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RESEARCH ARTICLE

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Inflammatory and metabolic markers mediate the association of hepatic steatosis and fibrosis with 10-year ASCVD risk

Zihao Gui[a*], Xingying Chen[a*], Dongmei Wang[a*], Zhi Chen[a], Siyang Liu[a], Genfeng Yu[a], Yuqi Jiang[a], Hualin Duan[a], Daoyan Pan[b], Xu Lin[a], Lan Liu[a], Heng Wan[a] and Jie Shen[a]

[a]Department of Endocrinology and Metabolism, Shunde Hospital, Southern Medical University (The First People's Hospital of Shunde), Foshan, Guangdong, China; [b]Department of Endocrinology and Metabolism, The Third Affiliated Hospital of Southern Medical University, Guangzhou, People's Republic of China

ABSTRACT

Background and aims: Liver steatosis and fibrosis increase the predicted 10-year atherosclerotic cardiovascular disease (ASCVD) risk, though the roles of chronic inflammation and metabolic dysregulation remain unclear. This cross-sectional study quantitatively assesses this association and evaluates the mediating effects of metabolic dysregulation and chronic inflammation.

Methods: In this study, we enrolled 6110 adults from ten communities in Canton, China. Hepatic steatosis and fibrosis were assessed using vibration-controlled transient elastography (VCTE) through controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), while predicted 10-year ASCVD risk was calculated using the China-PAR project model. Associations between CAP/LSM values and predicted 10-year ASCVD risk were analyzed. Mediation analysis quantified the effects of high-sensitivity C-reactive protein (hs-CRP), homeostasis model assessment of insulin resistance (HOMA-IR), remnant cholesterol (RC), and non-high-density lipoprotein cholesterol (non-HDL-C). The main statistical methods used included logistic regression, restricted cubic splines (RCS) analysis, interaction calculations, and mediation analysis to examine the relationships and mediators.

Results: The study population had a mean age of 50.1 years (SD = 9.7), with 3927 females (64.3%) and 2183 males (35.7%). Additionally, 808 participants (13.2%) had type 2 diabetes, and 1911 participants (31.3%) had hypertension. Compared to the first CAP quartile (Q1), higher CAP quartiles showed increased odds ratios (OR) for predicted moderate to high 10-year ASCVD risk: 1.14 (0.89, 1.45), 1.37 (1.08, 1.73), and 2.44 (1.93, 3.10). Mediation analysis showed hs-CRP and HOMA-IR mediated CAP's link to ASCVD risk, with mediation proportions of 15.40% and 27.37%. RC and non-HDL-C mediated this association at 7.12% and 6.26%. Among patients with hepatic steatosis (CAP ≥ 248 dB/m), LSM Q4 participants had a significantly higher predicted 10-year ASCVD risk than those in LSM Q1 (OR 2.22, [1.52, 3.25]), with hs-CRP and HOMA-IR mediating 2.62% and 13.75%, respectively.

Conclusion: Liver steatosis and fibrosis were associated with the increased predicted ASCVD risk, with mediation effects from hs-CRP, HOMA-IR, RC, and non-HDL-C.

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAP: controlled attenuation parameters; CYP2E1: Cytochrome P450 2E1; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; HHD: hypertensive heart disease; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; hs-CRP: high-sensitivity C-reactive protein; IHD: ischemic heart disease; LSM: liver stiffness measurements; MAFLD: metabolic dysfunction-associated fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease; NAFLD: non-alcoholic fatty liver disease; PAI-1: plasminogen activator inhibitor-1; SBP: systolic blood pressure; sdLDL-C: small dense low-density lipoprotein cholesterol; sNOX2-dp: soluble NOX2-derived peptide; T2DM: Type 2 Diabetes; TC: total cholesterol; VCTE: vibration-controlled transient elastography; WC: waist circumference.

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CONTACT Jie Shen sjiesy@smu.edu.cn; Heng Wan wanhdr@163.com Institute and Department of Endocrinology and Metabolism, Shunde Hospital of Southern Medical University (The First People's Hospital of Shunde), No.1 of Jiazi Road, Lunjiao, Shunde District, Foshan City 528308, Guangdong Province, China
*These authors contributed equally to this work.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) imposes a tremendous burden on global healthcare systems, costing over $200 billion annually and claiming nearly 18 million lives each year [1]. Given its significant mortality and morbidity, accurate and early identification of individuals at risk is a critical step in ASCVD prevention. Currently known causes, such as age, sex, smoking, alcohol consumption, obesity, diabetes, and hypertension, do not fully explain ASCVD risk [2]. Metabolic dysfunction-associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD), characterized by SLD, is the most common cause of chronic liver disease worldwide, affecting approximately 30% of the global adult population. Although MASLD and ASCVD share some risk factors, numerous studies have found that steatotic liver disease (SLD) is associated with an increased risk of ASCVD [3].

The definition of MAFLD emphasizes high-sensitivity C-reactive protein (hs-CRP) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), which more comprehensively reflects the clinical features of metabolic disorders associated with the disease. However, the definition of MASLD, compared to MAFLD, places less emphasis on HOMA-IR and hs-CRP [4]. HOMA-IR reflects systemic insulin resistance, which promotes endothelial dysfunction, dyslipidemia, and chronic inflammation – key pathways in atherosclerosis progression. For instance, insulin resistance in endothelial cells reduces nitric oxide bioavailability, leading to impaired vasodilation and increased oxidative stress, thereby accelerating plaque formation. Studies have shown that even after excluding the impact of T2DM, elevated HOMA-IR remains an independent predictor of ASCVD [4]. Furthermore, recently identified metabolic markers, such as Remnant Cholesterol (RC) [5] and Non-High-Density Lipoprotein Cholesterol (non-HDL-C) [6], have also been associated with ASCVD. Their potential role in mediating the MASLD and ASCVD risk relationship warrants further investigation.

Activation of the immune system and chronic inflammation are essential mechanisms in the pathogenesis of ASCVD, and hs-CRP, as an indicator of systemic inflammation, has been shown in numerous studies to be associated with ASCVD [7,8]. Studies have shown that MAFLD/MASLD is associated with increased cardiovascular event risks [9]. Zhou et al. reported that hepatic steatosis assessed by the fatty liver index (FLI) correlates with ASCVD risk [10]. Meyersohn et al. further demonstrated that hepatic steatosis independently predicts major adverse cardiovascular events (MACE), even after adjustment for traditional cardiovascular risk factors and coronary artery disease severity [11]. However, the mediating roles of HOMA-IR and hs-CRP in this pathophysiological association remain underexplored in current research paradigms. In addition, other inflammatory markers, such as the Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI) [12], and Lymphocyte-to-Monocyte Ratio (LMR) [13], have been linked to an elevated risk of ASCVD in multiple studies. However, whether these markers mediate this association or provide better predictive power for ASCVD compared to hs-CRP remains unreported.

In past large-scale surveys, steatosis or liver fibrosis assessment was generally conducted using ultrasound, which allows for qualitative diagnosis but not quantitative analysis. Vibration Controlled Transient Elastography (VCTE) diagnoses the degree of hepatic steatosis by deriving the Controlled Attenuation Parameter (CAP) from ultrasound echo attenuation. Additionally, it quantifies liver stiffness by measuring the speed of mechanically induced shear waves in the liver tissue, providing Liver Stiffness Measurement (LSM) values as an indicator of liver fibrosis. In this study, we utilized VCTE to measure patients' CAP and LSM values. Compared to traditional ultrasound diagnostics, VCTE offers a quantitative assessment of hepatic steatosis and fibrosis, allowing for the analysis of ASCVD risk across varying degrees of liver pathology. Numerous studies have confirmed the high diagnostic accuracy of this method [14,15]. No large-scale studies have evaluated the association between the degree of hepatic steatosis and fibrosis with 10-year ASCVD risk using VCTE.

Therefore, this study is the first to evaluate the association between CAP and the predicted 10-year ASCVD risk and the mediating roles of inflammatory and metabolic markers in this relationship. Additionally, we assessed the relationship between LSM and the predicted 10-year ASCVD risk in the population with hepatic steatosis, examining whether this risk is independent of CAP and the mediating roles of HOMA-IR and hs-CRP.

Methods

Study design and participants

Participants in the study were enrolled from the Shunde region of Guangdong, China, as part of the Shunde Epidemiological Study of Metabolic Diseases and Risk Factors (SPEED-Shunde) project (www.chictr.

org.cn, ChiCTR 2100054130). Using a multistage stratified cluster sampling method, participants were recruited from 10 research centers between November 2021 and September 2022. The study included individuals aged 18 years or older who had lived in Shunde for more than six months, excluding those with acute diseases, infections, or pregnancy. A total of 13,535 individuals participated in this survey. Based on the ASCVD risk prediction model, we excluded subjects younger than 35 ($n=2395$) and older than 75 ($n=204$). Additionally, we excluded participants with missing VCTE results ($n=2770$), no blood samples ($n=439$), acute inflammation ($n=485$), a history of coronary heart disease ($n=200$), a history of viral hepatitis ($n=717$), and excessive alcohol consumption ($n=215$). Finally, 6110 participants were included in this study for analysis (Figure 1). All participants provided their written informed consent, and the Ethics Committee of Shunde Hospital, Southern Medical University, approved the study. The study followed the ethical guidelines of the 1975 Declaration of Helsinki and the protocol (20211103) approved in China.

Data collection

Trained staff collected information using a questionnaire, which included data on sociodemographic characteristics, medical history, and lifestyle factors, and conducted physical examinations. For detailed study protocols, refer to our previous research [16]. After fasting for at least 10 h, each subject had 30 ml of blood drawn. The samples were transported to the central laboratory within 2 h, with the cold chain maintained during storage and transportation.

VCTE using FibroScan systems is a guideline-endorsed modality for assessing CAP and LSM in MASLD [17]. In this study, the examinee was required to fast for 3 h before the examination, and certified operators performed measurements with standardized M/XL probe selection, adhering to quality criteria requiring ≥10 valid acquisitions and interquartile range/median ratio <30%. Prior validation studies have established its inter-operator/system reproducibility (coefficient of variation 35.6%) [18] and prognostic value for liver-related outcomes (Harrell's C-index 0.878 in NAFLD cohorts) [19]. This non-invasive procedure offers an effective alternative to traditional liver biopsy for evaluating liver stiffness and fat content.

Definitions

The diagnostic criteria for type 2 diabetes mellitus (T2DM) are based on the standards set by the American Diabetes Association (ADA) from 2020 to 2022 [16]. Hypertension was defined as having a SBP ≥140 mmHg or a DBP ≥90 mmHg or receiving antihypertensive medication treatment within the past two weeks [20]. The 10-year predicted risk of ASCVD was calculated using the China-PAR project (Prediction for ASCVD Risk in China) model. Developed from four contemporary Chinese cohorts, this model has been proven to predict ASCVD risk in the Chinese population [21,22].

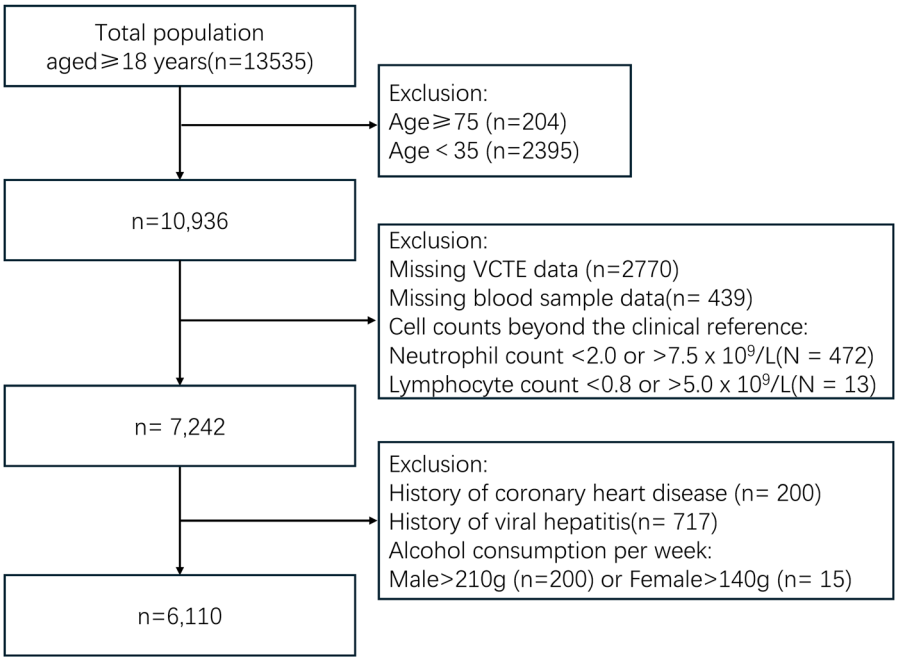

Figure 1. Flowchart of the study participants.

The risk prediction factors included age, gender, WC, SBP, DBP, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), T2DM, family history of ASCVD, geographic region (north/south), and urbanization (rural/urban). In this study, patients were categorized based on their 10-year predicted risk of ASCVD into low-risk (<5%) and moderate-to-high-risk (≥5%) groups [23]. Hepatic steatosis was defined as a CAP value of ≥ 248 dB/m [24]. The calculation methods for these indices were as follows: HOMA-IR = (fasting plasma glucose in mmol/L × fasting serum insulin in pmol/L) ÷ 22.5 [25]. SII = (Platelet count × Neutrophil count) ÷ Lymphocyte count; SIRI = (Neutrophil count × Monocyte count) ÷ Lymphocyte count [12]; LMR = Lymphocyte count ÷ Monocyte count [13]; RC = Total cholesterol − LDL-C − HDL-C[5]; non-HDL-C = Total cholesterol − HDL-C[6].

Covariates

Education level was categorized into three groups: below high school, high school graduate, and above high school. Smoking status was classified as non-smoker, previous smoker (having quit smoking for more than 6 months), and present smoker (having smoked at least 100 cigarettes in the past and currently smoking or having smoked within the last 6 months). Based on self-reported questionnaires, physical exercise intensity was defined as "no exercise," "low-intensity exercise," "moderate-intensity exercise," and "high-intensity exercise" [24].

Statistical analysis

The baseline characteristics of the study participants were summarized based on their 10-year CVD risk prediction, with continuous variables presented as mean (standard deviation) or median (interquartile range) depending on their distribution and categorical variables presented as proportions (%). Group differences for continuous variables were assessed using the Student's t-test or Mann-Whitney U test, and differences among categories were analyzed using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. CAP and LSM data were standardized for further analysis.

Multivariable logistic/linear regression analyses were conducted to explore the relationships between CAP and LSM, metabolic indicators, and 10-year ASCVD predicted risk, calculating odds ratios (OR) and 95% confidence intervals (95% CI). The models were adjusted for gender, age, BMI, education level, smoking status, and physical exercise. Subgroup analyses were also performed to elucidate the associations between CAP and 10-year ASCVD predicted risk, categorized by age (<50/≥50 years), gender (male/female), BMI (<18.5, 18.5–24.9, 25–29.9, ≥30), and different quartiles of inflammation and metabolic indicators.

To verify potential nonlinear relationships between CAP and 10-year CVD predicted risk, restricted cubic spline (RCS) analysis with three knots was used. Finally, mediation analysis was performed to quantify how inflammatory and metabolic markers mediate the association between CAP and increased predicted 10-year ASCVD risk. All data analyses were conducted using R version 4.4.1, with a two-tailed significance level set at 0.05.

Results

Basic characteristics of participants

Table 1 presents the baseline characteristics of the included participants. The study population had a mean age of 50.1 years (SD = 9.7), with 3927 females (64.3%) and 2183 males (35.7%). Comorbidities included type 2 diabetes in 808 participants (13.2%) and hypertension in 1911 participants (31.3%). Among the 6110 participants, 4957 (81.13%) were in the low-risk group and 1153 (18.87%) in the moderate-to-high-risk group for 10-year ASCVD prediction. The proportion of females in the moderate-to-high-risk group was higher compared to males. The participants' hs-CRP levels demonstrated a mean of 1.90 mg/L (SD = 3.54) and a median of 0.93 mg/L (IQR = 1.6). Additionally, the moderate-to-high-risk group exhibited significantly higher values in WC, BMI, CAP, LSM, hs-CRP, SII, SIRI, HOMA-IR, TG, TC, LDL-C, HDL-C, and educational level.

Association between hepatic steatosis, liver fibrosis, Hs-CRP, HOMA-IR, and predicted 10-year ASCVD risk

Table 2 shows that, compared to the first quartile (Q1), each increase in the quartile of CAP is associated with an increased odds ratio (OR) and 95% confidence interval (CI) for predicted moderate-to-high 10-year ASCVD risk: 1.14 (0.89, 1.45), 1.37 (1.08, 1.73), 2.44 (1.93, 3.10), with a significant trend ($p < 0.001$).

Compared to Q1, the predicted 10-year ASCVD risk significantly increased for hs-CRP in Q4 (OR 2.58, 95% CI [1.95, 3.42]). Other inflammation-related indices showed similar trends. In the Q4 group, SII demonstrated a strong association with ASCVD risk (OR 1.28, 95% CI: 0.99, 1.65), although it did not reach statistical significance ($p = 0.064$). SIRI in the Q4 group

Table 1. Basic characteristics of participants.

Variable	Low risk	Moderate to high risk	*P* value
N	4957 (81.13%)	1153 (18.87%)	<0.001
Age	47.38 (8.12)	61.8 (6.99)	<0.001
Sex			
Male	1604 (73.48%)	579 (26.52%)	<0.001
Female	3353 (85.38%)	574 (14.62%)	<0.001
WC	79.57 (9.41)	86.71 (8.7)	<0.001
BMI	23.61 (3.19)	25.01 (3.22)	<0.001
CAP	238.24 (48.65)	261.18 (52.98)	<0.001
LSM	5.45 (1.63)	6.01 (1.95)	<0.001
hs-CRP	1.76 (4.24)	2.52 (4.69)	<0.001
SII	440.47 (199.89)	413.7 (183.33)	<0.001
SIRI	0.77 (0.42)	0.81 (0.41)	<0.001
LMR	5.19 (1.59)	5.17 (1.61)	0.487
HOMA-IR	3.02 (4.91)	4.42 (6.14)	<0.001
FBG	4.83 (1.17)	5.79 (1.79)	<0.001
FINS	13.49 (18.93)	16.77 (21.31)	<0.001
HbA1c	5.71 (0.68)	6.36 (1.02)	<0.001
TG	1.57 (1.47)	2.02 (1.91)	<0.001
TC	5.46 (1.84)	5.63 (1.15)	<0.001
LDL-C	3.03 (0.71)	3.18 (0.79)	<0.001
HDL-C	1.47 (0.33)	1.36 (0.31)	<0.001
RC	0.96 (1.58)	1.09 (0.59)	<0.001
non-HDL-C	3.99 (1.78)	4.28 (1.11)	<0.001
Education			
Less than high school	1947 (70.44%)	817 (29.56%)	<0.001
Completed high school	1291 (85.5%)	219 (14.5%)	<0.001
Beyond high school	1719 (93.63%)	117 (6.37%)	<0.001
Physical exercise			
No exercise	2237 (81.61%)	504 (18.39%)	<0.001
Low intensity exercise	1538 (86.5%)	240 (13.5%)	<0.001
Moderate intensity exercise	652 (81.09%)	152 (18.91%)	<0.001
High intensity exercise	530 (67.34%)	257 (32.66%)	<0.001
Hypertension			
NO	3851 (91.71%)	348 (8.29%)	<0.001
YES	1106 (57.88%)	805 (42.12%)	<0.001
T2DM			
NO	4586 (86.5%)	716 (13.5%)	<0.001
YES	371 (45.92%)	437 (54.08%)	<0.001

Note: Participant characteristics were described as means (standard deviations) or medians (interquartile ranges) for continuous variables, and as frequencies (%) for categorical variables. Differences were tested using Student's *t*-test and Mann–Whitney *U* test or chi-square test. A two-tailed $p < 0.05$ was considered statistically significant.

WC: waist circumference; BMI: body mass index; CAP: controlled attenuation parameters; LSM: liver stiffness measurements; hs-CRP: high-sensitivity C-reactive protein; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; LMR: Lymphocyte-to-Monocyte Ratio; HOMA-IR: homeostasis model assessment of insulin resistance; FBG: fasting blood glucose; FINS: fasting insulin; HbA1c: hemoglobin A1c; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; RC: remnant cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol.

significantly increased ASCVD risk (OR 1.37, 95% CI [1.06, 1.78]). Similarly, LMR in the Q4 group was significantly associated with ASCVD risk (OR 1.38, 95% CI [1.07, 1.78]). Similar trends were observed for metabolic indicators, with HOMA-IR showing a significant increase in predicted 10-year ASCVD risk with each quartile increase compared to Q1: (OR 1.69, 95% CI [1.26, 2.27]), (OR 2.62, 95% CI [1.96, 3.51]), (OR 5.16, 95% CI [3.85, 6.90]). Furthermore, RC in the Q4 group was significantly associated with increased ASCVD risk (OR 1.66, 95% CI: [1.27, 2.16]), and non-HDL-C in the Q4 group was similarly associated with significantly increased risk (OR 1.68, 95% CI [1.29, 2.19]).

In a population with hepatic steatosis (CAP ≥ 248 dB/m), we investigated the correlation between the degree of liver fibrosis and the predicted 10-year ASCVD risk (Table 3). The results showed that after adjusting for age, gender, BMI, education, physical activity, and CAP, LSM remained significantly associated with a predicted 10-year ASCVD risk (OR 1.40, 95% CI [1.23, 1.58]).

Subgroup analysis

Figure 2 presents the correlations between CAP and predicted 10-year ASCVD risk across different subgroups based on sex, age, BMI, and inflammation and metabolic markers. Individuals aged ≤50 years with elevated CAP levels exhibited higher odds of 10-year ASCVD risk (OR = 1.89, 95% CI [1.48, 2.41]) compared to those >50 years (OR = 1.40, 95% CI [1.28, 1.53]), with a statistically significant interaction effect (P for interaction <0.001). Additionally, women exhibit a higher predicted 10-year ASCVD risk than men. BMI

Table 2. Association of inflammatory and metabolic indicators with predicted 10-year ASCVD risk.

	N	Moderate to high risk (%)	OR(95%CI)	*P* value
CAP	6110	1153 (18.9%)	1.46 (1.35, 1.59)	<0.001
Q1	1577	193 (12.2%)	Ref.	
Q2	1509	213 (14.1%)	1.14 (0.89, 1.45)	0.296
Q3	1524	298 (19.6%)	1.37 (1.08, 1.73)	0.009
Q4	1500	449 (29.9%)	2.44 (1.93, 3.10)	<0.001
P for trend				<0.001
hs-CRP	6110	1153 (18.9%)	1.12 (1.03, 1.22)	0.010
Q1	1547	169 (10.9%)	Ref.	
Q2	1521	257 (16.9%)	1.23 (0.92, 1.63)	0.165
Q3	1518	328 (21.6%)	1.82 (1.38, 2.40)	<0.001
Q4	1524	399 (26.2%)	2.58 (1.95, 3.42)	<0.001
P for trend				<0.001
SII	6110	1153 (18.9%)	1.09 (0.99, 1.20)	0.071
Q1	1528	332 (21.7%)	Ref.	
Q2	1527	296 (19.4%)	1.07 (0.84, 1.36)	0.572
Q3	1527	283 (18.5%)	1.20 (0.94, 1.54)	0.141
Q4	1528	242 (15.8%)	1.28 (0.99, 1.65)	0.064
P for trend				0.040
SIRI	6110	1153 (18.9%)	1.11 (1.02, 1.22)	0.016
Q1	1528	237 (15.5%)	Ref.	
Q2	1527	287 (18.8%)	1.18 (0.92, 1.52)	0.194
Q3	1527	320 (21.0%)	1.34 (1.04, 1.73)	0.024
Q4	1528	309 (20.2%)	1.37 (1.06, 1.78)	0.017
P for trend				0.010
LMR	6110	1153 (18.9%)	1.10 (1.00, 1.20)	0.041
Q1	1529	299 (19.6%)	Ref.	
Q2	1527	293 (19.2%)	1.15 (0.89, 1.49)	0.298
Q3	1527	262 (17.2%)	1.11 (0.86, 1.44)	0.427
Q4	1527	299 (19.6%)	1.38 (1.07, 1.78)	0.014
P for trend				0.022
HOMA-IR	6110	1153 (18.9%)	1.27 (1.18, 1.37)	<0.001
Q1	1528	163 (10.7%)	Ref.	
Q2	1527	224 (14.7%)	1.69 (1.26, 2.27)	<0.001
Q3	1527	297 (19.4%)	2.62 (1.96, 3.51)	<0.001
Q4	1528	469 (30.7%)	5.16 (3.85, 6.90)	<0.001
P for trend				<0.001
RC	6110	1153 (18.9%)	1.06 (1.01, 1.12)	0.030
Q1	1584	229 (14.5%)	Ref.	
Q2	1507	222 (14.7%)	1.04 (0.78, 1.39)	0.797
Q3	1516	324 (21.4%)	1.38 (1.05, 1.81)	0.019
Q4	1503	378 (25.1%)	1.66 (1.27, 2.16)	<0.001
P for trend				<0.001
Non-HDL-C	6110	1153 (18.9%)	1.08 (1.01, 1.16)	0.018
Q1	1531	210 (13.7%)	Ref.	
Q2	1525	247 (16.2%)	1.23 (0.92, 1.65)	0.158
Q3	1540	300 (19.5%)	1.28 (0.97, 1.68)	0.085
Q4	1514	396 (26.2%)	1.68 (1.29, 2.19)	<0.001
P for trend				<0.001

Note: The model was adjusted for age, gender, education, physical exercise and BMI.
CAP: controlled attenuation parameters; hs-CRP: high-sensitivity C-reactive protein; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; LMR: Lymphocyte-to-Monocyte Ratio; HOMA-IR: homeostasis model assessment of insulin resistance; RC: remnant cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol.

Table 3. The association between LSM and predicted 10-year ASCVD risk among patients with hepatic steatosis.

	N	Moderate to high risk (%)	Model 1		Model 2	
LSM	2543	655 (25.8%)	1.47 (1.30, 1.66)	<0.001	1.40 (1.23, 1.58)	<0.001
Q1	673	113 (16.8%)	1.00 (1.00, 1.00)	Ref.	1.00 (1.00, 1.00)	Ref.
Q2	603	137 (22.7%)	1.18 (0.81, 1.73)	0.380	1.09 (0.75, 1.60)	0.642
Q3	662	200 (30.2%)	2.19 (1.53, 3.13)	<0.001	1.97 (1.37, 2.85)	<0.001
Q4	605	205 (33.9%)	2.65 (1.83, 3.83)	<0.001	2.22 (1.52, 3.25)	<0.001
P for trend				<0.001		<0.001

Note: Model1 was adjusted for age, gender, education, physical exercise and BMI; Model2 was adjusted for age, gender, education, physical exercise, BMI and CAP.
LSM: liver stiffness measurements; BMI: body mass index; CAP: controlled attenuation parameters.

subgroups were defined according to WHO classification: <18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m^2 [26]. Among these categories, the subgroup with a BMI less than 18.5 kg/m^2 shows a significantly higher risk compared to other BMI subgroups (OR = 7.81, 95% CI [2.32, 26.34]; P for interaction <0.001).

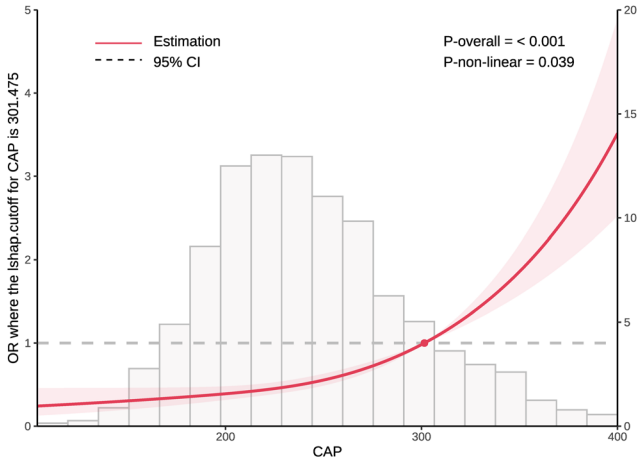

Figure 2. Subgroup analysis of the association between CAP and predicted 10-year ASCVD risk. Note: Adjusted for age, gender, education, physical exercise, and BMI. CAP: controlled attenuation parameters; BMI: body mass index; LSM: liver stiffness measurements; hs-CRP: high-sensitivity C-reactive protein; HOMA-IR: homeostasis model assessment of insulin resistance.

Variable	Count	OR(95%CI)	P value	P for interaction
Total	6110	1.46 (1.35, 1.59)	<0.001	
Age				<0.001
<=50	3238	1.89 (1.48, 2.41)	<0.001	
>50	2872	1.40 (1.28, 1.53)	<0.001	
Sex				<0.001
Male	2183	1.28 (1.12, 1.46)	<0.001	
Female	3927	1.59 (1.43, 1.78)	<0.001	
BMI group				0.033
<18.5	187	7.81 (2.32, 26.34)	<0.001	
18.5−24.9	3864	1.47 (1.31, 1.66)	<0.001	
25−29.9	1803	1.41 (1.24, 1.61)	<0.001	
>=30	256	1.52 (1.08, 2.15)	0.017	
hs−CRP				0.053
Q1	1547	1.73 (1.35, 2.20)	<0.001	
Q2	1521	1.24 (1.03, 1.50)	0.026	
Q3	1518	1.28 (1.09, 1.49)	0.002	
Q4	1524	1.46 (1.27, 1.69)	<0.001	
HOMA−IR				0.396
Q1	1528	1.01 (0.78, 1.31)	0.918	
Q2	1527	1.30 (1.06, 1.60)	0.011	
Q3	1527	1.35 (1.13, 1.61)	<0.001	
Q4	1528	1.31 (1.14, 1.49)	<0.001	

Figure 3. The nonlinear relationship between CAP and predicted 10-year ASCVD risk. Note: Restricted cubic spline (RCS) analysis was conducted. The model was adjusted for age, gender, education, physical exercise, and BMI.

Nonlinear relationship between hepatic steatosis and predicted 10-year ASCVD risk

In Figure 3, we used RCS analysis to flexibly model and visualize the relationship between the degree of hepatic steatosis and the predicted 10-year ASCVD risk. After adjusting for covariates (age, gender, education, physical exercise, and BMI), we found a nonlinear positive association between CAP values and the predicted 10-year ASCVD risk (P-overall <0.001, P-non-linear = 0.039). As CAP values increased, ASCVD risk showed a significant upward trend. When the CAP value reached 301.475, the OR for ASCVD risk was approximately 5, indicating a marked increase in ASCVD risk beyond this threshold.

Mediation analysis of the association between liver steatosis, liver fibrosis, and predicted 10-year ASCVD risk

Building on the previous analysis, we further investigated how inflammatory and metabolic markers

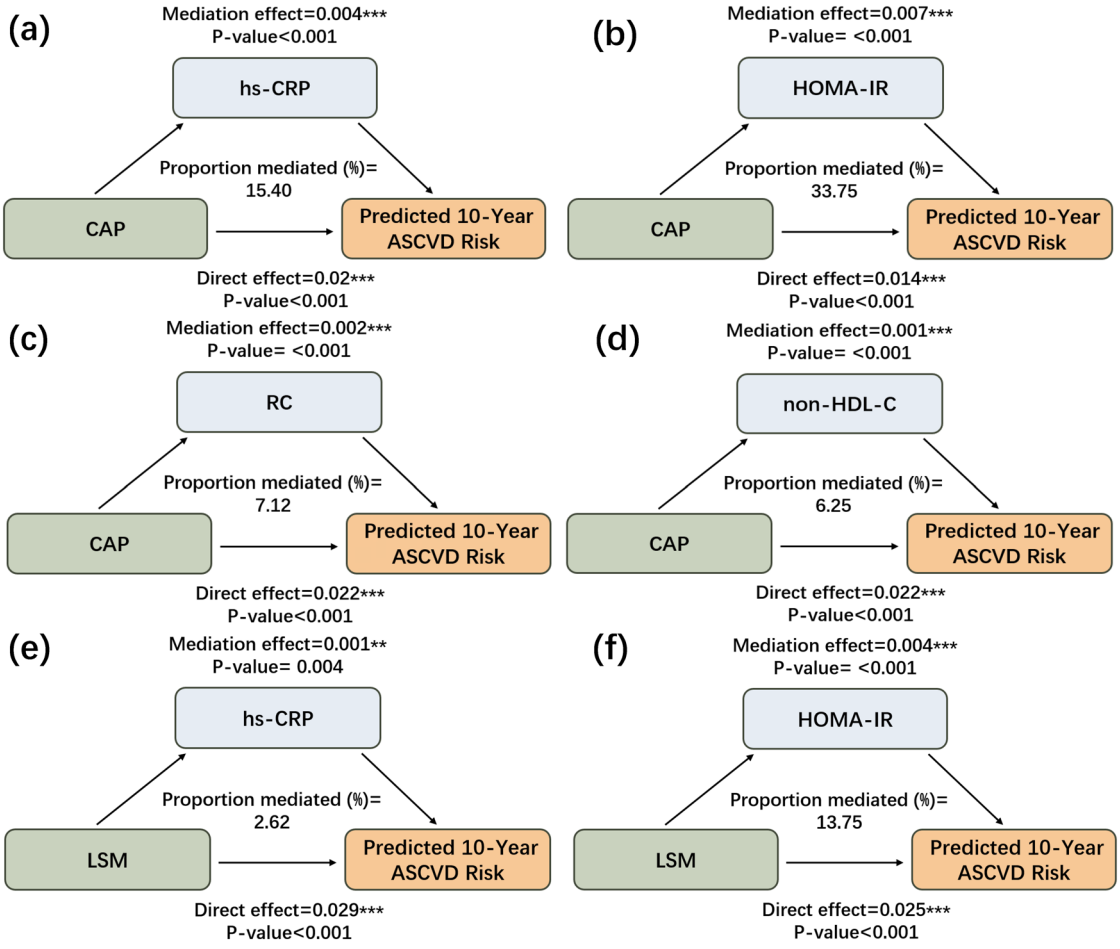

Figure 4. The mediating role of inflammatory and metabolic markers in the relationship between CAP and LSM and the predicted 10-year ASCVD risk. Note: Mediation analyses results. The mediating role of hs-CRP and HOMA-IR in the relationship between CAP and the predicted 10-year ASCVD risk (a and b). The mediating role of RC and non-HDL-C in the relationship between CAP and the predicted 10-year ASCVD risk (c and d). In the population with liver steatosis, hs-CRP and HOMA-IR mediate the relationship between LSM and the predicted 10-year ASCVD risk (e and f). CAP: controlled attenuation parameters; LSM: liver stiffness measurements; hs-CRP: high-sensitivity C-reactive protein; HOMA-IR: homeostasis model assessment of insulin resistance; RC: remnant cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol.

mediate the relationship between the CAP and predicted 10-year ASCVD risk. We performed a mediation analysis using hs-CRP and HOMA-IR as mediators, adjusting for sex, age, BMI, education level, and physical activity.

The results indicate that hs-CRP partially mediates the relationship between CAP and predicted 10-year ASCVD risk. The direct and indirect effects were 0.02 (95% CI [0.016, 0.025]) and 0.004 (95% CI [0.003, 0.005]), respectively, with a mediation proportion of 15.40% (Figure 4(a)). In contrast, the inflammatory markers SII, SIRI, and LMR did not significantly mediate the relationship between CAP and the predicted 10-year ASCVD risk (Figure 5). In the metabolic domain, HOMA-IR also partially mediated this effect, with direct and indirect effects of 0.007 (95% CI [0.005, 0.009]) and 0.014 (95% CI [0.009, 0.019]), respectively, accounting for 33.75% of the mediation (Figure 4(b)). Furthermore, the metabolic indicators RC and non-HDL-C both demonstrated significant mediating effects. The proportions mediated by RC and non-HDL-C were 7.12% and 6.26%, respectively (Figure 4(c and d)). In the population with liver steatosis, we also conducted mediation analyses and found that the relationship between LSM and the predicted 10-year ASCVD risk is mediated by hs-CRP and HOMA-IR, accounting for 2.62% and 13.75% of the effect, respectively (Figure 4(e and f)).

Discussion

To our knowledge, this is the first study to evaluate the mediating role of hs-CRP and HOMA-IR in the increased predicted 10-year ASCVD risk associated with higher CAP and LSM levels. We demonstrated that higher CAP levels are significantly associated with

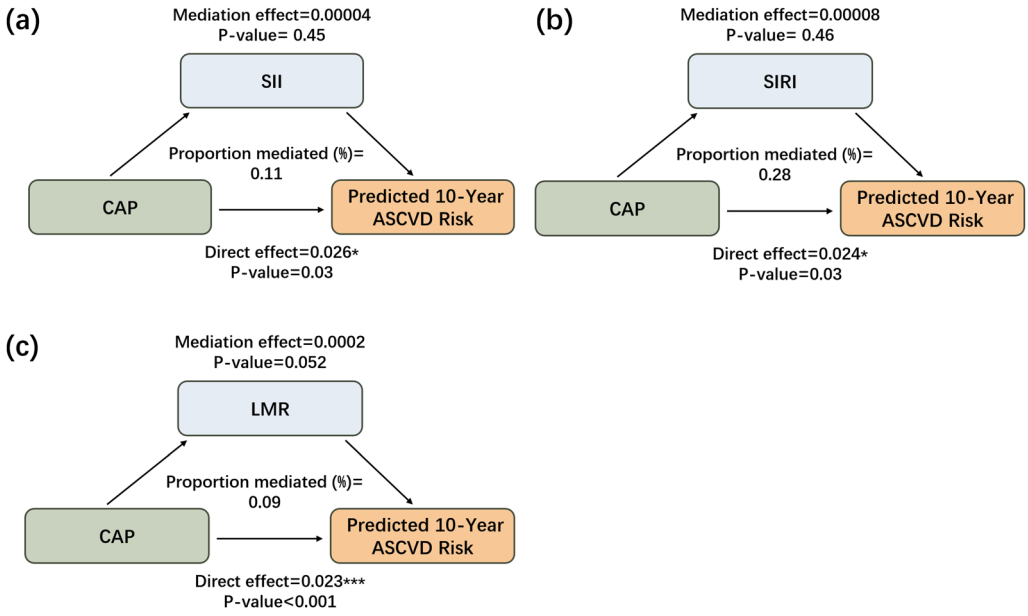

Figure 5. The mediating role of SII, SIRI, and LMR in the relationship between CAP and the predicted 10-year ASCVD risk. Note: Mediation analyses results. The mediating role of SII, SIRI, and LMR in the relationship between CAP and the predicted 10-year ASCVD risk (a, b, and c). CAP: controlled attenuation parameters; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; LMR: Lymphocyte-to-Monocyte Ratio.

an increased predicted 10-year ASCVD risk, and hs-CRP and HOMA-IR partially mediate this association. Additionally, our RCS analysis showed that when CAP values exceed the threshold of 301.475, the predicted 10-year ASCVD risk escalates more rapidly. Furthermore, we found that in patients with hepatic steatosis, the degree of liver fibrosis also increases the predicted 10-year ASCVD risk independently of hepatic steatosis. This association is also mediated by hs-CRP, HOMA-IR, RC, and non-HDL-C, highlighting the importance of controlling inflammation and metabolic disturbances in reducing ASCVD risk. Stratified analyses demonstrated significant heterogeneity in the association between CAP and 10-year ASCVD risk across age, sex, and BMI subgroups. Specifically, this association was markedly stronger in younger individuals (≤50 years versus >50 years), females (compared to males), and underweight participants (BMI <18.5 kg/m^2). These findings underscore the need for targeted ASCVD risk surveillance in these demographic subgroups. Notably, no significant effect modification was observed across strata of inflammatory biomarkers (hs-CRP quartiles: P for interaction =0.053) or insulin resistance status (HOMA-IR quartiles: P for interaction = 0.396).

Multiple studies have indicated that MASLD is a risk factor for CVD [27,28]. Huang et al. reported that MASLD is associated with an increased risk of CVD mortality (HR 2.01, 95% CI [1.66–2.44]) [29]. Moon et al. found that this association persists even after adjusting for cardiometabolic risk factors (HR 1.36, 95% CI [1.08–1.73]), demonstrating that MAFLD is an independent risk factor distinct from known risk factors [30]. Our findings are consistent with theirs. Regarding the definitions of the two types of fatty liver, Pan et al. [31] found that the MAFLD definition better predicts ASCVD risk compared to MASLD, and this advantage remains after adjusting for common risk factors. Rui et al. [32] found that both MASLD and MALFD definitions are associated with a higher risk of all-cause mortality compared to the NAFLD definition.

The association between the hs-CRP and CVD risk has been reported in numerous studies [33,34]. Rolver et al. [35] found that elevated plasma CRP levels are progressively associated with an increased risk of ischemic heart disease (IHD) and CVD mortality (HR 1.50, 95% CI [1.38, 1.62]), with the risk further increasing when CRP levels are in the highest 20% (HR 2.44, 95% CI [1.93, 3.10]). Kuppa et al. [36], using a Mendelian randomization (MR) study, discovered a direct causal relationship between elevated CRP levels and an increased risk of hypertensive heart disease (HHD). Lee et al. [4] demonstrated that elevated HOMA-IR is independently positively associated with cardiovascular events and cardiovascular mortality. Wang et al. [37] found that the highest quartile of HOMA-IR, compared to the lowest quartile, significantly increases the risk of CVD (HR 1.36; 95% CI [1.22–1.50]).

The pathophysiological mechanisms by which MASLD leads to the development of CVD are primarily associated with inflammation and metabolic abnormalities.

Regarding inflammation, MASLD results in elevated levels of plasma CRP, oxidized-LDL, and plasminogen activator inhibitor-1 (PAI-1), all of which contribute to a pro-atherosclerotic environment, promoting the development of CVD [38]. Hepatic adipose tissue serves as a physiological reservoir for fatty acids. When the fatty acid content surpasses the storage capacity, ectopic lipid accumulation leads to lipotoxicity, which induces low-grade inflammation and insulin resistance in the liver. This process triggers oxidative stress, promoting inflammation and fibrosis. It is considered a critical mechanism in the progression of MASLD patients from simple steatosis to non-alcoholic steatohepatitis (NASH). On the other hand, insulin resistance leads to dyslipidemia, characterized by elevated levels of triglycerides (TG), low levels of high-density lipoprotein (HDL), and an increase in small dense low-density lipoprotein cholesterol (sdLDL-C) [25]. SdLDL-C is emerging as a key biomarker and is considered the most atherogenic lipoprotein. Additionally, insulin resistance can induce chronic inflammation, trigger oxidative stress, and cause endothelial dysfunction, further accelerating the progression of CVD [39]. Intestinal microbiome signatures are also implicated in the interaction between MAFLD and CVD. Dysfunction and metabolic alterations in the gut microbiota promote the production of pathogen-associated molecular patterns, leading to systemic low-grade inflammation, insulin resistance, and obesity, which contribute to the development of CVD [40]. Moreover, the gut microbiota of MAFLD has been shown to influence the progression of CVD [41].

Although numerous pathophysiological studies have established that hs-CRP and HOMA-IR play significant roles in the progression of ASCVD due to hepatic steatosis and fibrosis [42,43], there are currently no epidemiological studies reporting the mediating effects of these two indicators in this process. Our research is the first to elucidate that hs-CRP and HOMA-IR are critical mediating factors in the increased risk of ASCVD in patients with fatty liver and liver fibrosis. Compared to the more stringent and complex definition of MAFLD, which requires the presence of T2DM, obesity, or at least two other metabolic factors, the definition of MASLD includes more simplified metabolic risk factors. Although the populations defined by both terms are similar, several studies have shown that MASLD has a stronger ability to identify patients within the population than MAFLD [32,44]. In this study, hs-CRP and HOMA-IR were found to mediate the relationship between fatty liver and ASCVD as defined by MASLD. Considering the economic burden of widespread testing for these two indicators, MASLD offers better health economic benefits and patient identification capabilities. For patients diagnosed with MASLD, these two indicators can serve as tools for screening ASCVD risk. Targeted interventions to reduce chronic inflammation and improve insulin resistance may lower the risk of ASCVD. It is noteworthy that RC and non-HDL-C also mediate the role of hepatic steatosis in the progression of ASCVD. However, these two indicators currently receive relatively little attention. Further research is needed to explore whether pharmacological or other interventions targeting these markers in patients with MASLD are necessary to reduce the risk of ASCVD.

Currently, drugs under clinical investigation for treating MASLD, such as Glucagon-like peptide-1 receptor agonists (GLP1RAs), enhance insulin secretion and action, thereby improving insulin sensitivity and reducing insulin resistance [17]. Additionally, GLP1RAs have been shown to significantly lower the risk of ASCVD in patients with T2DM due to their ability to improve left ventricular function, reduce cardiac hypertrophy and fibrosis, and decrease inflammation and oxidative stress, thus maintaining the integrity and function of the vascular endothelium [45]. In the future development of MASLD therapies and treatment regimens, it is also essential to consider whether controlling risk factors such as hs-CRP, HOMA-IR, RC, and non-HDL-C can further reduce ASCVD risk. Our findings support the integration of liver stiffness measurement into existing cardiovascular risk prediction models, particularly for patients with concurrent metabolic dysregulation, to provide a more comprehensive risk stratification framework. Whether combination therapies with dual hepatoprotective and cardiometabolic benefits can yield synergistic effects in high-risk subgroups requires further validation in prospective cohort studies.

The strengths of this study lie in its use of CAP to assess hepatic steatosis, which provides a more accurate reflection of liver fat content compared to ultrasonography, and its quantification of the correlation between hepatic steatosis and ASCVD risk. Additionally, this study employs mediation analysis to quantify the effect size of hs-CRP, HOMA-IR, RC and non-HDL-C in the process by which hepatic steatosis leads to ASCVD. For patients with steatosis, LSM was used to evaluate the degree of liver fibrosis and its association with ASCVD risk, demonstrating that LSM is an ASCVD risk factor alongside CAP. This correlation is further mediated by hs-CRP, HOMA-IR, RC, and non-HDL-C, underscoring the significant role of inflammation and metabolic disorders in developing ASCVD.

Despite the significant clinical implications of our findings in understanding the progression and mechanisms of MASLD on ASCVD risk, several limitations

should be acknowledged. Firstly, our study cohort exclusively comprises individuals from China. It is important to emphasize that these findings may not be generalizable to populations outside of the Asian ethnicity range due to potential ethnic variations in genetic predisposition and disease progression patterns. Given the influence of ethnic factors on the genetic susceptibility and progression of MASLD, future research should compare our data with datasets from other regions to identify common patterns and characteristics across different populations. The cross-sectional design of this study has inherent limitations in establishing causal inference. Our research team will conduct longitudinal follow-up studies to validate these findings and generate supplementary clinical evidence. Thirdly, VCTE exhibits certain limitations compared to liver biopsy. In obese patients, increased subcutaneous fat thickness may lead to signal attenuation or failed valid measurements, necessitating specialized XL probes. Furthermore, diagnostic thresholds for significant steatosis may vary depending on the probe type [46], requiring further investigation.

Conclusions

CAP is significantly associated with an increased risk of ASCVD, with this association being largely mediated by inflammatory and metabolic markers. Among patients with fatty liver disease, elevated LSM levels increase the risk of ASCVD, independently of CAP, and this risk is also mediated by hs-CRP, HOMA-IR, RC, and non-HDL-C. Integrating CAP and LSM assessments into ASCVD risk stratification protocols may enhance cardiovascular risk evaluation for MASLD patients in clinical practice. Further prospective studies are needed to validate the conclusions.

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Authors contributions

CRediT: **Zihao Gui**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision; **Xingying Chen**: Conceptualization, Data curation, Formal analysis, Investigation, Software, Supervision; **Dongmei Wang**: Data curation, Formal analysis, Software, Supervision; **Zhi Chen**: Formal analysis; **Siyang Liu**: Data curation, Investigation; **Genfeng Yu**: Data curation, Investigation, Software; **Yuqi Jiang**: Data curation, Formal analysis, Investigation; **Hualin Duan**: Formal analysis, Investigation, Software; **Daoyan Pan**: Formal analysis, Investigation; **Xu Lin**: Data curation, Software, Validation; **Lan Liu**: Data curation, Formal analysis, Software; **Heng Wan**: Conceptualization, Data curation, Funding acquisition, Writing – original draft; **Jie Shen**: Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

Heng Wan http://orcid.org/0000-0003-3674-5920
Jie Shen http://orcid.org/0000-0001-6952-9541

Data availability statement

Data, analytic methods, and study materials will be available to other researchers upon request.

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