 (0.31, 1.79)	0.084	
> 5.1, *n* = 1605	1	1.21 (0.74, 1.97)	0.54 (0.31 0.96)	0.038	

BMI body mass index, *CA* calcium, *ACPA* anti-citrullinated protein antibodies, *DAS28* Disease Activity Score of 28 joints, *CRP* C-reactive protein, *HDL* high-density lipoprotein

Discussion

Our findings indicate a negative correlation between HDL levels and RA–OP risk, with a notable distinction from the RA–non-OP group. RCS analysis pinpointed an HDL value of 1.28 mmol/L as a critical threshold, below which the risk of developing OP escalates. This contrasts with prior research suggesting a positive association between higher HDL levels and OP risk [28], this difference may be attributed to the limited number of cases in the reference retrospective study, and there may be heterogeneity in the research results. Second, although there was no difference in gender or age between the two groups of patients in this study, there was no comparison of disease duration, as we all know, the course of RA is correlated with OP, and these factors may be the reason for the differences in our research results. In our study, we matched gender, age, and disease duration using the PSM method, resulting in more reliable research results and a larger sample size.

Contrasting opinions exist regarding whether elevated LDL is a determinant for OP onset [20, 21], Our retrospective analysis revealed a positive linear correlation between LDL levels and RA–OP incidence, with the RA–OP group exhibiting significantly higher LDL levels compared to the RA–non-OP group ($p = 0.004$). Binary logistic regression and RCS outcomes underscored LDL as a significant risk factor for RA–OP. Notably, the imbalance in the LDL/HDL ratio, more pronounced in the RA–OP group, merits further investigation as a potential OP risk factor.

Previous studies have identified risk factors for RA–OP, including glucocorticoid (GC) use, postmenopausal status, low body weight, increased disease activity, and varying ACPA levels [8, 29]. In our research, these factors were thoroughly analyzed due to the patient selection through PSM based on age, sex, and disease duration. Although the RA–OP group presented higher DAS28 ESR, DAS28 CRP, SDAI, and CDAI compared to the RA–non-OP group, binary logistic analysis did not establish a significant risk association. Furthermore, other lipoproteins such as TC, TG, ApoA1, and ApoB did not show marked differences between the RA–OP and

Table 4 Comparison of characteristics between patients with hyperlipidemia and those without hyperlipidemia

Variables	Hyperlipidemia ($n=1020$)	Non hyperlipidemia ($n=1653$)	*P*
RA–OP/RA–non-OP	442/578	685/968	0.368*
Sex (Man/Women)	149/871	228/1425	< 0.001*
Age, years	59.3 (9.6)	61.1 (9.3)	0.017†
BMI ($kg{\cdot}m^{-2}$)	22.7 (3.1)	22.0 (3.2)	0.002†
Disease duration (months)	60.0 (24.0, 120.0)	60.0 (24.0, 120)	0.786#
RF (U/L/)	95.0 (26.0, 181.1)	89.0 (24.6, 162.6)	0.578#
ACPA(RU/mL)	45.0 (217.4, 400.0)	163.8 (38.0, 400.0)	0.098#
SDAI	23.9 (18.3, 32.5)	21.7 (17.4, 28.3)	0.009#
CA(mmol/L)	2.4 (2.2, 2.5)	2.3 (2.2, 2.4)	0.012#
CDAI	20.0 (18.3, 32.5)	19.0 (17.0, 24.0)	0.003#
DAS28 ESR	5.7 (4.9, 6.4)	5.4 (4.6, 6.1)	< 0.001#
DAS28 CRP	5.0 (3.7, 6.0)	4.8 (3.6, 5.7)	0.111#
BMD(g/cm^2)			
Lumbar spine	−1.6 (−2.6, −0.6)	−1.6 (−2.6, −0.6)	0.692#
Left hip/femoral neck	−1.5 (−2.3, −0.6)	−1.6 (−2.3, −0.7)	0.201#
Right hip/femoral neck	−2.3 (−1.5, −0.6)	−1.6 (−2.3, −0.8)	0.427#

BMI body mass index, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibodies, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *DAS28* Disease Activity Score of 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *BMD* bone mineral density

* Chi-square test was used for analysis of enumeration data

Mann–Whitney *U* test was used for analysis of data

† The independent-samples *t* test was used for analysis of data

Table 5 Comparison of different characteristics between overweight and normal BMI patients

Variables	Overweight ($n=773$)	Normal BMI ($n=1900$)	*P*
RA–OP/RA–non-OP	215/558	912/988	< 0.001*
Sex (Man/Women)	108/665	269/1631	< 0.001*
Age, years	59.3 (53.3, 66.2)	61.5 (54.2, 67.3)	0.034#
Disease duration (months)	60.0 (24.0, 120.0)	61.0 (24, 120)	0.153#
RF (U/L/)	86.5 (21.9, 162.9)	92.9 (27.7, 168.4)	0.152#
ACPA(RU/mL)	174.7 (37.3, 400.0)	171.3 (42.8, 400.0)	0.909#
CA(mmol/L)	2.4 (2.2, 2.5)	2.3 (2.2, 2.4)	0.012#
SDAI	21.8 (17.6, 29.8)	22.4 (18.0, 29.9)	0.508#
CDAI	19.0 (17.0, 24.0)	20.0 (17.0, 25.0)	0.227#
DAS28 ESR	5.3 (4.7, 6.2)	5.5 (4.8, 6.2)	0.182#
DAS28 CRP	4.7 (3.7, 5.8)	4.9 (3.7, 5.8)	0.740#
Lipoproteins			
TC(mmol/L)	1.4 (1.0, 2.0)	4.3 (3.7, 5.0)	0.123#
TG(mmol/L)	1.3 (1.0, 1.5)	1.2 (0.9, 1.5)	< 0.001#
HDL(mmol/L)	1.3 (1.0, 1.5)	1.3 (1.1, 1.5)	0.359#
LDL(mmol/L)	2.7 (2.2, 3.3)	2.6 (2.1, 3.3)	0.165#
ApoA1(g/L)	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	0.794#
ApoB (g/L)	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)	< 0.001#

BMI body mass index, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibodies, *CA* calcium, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *DAS28* Disease Activity Score of 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TC* total cholesterol, *TG* triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ApoA1* apolipoprotein A1, *ApoB* apolipoprotein B, *BMD* bone mineral density

* Chi-square test was used for analysis of enumeration data

Mann–Whitney *U* test was used for analysis of data

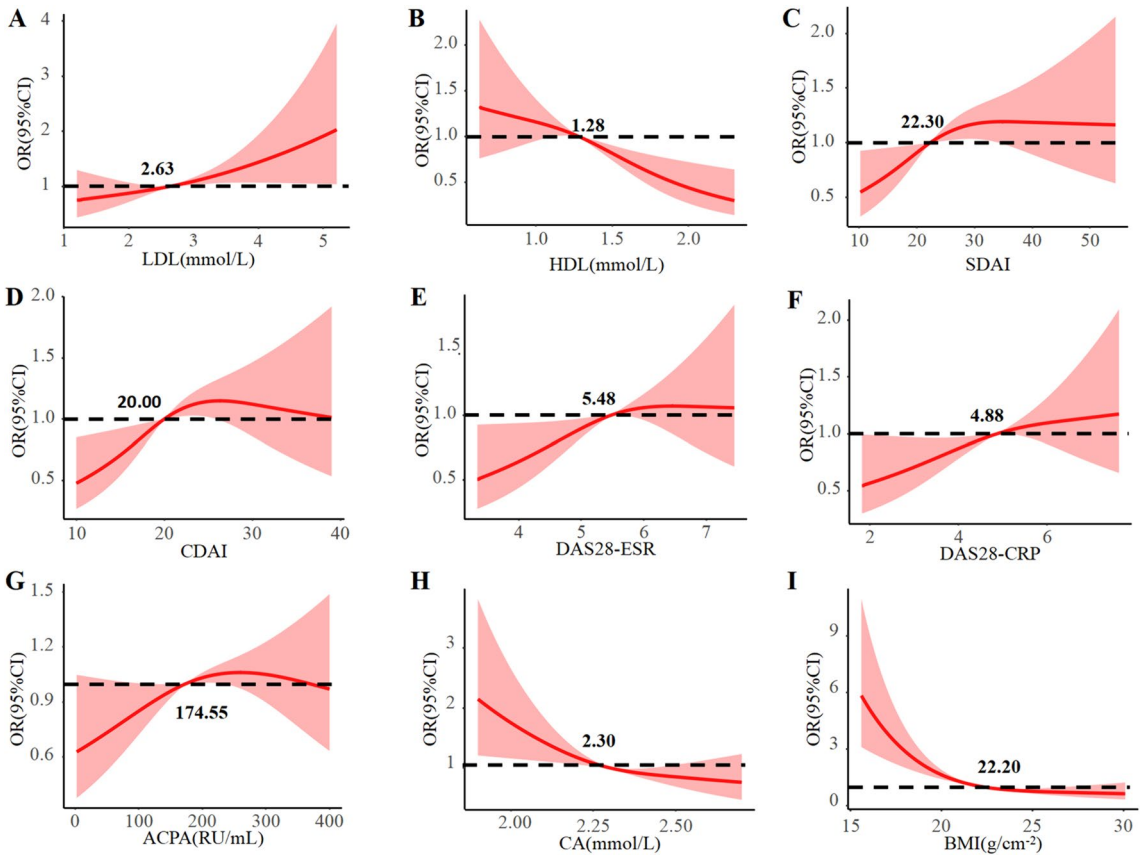

Fig. 3 RCS fitting effect of independent variables and OP risk. *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *DAS28* Disease Activity Score of 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ACPA* anti-citrullinated protein antibodies, *CA* calcium, *BMI* body mass index. **A**: RCS of LDL, **B**: RCS of HLD, **C**: RCSof SDAI, **D**: RCS of CDAI, **E**: RCS of DAS28-ESR, **F**: RCS of DAS28-CRP, **G**: RCS of ACPA, **H**: RCS of CA, **I**: RCSof BMI

RA–non-OP groups. Consistent with prior reports, low body weight, reduced CA levels, and both high and low ACPA levels were also implicated as OP risk factors. As is well known, GC is a risk factor for OP [30]. In our retrospective study, due to the late start of treatment for rheumatic immune disease in different regions and differences in patient education levels, we were unable to collect specific usage and cumulative amounts of GC. Therefore, we could only evaluate whether to use GC for ≥ 3 months in both groups of patients to further reduce the impact of confounding factors. The evaluation of vitamin D was also consistent.

In our study, the RCS analysis confirmed that LDL, CDAI, SDAI, DAS28 CRP, DAS28 ESR, and ACPA exhibited a positive linear correlation with RA–OP, whereas HDL demonstrated a negative linear relationship. This aligns with our preliminary findings, indicating a specific range of risk for RA–OP associated with each variable. However, in our research, subgroup analysis of hyperlipidemia disclosed no risk association between hyperlipidemia and osteoporosis.

The interrelation between dyslipidemia, OP, and RA has been a focal point of research. A notable correlation was identified between decreased serum HDL, increased LDL, and the extent of the inflammatory response in RA patients. A decline in HDL levels, often accompanied by reduced ApoA1 production, might impede cholesterol efflux from macrophages, culminating in macrophage aggregation and an intensified inflammatory response. Inflammation-induced alterations in HDL reduce its participation in reverse cholesterol transport and impair its protective capacity against LDL oxidation, rendering LDL more prone to oxidation and instability. While these modifications might confer short-term benefits by enhancing cholesterol availability in peripheral cells for host defense and reparative functions, they could potentially exacerbate inflammation and accelerate bone deterioration over an extended period [31]. Consequently, the influence of inflammation on the structural and functional dynamics of HDL and LDL in RA warrants thorough consideration. Reports suggest a pivotal role of lipids in the interactions and various biological functions

Table 6 Comparison of HDL and LDL cutoff points between two groups

Variables	HDL ≤ 1.28 mmol/L	HDL > 1.28 mmol/L	P	LDL ≤ 2.63 mmol/L	LDL > 2.63 mmol/L	P
n	1362	1311	–	1331	1342	–
Sex (Man/Women)	307/1056	143/1167	< 0.001*	235/1095	216/1127	0.570*
Age, mean (std),years	60.3 (9.7)	60.7 (9.3)	0.822#	60.4 (10.1)	60.5 (8.8)	0.089#
BMI ($kg{\cdot}m^{-2}$), mean (std)	22.2 (3.5)	22.3 (3.5)	0.472†	22.0 (3.5)	22.6 (3.4)	0.019†
Disease duration (months)	87.8 (94.5)	101.8 (105.5)	0.023#	95.1 (98.3)	94.2 (102.2)	0.621#
RF (U/L/), mean (std)	114.0 (103.0)	103.9 (95.4)	0.241#	107.0 (99.30	111.1 (99.7)	0.635#
ACPA(RU/mL), mean (std)	224.1 (162.7)	193.3 (165.6)	0.008#	211.0 (162.6)	207.0 (167.1)	0.452#
SDAI, mean (std)	27.0 (10.8)	23.0 (9.6)	< 0.001#	25.5 (10.8)	24.5 (10.0)	0.165#
CDAI, mean (std)	22.6 (7.1)	19.9 (5.9)	< 0.001#	21.4 (6.7)	21.1 (6.6)	0.307#
DAS28 ESR, mean (std)	5.7 (1.1)	5.2 (1.0)	< 0.001#	5.5 (1.1)	5.4 (1.0)	0.202#
DAS28 CRP, mean (std)	5.1 (1.4)	4.4 (1.4)	< 0.001#	4.9 (1.4)	4.6 (1.5)	0.059#
BMD(g/cm^{-2})						
Lumbar spine	−1.6 (1.5)	−1.5 (1.4)	0.079#	−1.4 (1.5)	−1.7 (1.4)	0.010#
Left hip/femoral neck	−1.5 (1.2)	−1.4 (1.2)	0.091#	−1.4 (1.2)	−1.5 (1.2)	0.089#
Right hip/femoral neck	−1.5 (1.2)	−1.4 (1.1)	0.205#	−1.3 (1.2)	−1.6 (1.2)	0.024#

BMI body mass index, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibodies, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *DAS28* Disease Activity Score of 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *BMD* bone mineral density

* Chi-square test was used for analysis of enumeration data

Mann–Whitney *U* test was used for analysis of data

† the independent-samples *t* test was used for analysis of data

of plant extracellular vesicles (PEVs). PEVs are known to regulate T cell homeostasis, potentially decelerating RA progression. The potential of PEVs as a mediator between lipids and RA merits further exploration [32]. In addition, research indicates that mesenchymal stem cell-derived extracellular vesicles, shielded by lipid biomolecules, can maintain a dynamic equilibrium between osteoclasts, osteoblasts, and osteocytes in OP, thereby reducing bone loss [33]. In the context of RA, these vesicles can curb bone erosion and destruction, underlining the critical role of lipids in these biological functions [34]. The RANKL/RANK/OPG signaling pathway is pivotal in bone metabolism regulation and a key target in OP therapy. Research on the novel glycopeptide OM-2 for RA–OP treatment revealed its potential to modulate the RANKL/RANK/OPG pathway and inhibit osteoclast activation, suggesting a strategic approach for RA–OP management [35]. Animal studies have demonstrated that the lipid-lowering drug atorvastatin can attenuate bone loss, reduce inflammatory responses, decrease RANK/RANKL, and elevate OPG levels, highlighting the significant role of lipid metabolism in bone health [36]. Regarding RA–OP treatment, beyond conventional anti-osteoporosis medications and immunosuppressants, natural remedies emerge as a promising alternative, there have been reports on natural products that can improve lipid metabolism and OP [37]. Although natural drugs have shown efficacy in treating RA or OP individually, research on their effectiveness in managing RA–OP is scant, pointing to a potential direction for future investigations.

RA has been acknowledged as a risk factor for OP [4], as have disturbances in lipid metabolism [16]. The primary pathological transformation in RA involves synovitis, with periarticular cortical bone loss due to synovitis possibly serving as an early OP trigger in RA. HDL primarily influences OP by altering mesenchymal intervention functions and activating metabolic pathways in osteoclasts [38]. Our study not only found that low HDL levels may be a risk factor for the occurrence of OP, but also noted that patients with reduced HDL had increased inflammation levels, suggesting that low HDL-mediated inflammatory responses might further contribute to OP. In addition, LDL can enhance osteoclast survival by impeding apoptosis, thereby increasing the likelihood of OP [39, 40]. Hence, vigilance is required for OP onset when HDL < 1.28 mmol/L or LDL > 2.63 mmol/L in patients with RA. Moreover, lipids might influence vitamin D availability, often linked with vitamin D deficiency in RA patients, potentially contributing to OP development [41].

Our retrospective clinical analysis identified potential indicators for predicting OP in patients with RA, offering a convenient marker for OP prevention. However, our study has its limitations. First, being a single-center study with a relatively small sample size, it may not reflect

the full spectrum of levels. Second, we can't assert that all OP cases are directly tied to RA. In addition, despite conducting interaction studies and finding no significant interactions, it's recognized that gender, age, BMI, glucocorticoid usage, among other factors, can influence OP occurrence. Furthermore, multiple factors may interact, potentially skewing the results. Then, our samples all come from the same race, and the research results may not be applicable to studies of other races. Finally, lipid levels are significantly diet-dependent, and due to the retrospective nature of our study, we can't ensure that all patients were assessed in a fasted state.

Conclusion

In conclusion, our research established notable associations between HDL, LDL, and the incidence of RA–OP, presenting them as potential markers for OP occurrence in patients with RA.

Author contributions

Z.J drafted the manuscript, and X.Y performed the statistical analysis. All authors participated in the design of study and the analysis and/or interpretation of data. All authors have read and approved this final version of the manuscript for submission.

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Availability of data and materials

The data are sourced from The Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine. Due to the need for further data analysis and reuse by the data committee, other data analyses are being conducted. The data that support the findings of this study are available on request from the corresponding author F, T, on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (KYW2022020) and exempted from signing patient informed consent forms.

Competing interests

The authors declare no competing interests.

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