

Association of RC/HDL-C Ratio with Osteoporosis in Elderly Chinese Patients with MAFLD and Its Precursor States: A Cross-Sectional Study

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1 **Original article**

2 **TITLE:** Association of RC/HDL-C Ratio with Osteoporosis in Elderly Chinese Patients with
3 MAFLD and Its Precursor States: A Cross-Sectional Study

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#Abstract

Background The association between the remnant cholesterol to high-density lipoprotein cholesterol ratio (RC/HDL-C) and osteoporosis in elderly patients with metabolic dysfunction-associated fatty liver disease (MAFLD) remains unclear, particularly across different metabolic subtypes. This study aimed to investigate the relationship between RC/HDL-C ratio and osteoporosis in elderly Chinese individuals with MAFLD and its precursor states.

Methods This cross-sectional study included 71,140 elderly individuals (aged ≥ 65 years) with fatty liver disease from the Zhangjiagang National Health Information Platform (2024). Participants were categorized into four groups according to metabolic status: pre-MAFLD (simple hepatic steatosis, $n=10,814$), overweight/obese MAFLD (OW-MAFLD, $n=29,210$), lean MAFLD (Lean-MAFLD, $n=10,521$), and diabetic MAFLD (DM-MAFLD, $n=20,595$). Binary logistic regression with four stepwise-adjusted models was used to evaluate the association between RC/HDL-C ratio and osteoporosis. Restricted cubic spline (RCS) regression was performed to explore the dose-response relationship. Subgroup analyses and interaction tests were conducted to identify potential effect modifiers.

Results Multivariable analysis showed that RC/HDL-C ratio was significantly and negatively associated with osteoporosis across all four subgroups (all $P < 0.001$). In the fully adjusted model, the strongest protective effect was observed in the OW-MAFLD group (OR = 0.664, 95% CI: 0.615–0.716), while the weakest effect was found in the DM-MAFLD group (OR = 0.788, 95% CI: 0.731–0.851). RCS analysis revealed a significant non-linear inverted U-shaped relationship between RC/HDL-C ratio and osteoporosis in all subgroups (all P for non-linearity < 0.001), with a protective threshold of approximately 0.4. Subgroup analyses showed that triglycerides modified the association in the pre-MAFLD, OW-MAFLD, and DM-MAFLD groups (P for interaction = 0.030, <0.001 , and <0.001 , respectively), with hypertriglyceridemia significantly attenuating the protective effect of RC/HDL-C ratio. Additionally, sex was identified as a significant effect modifier in the OW-MAFLD (P for interaction = 0.004) and DM-MAFLD (P for interaction = 0.008) groups, with a stronger protective effect observed in women than in men.

Conclusions RC/HDL-C ratio serves as an independent protective factor against osteoporosis in elderly Chinese individuals with fatty liver disease. The protective effect is already present in the early stage (simple hepatic steatosis) but is significantly weakened in the presence of type 2

diabetes mellitus. A non-linear inverted U-shaped dose–response relationship with a protective threshold (approximately 0.4) exists between RC/HDL-C ratio and osteoporosis. Hypertriglyceridemia significantly attenuates the protective effect of RC/HDL-C ratio and represents a key factor to be addressed in bone health management in this population.

Keywords Elderly; Metabolic dysfunction-associated fatty liver disease; RC/HDL-C ratio; Osteoporosis

#Introduction

Osteoporosis is a systemic metabolic bone disorder characterized by reduced bone mass and deterioration of bone microarchitecture, leading to increased bone fragility and a heightened risk of fractures[1].With the accelerating aging of the population, osteoporosis and its associated fragility fractures have become a global public health concern. According to the Global Burden of Disease Study, the global burden of hip fractures attributable to falls in older adults has continuously increased from 1990 to 2021 and is projected to continue rising through 2036[2].In China, osteoporosis prevalence rises significantly with age, especially in the elderly, making it a major chronic disease that impairs quality of life[3].

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a recently proposed concept whose diagnostic criteria emphasize the presence of hepatic steatosis together with at least one of the following: overweight/obesity, type 2 diabetes mellitus, or metabolic dysfunction[4, 5].This diagnostic framework highlights the central role of metabolic disturbances in the pathogenesis of fatty liver disease. As a multisystem disease, MAFLD is not only associated with cardiovascular disease, chronic kidney disease, and malignant tumors but has also been increasingly recognized to affect extrahepatic organs, including the skeletal system, through metabolic pathways[6, 7].In patients with MAFLD, hepatic steatosis is associated with significant changes in bone turnover markers, suggesting that MAFLD may affect bone metabolism through chronic low-grade inflammation[8].

Current evidence regarding the association between MAFLD and osteoporosis remains controversial. Some studies have found that patients with MAFLD have higher bone mineral density; This association was attenuated after adjusting for BMI, suggesting that obesity is a potential confounder[9]. In contrast, the degree of liver fibrosis is negatively correlated with bone mineral density[10], In patients with type 2 diabetes mellitus and MAFLD, high triglyceride levels

significantly enhanced this negative association[11], These conflicting findings suggest that the relationship between MAFLD and osteoporosis may be modified by multiple metabolic factors, and that analyzing the MAFLD population as a whole may obscure heterogeneity across subgroups.

Dyslipidemia is common in patients with MAFLD. Remnant cholesterol (RC), the cholesterol component of triglyceride-rich lipoproteins, has recently been confirmed to be closely associated with cardiovascular and metabolic diseases[12, 13], RC may impair bone metabolism by promoting inflammatory responses and oxidative stress[14]. In contrast, high-density lipoprotein cholesterol (HDL-C) exerts protective effects on bone metabolism through anti-inflammatory and antioxidant mechanisms[15, 16]. The RC/HDL-C ratio, as a novel metabolic risk indicator, integrates information on the imbalance between pro-atherogenic and anti-atherogenic lipid components and has been used to assess the risk of various metabolic diseases[17, 18]. Notably, under conditions of chronic inflammation and metabolic disease, HDL-C may undergo functional changes, shifting from an anti-inflammatory and antioxidant state to a pro-inflammatory and pro-oxidant state—a phenomenon known as "HDL-C dysfunction"[19].

Previous studies have explored the association between the RC/HDL-C ratio and BMD[20]. They were based on the general US adult population (aged 20~59 years), did not specifically target patients with MAFLD, and overlooked the heterogeneity among its subtypes. MAFLD is highly heterogeneous, and the metabolic characteristics and bone metabolism status of different subtypes may differ significantly. Furthermore, the bone metabolism characteristics of the precursor state of MAFLD—simple hepatic steatosis—remain unclear.

Therefore, this study aimed to investigate the association between the RC/HDL-C ratio and osteoporosis across different subgroups of elderly Chinese patients with MAFLD, compare the strength of this association across subgroups, and explore potential effect modifiers, thereby providing evidence-based support for bone health risk assessment and individualized intervention in patients with MAFLD.

#Methods

##Study Population

This study was a retrospective cross-sectional analysis based on data extracted from the

Zhangjiagang National Health Information Platform in China in 2024. Individuals aged ≥ 65 years registered on this platform between January 1, 2024 and December 31, 2024 were included. The exclusion criteria, adapted from previously published literature[21], were as follows: (1) liver fluke infection, liver cirrhosis, hepatocellular carcinoma, or hepatic space-occupying lesions; (2) malignant tumors; (3) history of tuberculosis; and (4) missing data. A total of 71,140 participants were ultimately included in the analysis. The study protocol was approved by the Ethics Committee of Zhangjiagang Center for Disease Control and Prevention, and the requirement for informed consent was waived.

##Data Collection and Definitions

Demographic and Anthropometric Measurements: Age, sex, height, weight, waist circumference, blood pressure, body mass index (BMI), platelet count, fasting plasma glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, blood urea nitrogen, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and heel bone mineral density (BMD) were extracted from the data platform.

The diagnosis and subclassification of MAFLD were performed according to the criteria established by Lim et al[22], MAFLD was defined as the presence of hepatic steatosis detected by ultrasound, together with at least one of the following criteria: (1) $\text{BMI} \geq 24 \text{ kg/m}^2$; (2) type 2 diabetes mellitus (based on medical history, use of glucose-lowering medications, or $\text{FPG} \geq 7.0 \text{ mmol/L}$); (3) evidence of metabolic dysregulation (at least two components). Based on these criteria, participants were classified into four groups: (1) individuals with ultrasound-detected hepatic steatosis but not fulfilling MAFLD criteria (pre-MAFLD group); (2) individuals with overweight/obesity ($\text{BMI} \geq 24 \text{ kg/m}^2$) without diabetes (overweight-MAFLD group); (3) individuals with normal weight or underweight ($\text{BMI} < 24 \text{ kg/m}^2$) without diabetes but with two or more metabolic risk abnormalities (lean/non-overweight MAFLD group); and (4) individuals with diabetes (diabetic MAFLD group).

Definition of Metabolic Dysregulation

Metabolic dysregulation was defined as the presence of two or more of the following criteria:

- ① Waist circumference ($\geq 90 \text{ cm}$ in men or $\geq 85 \text{ cm}$ in women);
- ② Blood pressure (systolic blood pressure $\geq 140 \text{ mmHg}$ or diastolic blood pressure $\geq 90 \text{ mmHg}$, or

receiving antihypertensive treatment);

③ Triglycerides ≥ 1.70 mmol/L or receiving treatment;

④ Low-density lipoprotein cholesterol (LDL-C) ≥ 4.1 mmol/L;

⑤ Reduced high-density lipoprotein cholesterol (HDL-C) (< 1.0 mmol/L in men or < 1.3 mmol/L in women) or receiving treatment; and

⑥ Total cholesterol ≥ 6.2 mmol/L.

Definition of Osteoporosis

Osteoporosis was defined as a heel bone mineral density T-score of ≤ -2.5 [23].

##Statistical Analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test, combined with skewness and kurtosis. All continuous variables were not normally distributed (all $P < 0.001$, Shapiro-Wilk test) and were therefore presented as medians with interquartile ranges (IQR).

Categorical variables were presented as frequencies (percentages). Comparisons of baseline characteristics among the four groups were performed using the Kruskal–Wallis H test for continuous variables and the chi-square (χ^2) test for categorical variables. All tests were two-tailed, and a P value < 0.05 was considered statistically significant. Univariate binary logistic regression analysis was conducted to evaluate the association of each variable with osteoporosis.

Multivariable binary logistic regression models were then constructed to assess the independent association between the RC/HDL-C ratio and osteoporosis. For sensitivity analysis, multiple linear

regression analysis was performed with bone mineral density (BMD) treated as a continuous outcome variable, adjusting for the same covariates as those in Model 4 of the primary

analysis. Restricted cubic spline (RCS) regression and subgroup analyses were performed using R software (version 4.5.1), with adjustment for the same sets of covariates as in Model 4. The

likelihood ratio test was used to compare the goodness-of-fit between linear and non-linear models, and non-linearity was considered significant at P for non-linearity < 0.05 . Threshold or inflection

points were identified based on the RCS curve. For subgroup analyses, multivariable logistic regression models (adjusted for the same covariates as in Model 4) were used to calculate the odds

ratios (ORs) and 95% confidence intervals (CIs) for the association between the RC/HDL-C ratio and osteoporosis. Interaction terms (RC/HDL-C $\times$ stratifying variable) were introduced to

calculate P values for interaction, and P for interaction < 0.05 was considered to indicate

significant effect modification.

#Results

##Baseline Characteristics of the Four Subgroups

A total of 71,140 participants were included in this study. According to their metabolic status, they were divided into four groups: the pre-MAFLD group (n = 10,814), the OW-MAFLD group (n = 29,210), the Lean-MAFLD group (n = 10,521), and the DM-MAFLD group (n = 20,595). The baseline characteristics of the four groups are shown in Table 1. Regarding demographic characteristics, the median age was 71 years across all four subgroups, and the proportion of females was predominant in all groups. Statistically significant differences were observed among the four groups in BMI, waist circumference, blood pressure, fasting plasma glucose (FPG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, blood urea nitrogen, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), high-density lipoprotein cholesterol (HDL-C), remnant cholesterol (RC) levels, RC/HDL-C ratio, bone mineral density T-score, and the prevalence of osteoporosis, with all $P < 0.05$. Osteoporosis prevalence chi-square test: $\chi^2 = 20.010$, $df = 3$, $P < 0.001$

##Correlation between RC/HDL-C Ratio and BMD in the Four Subgroups

Since the diagnosis of osteoporosis is directly based on bone mineral density T-score ($T \leq -2.5$), Spearman correlation analysis was first performed to preliminarily assess the association between the RC/HDL-C ratio and BMD. As all continuous variables deviated from a normal distribution, the Spearman rank correlation coefficient was used for analysis. The results are shown in Table 2. In all four subgroups, the RC/HDL-C ratio was significantly and positively correlated with BMD (all $P < 0.001$). Among them, the correlation coefficient was highest in the OW-MAFLD group ($\rho = 0.101$, 95% CI: 0.089–0.113) and lowest in the DM-MAFLD group ($\rho = 0.064$, 95% CI: 0.050–0.078), indicating that a higher RC/HDL-C ratio was associated with higher BMD.

##Univariate Logistic Regression Analysis of Factors Associated with Osteoporosis in the Four Subgroups

The associations of various factors with osteoporosis risk differed across the four subgroups, with some factors showing consistent trends. Age, systolic blood pressure, platelet count, and HDL-C were consistently and significantly positively associated with osteoporosis risk in all four

subgroups (all $P < 0.05$). In contrast, male sex, remnant cholesterol, and the RC/HDL-C ratio were consistently and significantly negatively associated with osteoporosis risk across all four subgroups (all $P < 0.05$). Non-HDL-C showed a significant negative association in the pre-MAFLD, OW-MAFLD, and Lean-MAFLD groups, but not in the DM-MAFLD group. Triglycerides were significantly negatively associated with osteoporosis only in the OW-MAFLD group. Diastolic blood pressure showed a significant negative association in the OW-MAFLD and DM-MAFLD groups but was not significant in the pre-MAFLD or Lean-MAFLD groups. ALT was significantly negatively associated with osteoporosis in the OW-MAFLD and DM-MAFLD groups. Total bilirubin was also significantly negatively associated in these two groups. No significant associations with osteoporosis risk were observed for waist circumference, AST, creatinine, blood urea nitrogen, total cholesterol, or LDL-C in any of the four subgroups (all $P > 0.05$). For a complete list of all variables and their estimates, please refer to Table 3.

##Association Between the RC/HDL-C Ratio and Osteoporosis

Based on the results of univariate analyses, four multivariable logistic regression models were constructed to investigate the association between the RC/HDL-C ratio and osteoporosis in each of the four subgroups. All results are presented in Table 4.

In the pre-MAFLD group, the RC/HDL-C ratio was significantly and negatively associated with osteoporosis across all four models, with the protective effect remaining stable after stepwise adjustment for confounding factors (all $P < 0.001$). In the OW-MAFLD group, a consistently significant negative association was observed across all models, and this subgroup exhibited the strongest protective effect among the four groups (OR range across models: 0.663–0.673, all $P < 0.001$). In the Lean-MAFLD group, the protective effect of the RC/HDL-C ratio was similar to that observed in the pre-MAFLD group, with significant negative associations consistently observed across all models (OR range: 0.702–0.727, all $P < 0.001$). In the DM-MAFLD group, the RC/HDL-C ratio was also significantly and negatively associated with osteoporosis across all models; however, this subgroup exhibited the weakest protective effect among the four groups (OR range: 0.788–0.797, all $P < 0.001$).

Across all four subgroups, the RC/HDL-C ratio was significantly and negatively associated with osteoporosis, with each one-unit increase in the RC/HDL-C ratio corresponding to a risk reduction ranging from approximately 21% in the DM-MAFLD group to 34% in the OW-MAFLD group.

This association remained stable after stepwise adjustment for age, sex, blood pressure, platelet count, liver function, and other confounding factors, indicating that the RC/HDL-C ratio is an independent protective factor against osteoporosis in the elderly population with fatty liver disease.

##Sensitivity Analysis

To validate the robustness of the above findings, osteoporosis as a binary outcome was replaced with bone mineral density (BMD) as a continuous variable (T-score). Multiple linear regression analysis was performed, adjusting for the same covariates as those in Model 4 of the primary analysis, to reassess the association between the RC/HDL-C ratio and BMD. The results showed a significant positive association between the RC/HDL-C ratio and BMD in all four subgroups: pre-MAFLD group ($\beta = 0.223$, 95% CI: 0.159–0.286, $P < 0.001$), OW-MAFLD group ($\beta = 0.217$, 95% CI: 0.176–0.257, $P < 0.001$), Lean-MAFLD group ($\beta = 0.221$, 95% CI: 0.158–0.285, $P < 0.001$), and DM-MAFLD group ($\beta = 0.142$, 95% CI: 0.100–0.184, $P < 0.001$). These findings indicate that a higher RC/HDL-C ratio is associated with higher BMD, which is directionally consistent with the primary analysis showing that a higher RC/HDL-C ratio reduces the risk of osteoporosis. All results are presented in Table 5.

##Restricted Cubic Spline (RCS) Analysis

To further explore whether a non-linear relationship exists between the RC/HDL-C ratio and osteoporosis, restricted cubic spline (RCS) regression analysis was performed to evaluate the dose–response relationship in each of the four subgroups. The models were adjusted for the same covariates as those in Model 4 of the primary analysis. In all four subgroups, an inverted U-shaped curve was observed, indicating a significant non-linear relationship between the RC/HDL-C ratio and the risk of osteoporosis (all P for non-linearity < 0.001). Three distinct phases were observed: (1) a sharp increase in osteoporosis risk when the RC/HDL-C ratio was below approximately 0.25; (2) a sharp decrease in osteoporosis risk when the RC/HDL-C ratio ranged between approximately 0.25 and 0.4; and (3) a gradual decline in osteoporosis risk when the RC/HDL-C ratio exceeded approximately 0.4. The osteoporosis risk showed a turning point of sharp increase followed by sharp decrease when the odds ratio (OR) was below 1, and a gradual decline when the OR was above 1. This inverted U-shaped curve suggests the presence of a threshold or saturation effect between the RC/HDL-C ratio and the risk of osteoporosis, highlighting the clinical value of the

RC/HDL-C ratio as a biomarker for osteoporosis risk assessment in the elderly population with fatty liver disease. All results are presented in Figure 1.

##Subgroup Analysis Results

Subgroup analyses and interaction tests were performed to evaluate the potential modifying effects of various factors on the association between the RC/HDL-C ratio and osteoporosis. The results are summarized in Figure 2. Effect modification by triglycerides: Triglycerides significantly modified the protective effect of the RC/HDL-C ratio in the pre-MAFLD, OW-MAFLD, and DM-MAFLD groups (P for interaction = 0.030, <0.001, and <0.001, respectively). In all three subgroups, the protective effect of the RC/HDL-C ratio was markedly stronger in individuals with low triglyceride levels (< 1.7 mmol/L) than in those with high triglyceride levels ($\geq$ 1.7 mmol/L). For example, in the OW-MAFLD group, the OR for the RC/HDL-C ratio was 0.420 (95% CI: 0.352–0.500) in the low triglyceride subgroup compared with 0.722 (95% CI: 0.658–0.792) in the high triglyceride subgroup. No significant effect modification by triglycerides was observed in the Lean-MAFLD group (P for interaction = 0.067). Effect modification by sex: Sex significantly modified the association in the OW-MAFLD and DM-MAFLD groups (P for interaction = 0.004 and 0.008, respectively). In both subgroups, the protective effect of the RC/HDL-C ratio was stronger in women than in men. For instance, in the OW-MAFLD group, the OR was 0.616 (95% CI: 0.559–0.680) for women and 0.729 (95% CI: 0.648–0.821) for men. No significant effect modification was observed for age, systolic blood pressure, diastolic blood pressure, waist circumference, total bilirubin, or platelet count in any of the four subgroups (all P for interaction > 0.05).

#Discussion

This study is the first to systematically investigate the association between the RC/HDL-C ratio and osteoporosis across different metabolic phenotypes in an elderly Chinese population with MAFLD and its precursor states. Correlation analysis revealed a significant positive association between the RC/HDL-C ratio and bone mineral density, providing preliminary evidence for the relationship between this ratio and osteoporosis. Multivariable analysis further confirmed that the RC/HDL-C ratio was significantly and negatively associated with osteoporosis in all subgroups, serving as an independent protective factor. The strongest protective effect was observed in the OW-MAFLD group, while the weakest was observed in the DM-MAFLD group. A non-linear

inverted U-shaped dose–response relationship with a threshold effect was identified between the RC/HDL-C ratio and osteoporosis. Triglycerides significantly modified the association in the pre-MAFLD, OW-MAFLD, and DM-MAFLD groups, with hypertriglyceridemia substantially attenuating the protective effect of the RC/HDL-C ratio. Sex also showed a significant modifying effect in the OW-MAFLD and DM-MAFLD groups. These findings expand the current understanding of the role of lipid metabolism in bone health in the elderly MAFLD population. Dyslipidemia plays an important role in bone health. Population-based studies have shown that low-density lipoprotein cholesterol (LDL-C) is negatively correlated with bone mineral density (BMD) [24], while high-density lipoprotein cholesterol (HDL-C) is positively correlated with BMD[25]. Our study found that the RC/HDL-C ratio, as a novel metabolic risk indicator, was negatively associated with osteoporosis. This suggests that a systemic metabolic disturbance of hepatic origin, rather than a direct effect, may mediate the impact of the RC/HDL-C ratio on bone metabolism. On the one hand, patients with MAFLD often present with hepatic lipid accumulation and chronic low-grade inflammation, leading to an increase in triglyceride-rich lipoprotein components such as remnant cholesterol (RC)[13]. As a hepatically derived pro-atherogenic particle, RC can promote macrophage activation and oxidative stress by activating inflammatory pathways such as TLR4/NF- κ B, thereby impairing osteoblast function and enhancing osteoclast activity[14]. In contrast, HDL-C exerts protective effects on bone metabolism through its anti-inflammatory, antioxidant, and reverse cholesterol transport functions[15, 16]. In the chronic inflammatory microenvironment of MAFLD, HDL-C undergoes functional remodeling, shifting from an anti-inflammatory to a pro-inflammatory state and thereby losing its normal bone-protective effects. Consequently, the RC/HDL-C ratio amplifies the imbalance between the "hepatic-derived detrimental signal" of RC and the "functional inactivation" of HDL-C[19], thus, the RC/HDL-C ratio provides a more comprehensive assessment of lipid-related bone risk than individual lipid parameters alone. In this study, HDL-C alone was positively associated with osteoporosis (OR = 1.30–1.53), directly supporting the "MAFLD-related HDL-C dysfunction" hypothesis, which is consistent with previous findings in chronic inflammatory states. Our findings differ from those of Qiu et al.[20], who reported a negative association between the RC/HDL-C ratio and bone mineral density (β = -0.019) based on the NHANES database, whereas the present study found a negative association between the RC/HDL-C ratio and osteoporosis.

This discrepancy likely stems from fundamental differences in study populations. Qiu et al. included a general adult population in the United States (aged 20–59 years), while our study focused on an elderly Chinese population with fatty liver disease (aged ≥ 65 years). In the elderly population, a lower RC/HDL-C ratio may reflect malnutrition or a chronic wasting state, which is paradoxically associated with decreased bone mineral density, thereby leading to an opposite direction of association. In addition, differences in ethnicity and metabolic status may also explain this discrepancy[7, 26].

The protective effect of the RC/HDL-C ratio was highly consistent across the pre-MAFLD, OW-MAFLD, and Lean-MAFLD groups. This finding suggests that the bone-protective effect of the RC/HDL-C ratio does not strengthen with increasing severity of metabolic disturbances in MAFLD, but rather becomes fully established at a very early stage of fatty liver disease, specifically during the period of simple hepatic steatosis. The strongest protective effect observed in the OW-MAFLD group may be attributed to the impact of overweight/obesity itself on bone mineral density, as increased body weight stimulates bone formation through mechanical loading, thereby increasing BMD[26]. The protective effect was weakest in the DM-MAFLD group. Diabetes itself is a risk factor for osteoporosis, as hyperglycemia can lead to glycation of bone matrix proteins, impairment of osteoblast function, and imbalance in bone turnover[27]. Under diabetic conditions, the protective effect of the RC/HDL-C ratio may be counteracted by diabetes-related bone metabolic disorders. Furthermore, patients with diabetes often present with enhanced chronic inflammation and oxidative stress, which may attenuate the protective effect of the RC/HDL-C ratio on bone metabolism[28].

RCS analysis revealed a significant non-linear inverted U-shaped relationship between the RC/HDL-C ratio and the risk of osteoporosis in all four subgroups. A very low RC/HDL-C ratio may indicate malnutrition or reduced metabolic function, which paradoxically correlates with an increased risk of osteoporosis. The protective effect of the RC/HDL-C ratio emerged rapidly within the range of approximately 0.25 to 0.4, suggesting the presence of a protective threshold. When the RC/HDL-C ratio exceeded approximately 0.4, the protective effect plateaued, indicating a saturation effect. This finding is consistent with previous studies reporting non-linear relationships between lipid profiles and bone mineral density[29]. This threshold effect suggests that maintaining the RC/HDL-C ratio above approximately 0.4 may provide the greatest

bone-protective benefit, offering a potential lipid control target for bone health management in patients with MAFLD.

Triglycerides were the most significant effect modifier among the three subgroups. The protective effect of the RC/HDL-C ratio was significantly stronger in the low triglyceride group (< 1.7 mmol/L) than in the high triglyceride group (≥ 1.7 mmol/L). In the OW-MAFLD group, the OR for the RC/HDL-C ratio was 0.420 in the low TG group compared with 0.722 in the high TG group, indicating that hypertriglyceridemia attenuated the protective effect by approximately 42%. Hypertriglyceridemia is not only a marker of energy metabolic disturbance but also reflects an excessive burden of hepatic lipid metabolism in patients with MAFLD. In the context of liver–bone axis regulation[30], hypertriglyceridemia may indirectly inhibit osteoblast differentiation and promote osteoclast formation by enhancing hepatic oxidative stress and releasing pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α)[31]. In patients with MAFLD, hypertriglyceridemia is associated with more severe hepatic steatosis and fibrosis, which in turn are linked to decreased bone mineral density[10, 11], thus, by exacerbating hepatic metabolic burden and systemic inflammation, hypertriglyceridemia acts as a key driver of MAFLD-related osteoporosis progression.

Sex significantly modified the association between the RC/HDL-C ratio and osteoporosis in the OW-MAFLD and DM-MAFLD groups, with a stronger protective effect observed in women than in men. Estrogen regulates lipoprotein metabolism by activating estrogen receptor alpha (ER α) and estrogen receptor beta (ER β): on the one hand, it promotes HDL-C synthesis and reverse cholesterol transport; on the other hand, it reduces triglyceride and low-density lipoprotein cholesterol levels[32], in women, the RC/HDL-C ratio may more sensitively reflect the metabolic disturbances induced by declining estrogen levels, thereby serving as a more effective biomarker for bone health risk. Furthermore, estrogen may enhance the anti-inflammatory and antioxidant functions of HDL-C, a key component of the RC/HDL-C ratio, thereby amplifying the overall protective effect of the ratio[10]. Sex chromosomes themselves may also independently influence lipid metabolism and bone metabolism. The X chromosome carries multiple genes related to lipid metabolism and bone metabolism, including the gene for hydroxymethylglutaryl-CoA reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis, and the vitamin D receptor (VDR) gene, among others[33, 34], women have two X chromosomes, whereas men have only one. This

dosage difference may confer a potential genetic advantage to women in the regulation of both lipid metabolism and bone metabolism. In this study, sex showed a modifying effect only in the subgroups with more severe metabolic disturbances, suggesting that metabolic status may influence the modulation of the RC/HDL-C ratio effect by sex.

The findings of this study have important clinical implications. (1) The RC/HDL-C ratio may serve as an auxiliary tool for bone health screening. (2) Maintaining the RC/HDL-C ratio above 0.4 may yield the maximum bone-protective benefit. (3) Patients with hypertriglyceridemia require more proactive bone health management strategies. (4) Bone health management should be individualized according to different MAFLD subtypes.

This study has several strengths. (1) The large sample size provides sufficient statistical power and robust results. (2) This is the first study to classify MAFLD-related populations into four subgroups according to metabolic status and to systematically compare the association between the RC/HDL-C ratio and osteoporosis across these subgroups. (3) Restricted cubic spline (RCS) analysis was employed to explore the dose–response relationship and to identify a protective threshold. This study also has several limitations. (1) The cross-sectional study design precludes the establishment of causal relationships. The direction of the association between the RC/HDL-C ratio and osteoporosis needs to be validated by prospective cohort studies. (2) This study did not collect information on the use of lipid-lowering agents (statins, fibrates) or anti-osteoporotic medications, and therefore cannot exclude their potential impact on the results. (3) This study did not assess important factors that may influence bone metabolism, such as bone turnover markers (e.g., osteocalcin, β -CTX), vitamin D levels, calcium intake, or physical activity. (4) The study population consisted of elderly Chinese individuals with fatty liver disease; whether these findings are generalizable to other ethnicities, age groups, or populations without fatty liver disease remains to be validated.

This study is the first to demonstrate that the RC/HDL-C ratio is significantly and negatively associated with osteoporosis in an elderly Chinese population with fatty liver disease, serving as an independent protective factor against osteoporosis in this population. The protective effect varied across different MAFLD subgroups. A non-linear inverted U-shaped dose–response relationship with a protective threshold (approximately 0.4) was identified between the RC/HDL-C ratio and osteoporosis. Hypertriglyceridemia significantly attenuated the protective

effect of the RC/HDL-C ratio. Future research should focus on conducting prospective cohort studies to validate the causal relationship between the RC/HDL-C ratio and osteoporosis, as well as the clinical significance of the identified protective threshold.

Authors' contributions

X. Jiang and Z. Li contributed to the conception and design of the study. L. Li, Y. Dai, H. Chen, X. Wang, J. Qian, and M. Wu contributed to data collection and analysis. X. Jiang and Z. Li contributed to data interpretation and manuscript writing. All authors reviewed and approved the final version of the manuscript.

Data availability statement

The data that support the findings of this study are available from the Zhangjiagang National Health Information Platform, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the corresponding author upon reasonable request and with permission of the Zhangjiagang Center for Disease Control and Prevention.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the Ethics Committee of the Zhangjiagang Center for Disease Control and Prevention.

Informed consent Informed consent was waived by the Ethics Committee of the Zhangjiagang Center for Disease Control and Prevention due to the retrospective nature of the study and the use of de-identified data.

Consent for publication All authors approved the publication of this manuscript.

Figure 1 Restricted cubic spline analysis of the association between RC/HDL-C ratio and osteoporosis risk by subgroup. RC/HDL-C, remnant cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; CI, confidence interval
Adjusted for the same covariates as in Model 4 of the primary analysis (covariates varied by subgroup). The solid red line represents the estimated odds ratio, and the shaded area represents the 95% confidence interval.

(A)Pre-MAFLD group; (B) OW-MAFLD group; (C) Lean-MAFLD group; (D) DM-MAFLD group.

Figure 2 Subgroup analyses examining the association between RC/HDL-C ratio and osteoporosis within each group

(A)Pre-MAFLD group; (B) OW-MAFLD group; (C) Lean-MAFLD group; (D) DM-MAFLD group.

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Table 1. Baseline characteristics of the study population by subgroup

Characteristic	Pre-MAFLD (n=10, 814)	OW-MAFLD (n=29, 210)	Lean-MAFLD (n=10, 521)	DM-MAFLD (n=20, 595)	<i>P</i>
Demographic characteristics					
Age (years), median (IQR)	71.0 (68.0–76.0)	71.0 (68.0–75.0)	71.0 (68.0–76.0)	71.0 (67.0–75.0)	<0.001
Male, n (%)	4,208 (38.9)	12,047 (41.2)	4,051 (38.5)	8,278 (40.2)	<0.001
Anthropometric measures					
BMI (kg/m ²), median (IQR)	22.77 (21.78–23.44)	26.60 (25.30–28.31)	22.77 (21.78–23.44)	25.64 (23.80–27.70)	<0.001
Waist circumference (cm), median (IQR)	80.0 (77.0–84.0)	88.0 (84.0–94.0)	80.0 (77.0–84.0)	87.0 (82.0–92.0)	<0.001
Blood pressure					
SBP (mmHg), median (IQR)	139.0 (128.0–151.0)	141.0 (130.0–154.0)	140.0 (128.0–152.0)	142.0 (131.0–155.0)	<0.001
DBP (mmHg), median (IQR)	80.0 (73.0–86.0)	81.0 (75.0–88.0)	80.0 (73.0–86.0)	80.0 (73.0–86.0)	<0.001
Laboratory measures					
Fasting glucose (mmol/L), median (IQR)	5.74 (5.37–6.15)	5.77 (5.39–6.20)	5.74 (5.37–6.15)	7.92 (7.18–9.25)	<0.001
ALT (U/L), median (IQR)	18.3 (14.0–25.0)	21.0 (16.0–28.7)	18.2 (14.0–25.0)	21.5 (16.0–30.5)	<0.001
AST (U/L), median (IQR)	23.3 (20.0–28.3)	24.0 (20.0–29.4)	23.2 (20.0–28.1)	23.0 (19.0–29.8)	<0.001

	)	)	)	)	
Total bilirubin (μ mol/L), median (IQR)	15.0 (11.7–19.5)	14.9 (11.8–19.1)	15.0 (11.7–19.4)	15.0 (11.8–19.4)	0.0 02
Creatinine (μ mol/L), median (IQR)	70.8 (61.0–83.0)	73.0 (62.0–86.0)	70.8 (61.0–83.0)	71.5 (60.0–85.5)	<0. 001
BUN (mmol/L), median (IQR)	5.74 (4.85–6.80)	5.80 (4.90–6.86)	5.75 (4.85–6.80)	6.00 (5.01–7.17)	<0. 001
Lipid profile					
Total cholesterol (mmol/L), median (IQR)	5.09 (4.39–5.79)	5.01 (4.30–5.70)	5.12 (4.44–5.82)	4.90 (4.12–5.68)	<0. 001
Triglyceride (mmol/L), median (IQR)	1.67 (1.19–2.39)	1.73 (1.26–2.42)	1.68 (1.21–2.40)	1.83 (1.31–2.65)	<0. 001
LDL-C (mmol/L), median (IQR)	2.87 (2.34–3.41)	2.88 (2.35–3.42)	2.90 (2.39–3.43)	2.74 (2.16–3.32)	<0. 001
HDL-C (mmol/L), median (IQR)	1.43 (1.20–1.68)	1.36 (1.17–1.58)	1.43 (1.20–1.68)	1.34 (1.14–1.57)	<0. 001
Non-HDL-C (mmol/L), median (IQR)	3.63 (3.00–4.25)	3.61 (3.00–4.24)	3.66 (3.06–4.27)	3.53 (2.83–4.23)	<0. 001
Remnant cholesterol (mmol/L), median (IQR)	0.67 (0.40–0.98)	0.64 (0.39–0.95)	0.67 (0.40–0.99)	0.68 (0.41–1.03)	<0. 001
RC/HDL-C ratio, median (IQR)	0.46 (0.27–0.73)	0.47 (0.27–0.73)	0.46 (0.27–0.74)	0.50 (0.29–0.81)	<0. 001
Bone mineral density					
BMD (T-score), median (IQR)	-1.50 (-2.40, -0.50)	-1.50 (-2.30, -0.40)	-1.50 (-2.40, -0.50)	-1.40 (-2.30, -0.40)	<0. 001
Osteoporosis, n (%)	2,458 (22.7)	6,340 (21.7)	2,379 (22.6)	4,299 (20.9)	< 0.0 01

Notes: Continuous variables are presented as median (interquartile range, IQR). P-values: Kruskal-Wallis H test for continuous variables, chi-square test for categorical variables.

Table 2. Spearman correlation between RC/HDL-C ratio and BMD across four subgroups

Subgroup	Spearman' s	95% CI	<i>P</i>
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	ρ		
Pre-MAFLD	0.073	(0.054, 0.092)	<0.001
OW-MAFLD	0.101	(0.089, 0.113)	<0.001
Lean-MAFLD	0.073	(0.054, 0.092)	<0.001
DM-MAFLD	0.064	(0.050, 0.078)	<0.001

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555 Table 3. Univariate logistic regression analysis of factors associated with osteoporosis by
556 subgroup

Variable (unit)	Pre-MAFLD group	P	OW-MAFLD group	P	Lean-MAFLD group	P	DM-MAFLD group	P
	OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Demographic and anthropometric measures								
Age (year)	1.052 (1.044, 1.060)	<0.01	1.059 (1.053, 1.065)	<0.01	1.052 (1.044, 1.060)	<0.01	1.052 (1.046, 1.058)	<0.01
Sex (male vs. female)	0.758 (0.690, 0.833)	<0.01	0.775 (0.732, 0.821)	<0.01	0.750 (0.681, 0.825)	<0.01	0.712 (0.664, 0.764)	<0.01
SBP (mmHg)	1.007 (1.005, 1.009)	<0.01	1.005 (1.003, 1.007)	<0.01	1.008 (1.006, 1.010)	<0.01	1.003 (1.001, 1.005)	0.00
DBP (mmHg)	0.996 (0.992, 1.000)	0.06	0.993 (0.991, 0.995)	<0.01	0.996 (0.992, 1.000)	0.08	0.994 (0.990, 0.998)	0.00
Waist circumference (cm)	1.006 (0.998, 1.014)	0.11	0.998 (0.994, 1.002)	0.34	1.005 (0.997, 1.013)	0.18	0.998 (0.994, 1.002)	0.23
Laboratory measures								
Platelet count ($\times 10^9/L$)	1.001 (1.000, 1.002)	0.04	1.001 (1.000, 1.002)	0.02	1.001 (1.000, 1.002)	0.04	1.001 (1.000, 1.002)	<0.01
ALT (U/L)	1.001 (0.999, 1.003)	0.70	0.998 (0.996, 1.000)	0.03	1.000 (0.996, 1.004)	0.99	0.997 (0.995, 0.999)	0.00
AST (U/L)	1.003 (1.000, 1.006)	0.09	0.999 (0.997, 1.001)	0.55	1.002 (0.998, 1.006)	0.17	0.999 (0.997, 1.001)	0.35
Total bilirubin	0.998	0.00	0.993	0.00	0.999	0.00	0.992	0.00

($\mu\text{mol/L}$)	(0.992, 1.004)	553	(0.989, 0.997)	001	(0.993, 1.005)	662	(0.986, 0.998)	002
Creatinine ($\mu\text{mol/L}$)	1.001 (0.999, 1.003)	020	1.001 (0.999, 1.003)	033	1.001 (0.999, 1.003)	017	1.001 (1.000, 1.002)	016
BUN (mmol/L)	1.017 (0.991, 1.044)	020	1.004 (0.987, 1.021)	066	1.020 (0.992, 1.048)	016	1.006 (0.989, 1.023)	048
Lipid profile								
Total cholesterol (mmol/L)	0.976 (0.935, 1.019)	026	0.994 (0.969, 1.020)	066	0.986 (0.943, 1.031)	054	1.016 (0.989, 1.044)	026
Triglyceride (mmol/L)	0.981 (0.951, 1.012)	024	0.963 (0.942, 0.984)	000	0.983 (0.953, 1.014)	028	1.003 (0.984, 1.022)	076
LDL-C (mmol/L)	0.994 (0.939, 1.052)	083	1.016 (0.983, 1.050)	036	1.009 (0.951, 1.070)	077	1.032 (0.993, 1.073)	010
HDL-C (mmol/L)	1.296 (1.148, 1.464)	<0.01	1.528 (1.405, 1.662)	<0.01	1.313 (1.160, 1.486)	<0.01	1.374 (1.243, 1.519)	<0.01
Non-HDL-C (mmol/L)	0.935 (0.892, 0.980)	000	0.946 (0.919, 0.974)	<0.01	0.942 (0.897, 0.990)	001	0.989 (0.958, 1.021)	048
Remnant cholesterol (mmol/L)	0.784 (0.712, 0.863)	<0.01	0.754 (0.710, 0.801)	<0.01	0.792 (0.719, 0.873)	<0.01	0.886 (0.832, 0.944)	<0.01
RC/HDL-C ratio	0.721 (0.642, 0.810)	<0.01	0.663 (0.615, 0.714)	<0.01	0.727 (0.647, 0.816)	<0.01	0.797 (0.739, 0.859)	<0.01

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558 Table 4. Multivariate logistic regression analysis of RC/HDL-C ratio and osteoporosis by subgroup

Subgroup	Model 1 (<i>OR</i> (95% CI))	<i>P</i>	Model 2 (<i>OR</i> (95% CI))	<i>P</i>	Model 3 (<i>OR</i> (95% CI))	<i>P</i>	Model 4 (<i>OR</i> (95% CI))	<i>P</i>
Pre-M AFLD	0.721 (0.643, 0.809)	<0.001	0.706 (0.628, 0.794)	<0.001	0.704 (0.626, 0.792)	<0.001	0.697 (0.619, 0.785)	<0.001
Lean-MAFLD	0.727 (0.647, 0.816)	<0.001	0.710 (0.631, 0.799)	<0.001	0.709 (0.630, 0.798)	<0.001	0.702 (0.623, 0.791)	<0.001
OW-MA FLD	0.663 (0.616, 0.714)	<0.001	0.669 (0.621, 0.722)	<0.001	0.673 (0.624, 0.725)	<0.001	0.664 (0.615, 0.716)	<0.001
DM-MA	0.797	<0.	0.794	<0.	0.796	<0.	0.788	<0.

FLD	(0.740, 0.001 0.859)	(0.736, 0.001 0.856)	(0.738, 0.001 0.858)	(0.731, 0.001 0.851)
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Notes: Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was further adjusted for SBP (Pre-MAFLD and Lean-MAFLD groups) or SBP and DBP (OW-MAFLD and DM-MAFLD groups). Model 4 was fully adjusted: Pre-MAFLD and Lean-MAFLD groups were further adjusted for platelet count; OW-MAFLD and DM-MAFLD groups were further adjusted for platelet count, ALT, and total bilirubin. Sex was coded with female as the reference group.*

Abbreviations: RC/HDL-C, remnant cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase.

Table 5. Sensitivity analysis: Linear regression of RC/HDL-C ratio and continuous BMD by subgroup

Subgroup	β (95% CI)	<i>P</i>
Pre-MAFLD	0.223 (0.159, 0.286)	<0.001
Lean-MAFLD	0.221 (0.158, 0.285)	<0.001
OW-MAFLD	0.217 (0.176, 0.257)	<0.001
DM-MAFLD	0.142 (0.100, 0.184)	<0.001

Figure 1

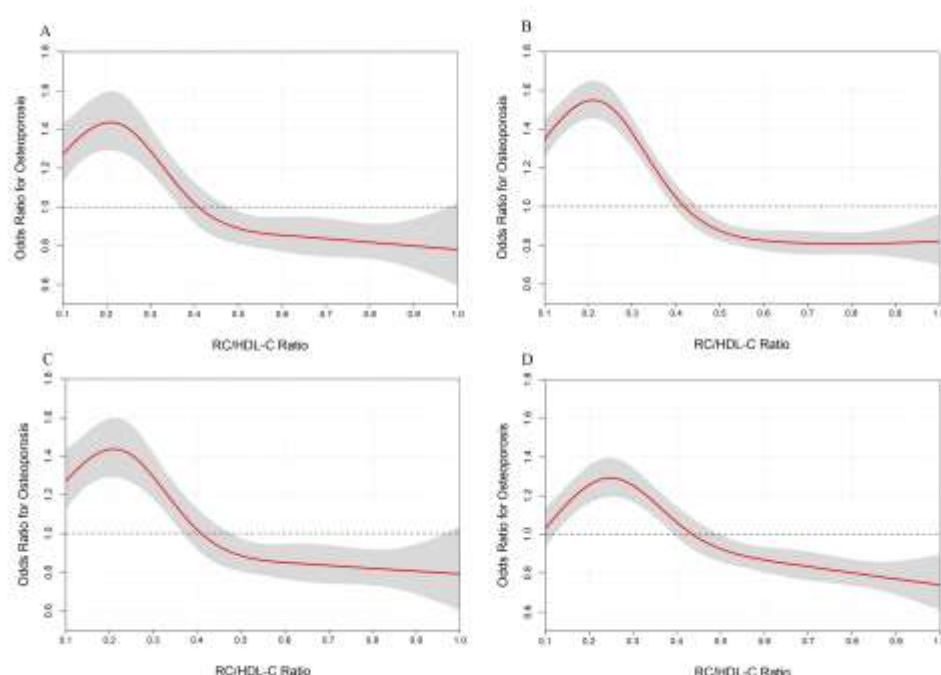


Figure 1 Restricted cubic spline analysis of the association between RC/HDL-C ratio and osteoporosis risk by subgroup. RC/HDL-C, remnant cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; CI, confidence interval

Adjusted for the same covariates as in Model 4 of the primary analysis (covariates varied by subgroup). The solid red line represents the estimated odds ratio, and the shaded area represents

the 95% confidence interval.
(A)Pre-MAFLD group; (B) OW-MAFLD group; (C) Lean-MAFLD group; (D) DM-MAFLD group.

Figure 2

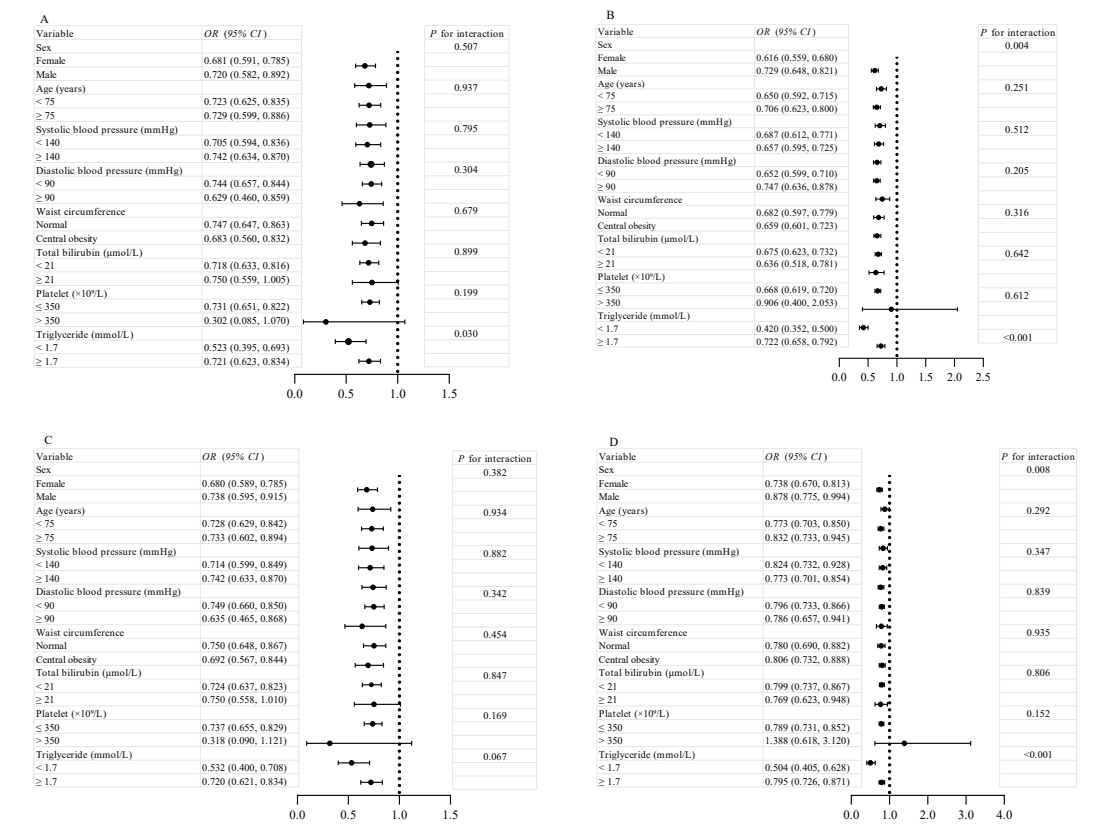


Figure 2 Subgroup analyses examining the association between RC/HDL-C ratio and

603 osteoporosis within each group
604 (A)Pre-MAFLD group; (B) OW-MAFLD group; (C) Lean-MAFLD group; (D) DM-MAFLD
605 group.
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