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High systemic inflammation response index and increased cardiovascular risk and mortality in MASLD: A prospective cohort study

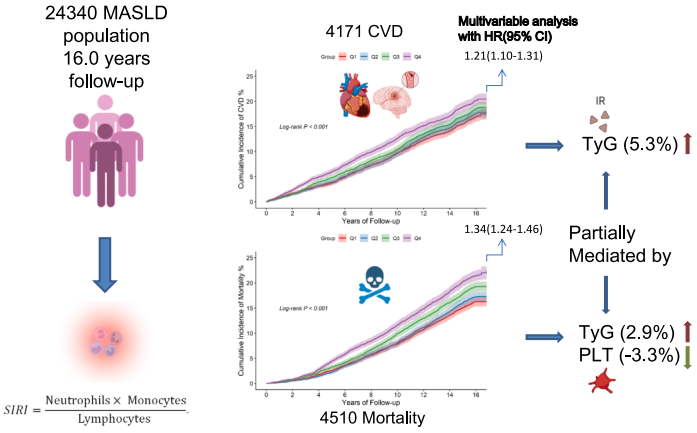
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Graphical abstract



High SIRI increase CVD risk and Mortality in individuals with MASLD

Highlights:

- This extensive prospective cohort study tracked over 24,000 Chinese adults with MASLD for a median duration of 16.0 years.
- Increased SIRI levels were independently linked to elevated risks of CVD and mortality.
- Insulin resistance, measured by the triglyceride-glucose index, partially mediated these associations.
- These findings identify SIRI as a potential prognostic marker in MASLD.

Impact and implications:

This study provides important evidence linking systemic inflammation, as measured by the systemic inflammation response index, to increased cardiovascular disease and mortality in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD), a prevalent condition with rising global burden. The findings underscore the clinical relevance of inflammation markers in cardiovascular risk stratification, particularly for patients and healthcare providers managing MASLD. Physicians and policymakers could incorporate systemic inflammation response index into routine assessments to identify patients with MASLD at higher risk of cardiovascular events, potentially guiding targeted interventions aimed at mitigating systemic inflammation and metabolic dysfunction. Nonetheless, due to the predominantly male, community-based cohort from northern China, further research across diverse populations is warranted to confirm these associations before widespread clinical implementation.

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Research article

JHEP|Reports

High systemic inflammation response index and increased cardiovascular risk and mortality in MASLD: A prospective cohort study

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Background & Aims: The correlation between systemic inflammation response index (SIRI) and both cardiovascular disease (CVD, including myocardial infarction and total stroke) and mortality in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD) remains unclear. We examined this association in a large Chinese cohort.

Methods: A population of 24,340 patients with MASLD from the Kailuan study were observed over a median of 16.0 years. SIRI was calculated based on neutrophil, monocyte, and lymphocyte counts. Cox proportional hazards models were used to estimate hazard ratios (HRs) for CVD and mortality across SIRI quartiles. Net reclassification improvement assessed SIRI's predictive value *vs.* high-sensitivity C-reactive protein and other indices. Mediation analysis assessed the roles of platelet count (PLT), Chinese visceral adiposity index and triglyceride-glucose index.

Results: During follow-up, 4,171 CVD events and 4,510 deaths occurred. Elevated SIRI was significantly linked to higher risks of CVD (HR for Q4 *vs.* Q1 1.21; 95% CI 1.10–1.31; p <0.001), including myocardial infarction (HR 1.22; 95% CI 1.01–1.48; p = 0.045), total stroke (HR 1.18; 95% CI 1.06–1.31; p = 0.003), and mortality (HR 1.34; 95% CI 1.24–1.46; p <0.001) in MASLD. Associations were stronger among women (HR 1.17; 95% CI 1.07–1.29; p <0.01) and physically inactive individuals (HR 1.09; 95% CI 1.05–1.13; p <0.01). SIRI improved outcome prediction over high-sensitivity C-reactive protein and other indices, with significant reclassification gains (5.84; 95% CI 2.57–9.12; p <0.001). Triglyceride-glucose index partially mediated these associations (5.3% for CVD, p = 0.006; 2.9% for mortality, p = 0.003), whereas PLT exhibited a slight inverse mediation effect on mortality (-3.3%, p = 0.032).

Conclusions: High SIRI independently correlates with increased risk of CVD and mortality in MASLD. These findings highlight the role of systemic inflammation and support SIRI as a potential biomarker for risk stratification in these individuals.

Clinical trial number: ChiCTR-TNC-11001489.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease (NAFLD), is acknowledged as a leading chronic liver disease globally.[1,2] Epidemiological research shows that about 25% of the world's adult population is affected by MASLD,[3] with its prevalence currently estimated to have increased to 38%.[4] Notably, MASLD is increasingly recognized as a significant factor in cardiovascular disease (CVD), the leading cause of morbidity and mortality among individuals with MASLD.[5,6]

Numerous studies have confirmed that MASLD independently elevates the risk of cardiovascular events, regardless of traditional risk factors.[7–9] The pathophysiological mechanisms of CVD in patients with MASLD are multifactorial, involving complex interactions between insulin resistance, dyslipidemia, oxidative stress, endothelial dysfunction, systemic inflammation, and other factors. Among these, systemic inflammation has been highlighted as a pivotal mediator bridging MASLD and elevated cardiovascular risk.[10]

Several hematologic biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII), are widely used to quantify systemic inflammation. The systemic inflammation response index (SIRI), derived from neutrophil, lymphocyte, and monocyte counts, is a newer composite marker that may offer a more comprehensive assessment by incorporating both innate and adaptive immune components.[11,12] A recent study supports its strong

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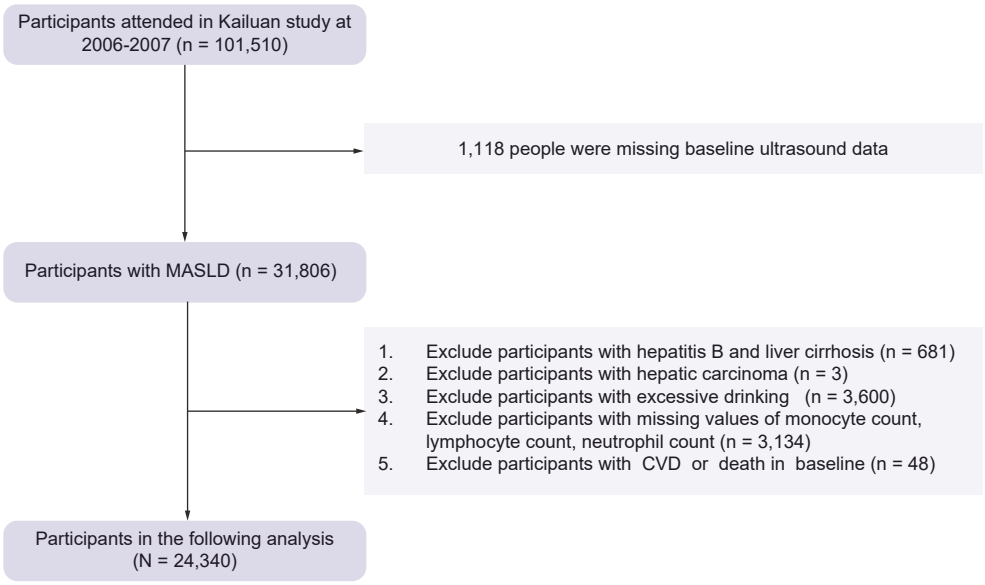


Fig. 1. Flowchart of the study selection. A total of 101,510 participants were enrolled during 2006–2007. After excluding individuals with missing baseline ultrasound data (n = 1,118), those with viral hepatitis B or liver cirrhosis (n = 681), hepatic carcinoma (n = 3), excessive alcohol consumption (n = 3,600), missing data for monocyte, lymphocyte, or neutrophil counts (n = 3,134), and those with cardiovascular disease or death at baseline (n = 48), a total of 24,340 participants with MASLD were included in the final analysis. Note: CVD including myocardial infarction and total stroke. Total stroke includes ischemic stroke and hemorrhagic stroke. CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease.

predictive value in chronic inflammatory conditions and malignancies.[13] Notably, elevated SIRI levels have been significantly linked to increased mortality and adverse cardiovascular events.[14–16] However, despite emerging evidence suggesting a connection between SIRI and CVD outcomes in various diseases,[17–20] research on the association between SIRI and cardiovascular events in MASLD remain scarce.

Herein, this study seeks to systematically investigate the link between SIRI levels and cardiovascular risk in Chinese adults with MASLD, addressing a current research gap. We proposed that increased SIRI levels are associated with a higher risk of subsequent CVD and mortality in Chinese adults with MASLD.

Patients and methods

Study design and population

This research analyzed data from the Kailuan Study, a substantial and ongoing prospective cohort involving participants aged 18 to 98 in Tangshan, China. The study design and methodology have been described in detail in previously published studies.[21,22] Since baseline in 2006-2007, the Kailuan cohort has enrolled 101,510 participants who completed comprehensive health examinations and standardized questionnaires at the Kailuan General Hospital and its ten affiliated hospitals. Detailed data on lifestyle, medical history and clinical characteristics were collected at baseline and have been updated every 2 years through follow-up visits. The study protocol received approval from the Kailuan Medical Group's Ethics Committee, ensuring compliance with the Declaration of Helsinki's ethical principles, and all participants provided written informed consent. This study initially included 31,806 individuals with MASLD from health examinations conducted between 2006 and 2007, excluding 1,118 participants with missing ultrasound data. The final analysis comprised 24,340 patients after further excluding those with missing monocyte, lymphocyte, or neutrophil counts (n = 3,134); hepatitis B or cirrhosis (n = 681); hepatocellular carcinoma (n = 3); excessive alcohol consumption (n = 3,600); and baseline CVD or death (n = 48). Fig. 1 depicts the study flowchart.

Data collection and definition

A standardized questionnaire was used to gather sociodemographic data, including age, sex, educational level (high school diploma or higher *vs*. no diploma), smoking status (current *vs.* non-smoker), and marital status (spouse *vs*. no spouse). Data were also collected on the use of medications for lowering blood pressure, glucose, and lipids, along with family history of CVD. Trained personnel measured height and body weight by a standardized protocol. BMI was determined by dividing weight in kilograms by height in meters squared (kg/m^2). Trained nurses measured blood pressure at least twice using either an automated device or a manual sphygmomanometer under standardized procedures, and the average of these measurements was used for analysis. Hematological parameters such as platelet, neutrophil, lymphocyte, and monocyte counts were evaluated using a Sysmex XT-1800i full blood count analyzer (Sysmex Corporation, Kobe, Japan). Fasting blood lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein [LDL-c], triglycerides), uric acid, alanine aminotransferase, and fasting blood glucose were analyzed using a Hitachi 7600 automated biochemical analyzer at Kailuan General Hospital's central laboratory. High-sensitivity C-reactive protein (hs-CRP) was measured via a particle-enhanced immunonephelometric assay (Cias Latex CRP-H; Kanto Chemical Co., Inc., Tokyo, Japan). Serum creatinine was assessed via enzymatic methods on a Beckman Coulter AU5400 analyzer, and the

estimated glomerular filtration rate was determined using the CKD-EPI equation.

Assessment of MASLD and SIRI

In the present study, hepatic steatosis was assessed using abdominal ultrasonography. All ultrasound procedures were performed using the same PHILIPS HD15 color Doppler ultrasound system (1–5 MHz convex probe) by trained sonographers with over 5 years of clinical experience who had received standardized training. Diagnosis was based on at least two of three predefined sonographic features (see Table S1). To ensure consistency, all images were independently reviewed and jointly confirmed by two senior sonographers. A random subset was re-evaluated by additional experts to assess reliability. Importantly, all sonographers were blinded to participants' clinical and laboratory data during both image acquisition and interpretation. MASLD was identified by ultrasound-detected hepatic steatosis, alongside at least one cardiometabolic risk factor, excluding other known liver disease causes.[1] This operational definition is also consistent with the latest EASL–EASD–EASO clinical practice guidelines on MASLD.[23] The specific diagnostic criteria used in the Kailuan study are detailed in Table S2. The SIRI was determined using formula below:

$$SIRI = \frac{\text{Neutrophils count}\left(10^9/\text{L}\right) \times \text{Monocytes count}\left(10^9/\text{L}\right)}{\text{Lymphocytes count}\left(10^9/\text{L}\right)}$$

Ascertainment of outcomes

The main outcomes of this study were the initial incidence of CVD events and mortality. Subtypes of CVD encompassed myocardial infarction (MI) and total stroke, including both ischemic and hemorrhagic forms. Incident CVD events and all-cause mortality data were sourced from the Tangshan municipal social insurance institution and discharge records of all 11 Kailuan-affiliated hospitals. The data sources, covering all participants in the Kailuan study, were updated annually during the follow-up period.[24] Potential CVD events were identified using ICD-10 codes. An expert panel evaluated the yearly discharge summaries from the participating hospitals to verify suspected CVD cases. MI diagnosis adhered to WHO criteria from the multinational CVD monitoring study, incorporating clinical symptoms, electrocardiographic changes, and dynamic myocardial enzyme level alterations, as detailed in a prior study.[25] Stroke diagnosis was determined through neurological symptoms and clinical signs, corroborated by brain imaging via computed tomography or magnetic resonance imaging, and categorized as ischemic or hemorrhagic.[26]

Statistical analysis

Study participants' baseline characteristics were described using means ± standard deviations or medians with IQR for continuous variables, and frequencies with percentages for categorical variables. Continuous variables were analyzed by ANOVA or the Kruskal–Wallis test based on their distribution, while categorical variables were evaluated with the chi-square test.

Person-years of follow-up were determined from baseline survey date to earliest of CVD occurrence, all-cause death, or the end of follow-up on December 31, 2021. The associations between the SIRI and the risk of CVD and mortality were assessed by Cox proportional hazards models. To minimize potential information loss from categorizing a continuous variable, SIRI was analyzed both as a continuous variable (evaluated per IQR increase) and as a categorical variable (by quartiles). The proportional hazards assumption was tested using Schoenfeld residuals, and no violations were detected (all p >0.05). For each model, hazard ratios (HRs) and 95% CIs were determined.

Three progressively adjusted multivariable models were constructed. Model 1 was adjusted for both age and sex. Model 2 was additionally adjusted for education level, physical activity, smoking status, marital status, hs-CRP, LDL-C, and alanine aminotransferase. Model 3 was further adjusted for family history of CVD and the use of medications for managing blood pressure, glucose, and lipid. The variance inflation factor was used to evaluate multicollinearity among the chosen covariates. Covariates with a variance inflation factor exceeding 10 indicated substantial collinearity. In our analysis, no covariate exceeded this threshold (Table S3), ensuring the reliability of the regression estimates. Trend p values were determined by treating the median value of each SIRI quartile as a continuous ordinal variable in the regression models. Kaplan–Meier analysis estimated survival probabilities during follow-up, with subgroup differences assessed via the log-rank test.

Restricted cubic spline (RCS) regression was used to evaluate non-linear dose-response relationships between SIRI and the risk of CVD and mortality in MASLD populations. Knots were placed at the 5th, 35th, 65th, and 95th percentiles of the SIRI distribution. These percentiles were chosen to balance model flexibility and stability and were selected based on minimizing the Akaike information criterion value. Linearity of the association was tested using the Wald test.

A discrimination and reclassification approach was applied to assess the incremental predictive value of SIRI for cardiovascular events in individuals with MASLD. The C-statistic, integrated discrimination improvement, and net reclassification improvement were calculated after incorporating SIRI into a fully adjusted model containing hs-CRP. Comparative analyses for SII and NLR were also conducted.

To investigate potential mediating pathways linking systemic inflammation to CVD and mortality in patients with MASLD, three biologically plausible mediators – Chinese visceral adiposity index (CVAI), platelet count (PLT), and triglyceride-glucose index (TyG) – were included in the analysis. CVAI captures visceral adiposity and metabolic dysfunction, PLT reflects inflammation-induced thrombogenicity, and TyG serves as a validated proxy for insulin resistance. These markers represent distinct inflammation-related pathophysiological processes through which SIRI may influence cardiovascular risk and mortality. Mediation analysis was performed using the survCox model from the 'regmedint' package to assess the mediating roles of CVAI, PLT, and TyG in the relationship between SIRI and CVD/mortality. The indirect effects of each mediator were calculated as the portion of the total effect of SIRI mediated by these variables, with the direct effect representing SIRI's independent impact. The proportion of mediation was determined by dividing the indirect effect by the total effect and multiplying by 100, indicating

the percentage of SIRI's total effect on CVD and mortality explained through these mediators.

Stratified analyses and interaction tests were performed across subgroups categorized by sex (male, female), age (under 60, 60 years and above), physical activity (yes, no), education level (high school or above, below high school), and family history of CVD (yes, no). Cox models incorporated interaction terms to evaluate potential effect modification.

Multiple sensitivity analyses were conducted to evaluate the robustness of the findings. To minimize reverse causality, analyses were conducted again after removing participants who encountered outcomes within the initial 2 years of follow-up. Second, analyses were restricted to participants not using blood pressure-lowering or hypoglycemic agents to account for confounding effects of pharmacologic treatment. Third, Fine and Gray hazard models were employed to address the competing risk of non-CVD mortality.[27]

Statistical analyses were performed using R Studio (v4.3.3) and SAS software (v9.4; SAS Institute Inc., Cary, NC, USA). A two-sided p value <0.05 was deemed statistically significant.

Results

Baseline characteristics

The final analytical population included 24,340 adults with MASLD, stratified by quartiles of the SIRI (Table 1). The average age of participants was 53.2 ± 11.7 years, with 78.9% being male. Individuals in higher SIRI quartiles tended to be male, less educated, current smokers, and exhibited higher blood pressure, heart rate, hs-CRP levels, along with a family history of CVD. Moreover, several metabolic indicators, including total cholesterol, LDL-C, fasting blood glucose and uric acid levels, tended to increase across higher SIRI quartiles. In contrast, estimated glomerular filtration rate showed a decreasing trend with increasing SIRI levels.

Associations between SIRI and risk of CVD and all-cause mortality

During a median follow-up of 15.9 (IQR 13.7-16.2) years for CVD outcomes and 16.0 (IQR 15.6-16.2) years for mortality, a total of 4,171 cases of CVD were identified, including 826 MI, 2,719 total stroke (2,414 ischemic stroke and 396 hemorrhagic stroke), and 4,510 cases of death from any cause (18.5%). Kaplan–Meier survival analysis indicated that participants in the highest SIRI quartile exhibited significantly reduced survival rates for both CVD and mortality compared to those in the lowest quartiles (Figs 2 and S1-4; all log-rank p <0.05). As shown in Table 2, higher SIRI levels were significantly associated with increased risks of both CVD and mortality. A significant dose-response relationship was identified across SIRI quartiles for all outcomes (p trend <0.05). The multivariable-adjusted HRs with 95% CIs for participants in the highest *vs*.

Table 1. Baseline characteristics of participants stratified by quartiles of SIRI.

		Quartiles of SIRI				
Variables	**Overall (N = 24,340)**	**Quartile1 (6,098)**	**Quartile2 (6,072)**	**Quartile3 (6,126)**	**Quartile4 (6,044)**	***p* values**
Sociodemographic						
Ages, years	53.2 ± 11.7	54.0 ± 11.5	53.4 ± 11.6	52.9 ± 11.7	52.6 ± 12.0	<0.01
Male, n (%)	19,203 (78.9)	4,282 (70.2)	4,719 (77.7)	5,009 (81.8)	5,193 (85.9)	<0.01
Have spouse, n (%)	23,445 (96.3)	5,840 (95.8)	5,864 (96.6)	5,911 (96.5)	5,830 (96.5)	0.07
High school diploma or above, n (%)	4,395 (18.1)	1,282 (21.0)	1,104 (18.2)	1,072 (17.5)	937 (15.5)	<0.01
Anthropometrics						
Heart rate, beats/min	74.47 ± 10.29	73.61 ± 10.19	74.16 ± 10.05	74.61 ± 10.27	75.44 ± 10.56	<0.01
SBP, mmHg	137.53 ± 20.95	135.00 ± 20.26	136.77 ± 20.22	137.93 ± 20.64	140.42 ± 22.25	<0.01
DBP, mmHg	87.31 ± 11.76	85.45 ± 11.09	86.97 ± 11.27	87.76 ± 11.87	89.07 ± 12.47	<0.01
Lifestyle						
Physical activity, n (%)	3,595 (14.8)	1,018 (16.7)	933 (15.4)	821 (13.4)	823 (13.6)	<0.01
Smoke, n (%)	8,315 (34.2)	1,919 (31.5)	2,001 (33.0)	2,133 (34.8)	2,262 (37.4)	<0.01
Blood biomarkers						
TC, mmol/L	5.08 ± 1.25	5.08 ± 1.29	5.05 ± 1.28	5.09 ± 1.22	5.11 ± 1.18	0.06
TG, mmol/L	1.77 (1.24-2.65)	1.74 (1.21-2.60)	1.78 (1.25-2.68)	1.78 (1.26-2.66)	1.77 (1.24-2.66)	0.02
LDL-c, mmol/L	2.36 (1.85-2.83)	2.35 (1.84-2.85)	2.33 (1.85-2.80)	2.37 (1.85-2.84)	2.38 (1.85-2.85)	0.27
FBG, mmol/L	5.30 (4.80-6.11)	5.27 (4.73-6.00)	5.30 (4.80-6.10)	5.31 (4.80-6.19)	5.35 (4.80-6.24)	<0.01
Uric acid, μmol/L	307.51 ± 89.41	305.31 ± 92.24	307.04 ± 88.57	306.13 ± 88.53	311.59 ± 88.12	<0.01
eGFR, ml/min/1.73 m^2	77.68 ± 18.54	79.13 ± 18.26	78.98 ± 19.12	77.44 ± 18.46	75.17 ± 18.02	<0.01
hs-CRP, mg/L	1.23 (0.50-3.20)	1.10 (0.48-2.80)	1.10 (0.47-2.82)	1.25 (0.51-3.25)	1.53 (0.60-4.00)	<0.01
ALT, U/L	21.0 (16.0-30.0)	21.0 (16.0-30.0)	21.0 (16.0-29.0)	22.0 (16.0-30.0)	21.0 (16.0-30.0)	0.10
PLT, $*10^9$/L	206.27 ± 57.62	201.96 ± 55.76	202.78 ± 56.75	208.53 ± 58.91	211.83 ± 58.43	<0.01
LYM, $*10^9$/L	2.41 ± 0.73	2.43 ± 0.76	2.40 ± 0.70	2.41 ± 0.71	2.40 ± 0.75	0.29
NEUT, $*10^9$/L	3.97 ± 1.20	3.08 ± 0.83	3.65 ± 0.80	4.15 ± 0.92	5.02 ± 1.27	<0.01
MONO, $*10^9$/L	0.40 (0.30-0.50)	0.20 (0.20-0.30)	0.30 (0.30-0.40)	0.40 (0.30-0.50)	0.60 (0.50-0.70)	<0.01
SIRI	0.62 (0.42-0.90)	0.31 (0.24-0.37)	0.51 (0.47-0.56)	0.74 (0.67-0.81)	1.18 (1.02-1.45)	<0.01
Family history of disease						
CVD, n (%)	1,465 (5.96)	328 (5.3)	361 (5.9)	364 (5.9)	412 (6.7)	0.02
History of drugs						
Antihypertensive drugs, n (%)	4,311 (17.5)	1,034 (16.8)	1,055 (17.2)	1,049 (17.1)	1,173 (19.1)	<0.01

Values are presented as mean ± SD or median (IQR) for continuous variables, and number (percentage) for categorical variables. Statistical significance was set at p <0.05.
ALT, alanine aminotransferase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; LYM, lymphocyte count; NEUT, neutrophil count; PLT, platelet count; SBP, systolic blood pressure; SIRI, systemic inflammation response index; TC, total cholesterol; TG, triglycerides.

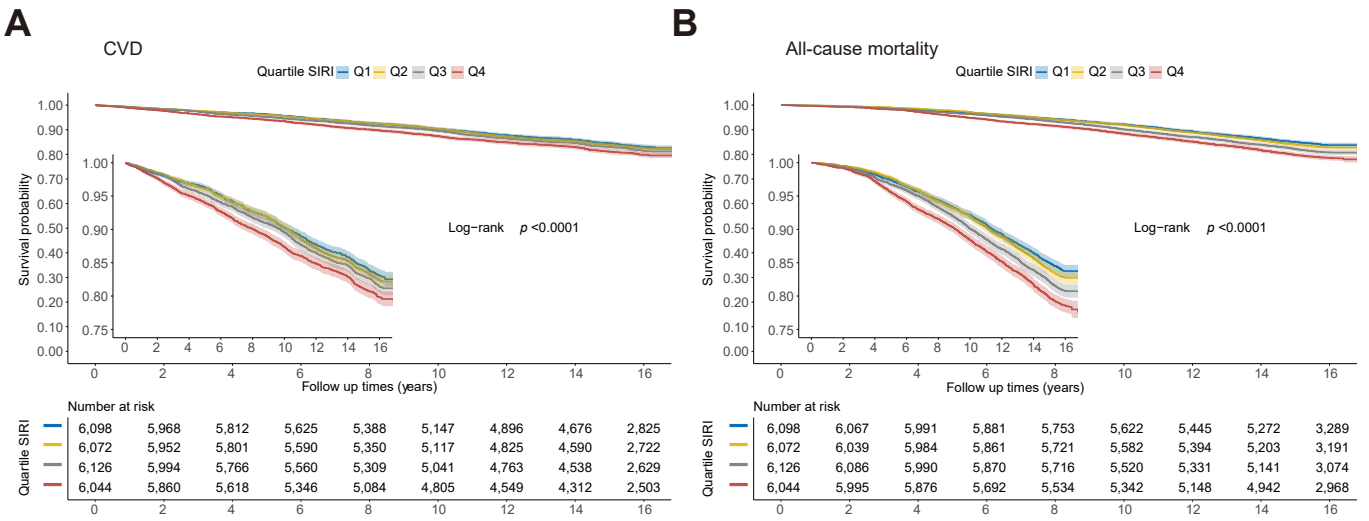


Fig. 2. Kaplan–Meier curves depicting survival probabilities in patients with MASLD according to SIRI quartiles. Panels show survival probability over a 16-year follow-up period stratified by SIRI quartiles (Q1–Q4) for: (A) CVD; (B) all-cause mortality. Statistical comparisons between groups were performed using the log-rank test, which revealed statistically significant differences in survival across SIRI quartiles for both CVD and all-cause mortality (p <0.0001). Insets show the same data plotted on an expanded y-axis for clarity. CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; SIRI, systemic inflammation response index.

lowest SIRI quartile were as follows: 1.21 (1.10-1.31) for CVD (p <0.001), 1.22 (1.01-1.48) for MI (p = 0.045), 1.18 (1.06-1.31) for total stroke (p = 0.003), 1.15 (1.03-1.29) for ischemic stroke (p = 0.017), 1.41 (1.07-1.86) for hemorrhagic stroke (p = 0.016), and 1.34 (1.24-1.46) for all-cause mortality (p <0.001). When modeled as a continuous variable per IQR increase in SIRI, the corresponding HRs (95% CIs) were 1.09 (1.05-1.12) for CVD (p <0.001), 1.08 (1.01-1.17) for MI (p = 0.040), 1.05 (1.02-1.09) for total stroke (p = 0.003), 1.05 (1.01-1.10) for ischemic stroke (p = 0.028), 1.14 (1.02-1.27) for hemorrhagic stroke (p = 0.020), 1.14 (1.11-1.18) for all-cause mortality (p <0.001).

RCS analyses

Further RCS analyses were performed to assess the dose-response relationship between SIRI and the risk of CVD and mortality, with adjustments for all covariates (Fig. 3). The plots indicated a linear relationship between SIRI and the risks of CVD, all-cause mortality, and total stroke, with all p values for non-linearity exceeding 0.05. In contrast, no significant dose-response relationships were found between SIRI and the risks of MI, ischemic stroke, or hemorrhagic stroke (all p for overall >0.05).

Predictive performance of SIRI for cardiovascular risk in patients with MASLD

To assess the incremental prognostic value of different inflammatory indices among individuals with MASLD, we compared the performance of SIRI, SII, and NLR for predicting incident CVD. Each index was added separately to a fully adjusted model that included conventional risk factors as well as hs-CRP, a traditional inflammatory marker. Among the three indices, SIRI demonstrated the best predictive performance. Adding SIRI modestly improved the C-statistic from 0.6587 to 0.6599, yielded a significant integrated discrimination improvement of 0.04% (95% CI 0.01–0.06, p = 0.012), and achieved a net reclassification improvement of 5.84% (95% CI 2.57–9.12, p <0.001). In contrast, the improvements from SII and NLR were smaller and not statistically significant. Detailed metrics are shown in Table 3. These findings suggest that SIRI offers superior value in cardiovascular risk stratification among patients with MASLD, beyond that provided by hs-CRP alone or other composite inflammatory indices.

Mediation analyses

Mediation analyses, illustrated in Fig. 4A,B, revealed that TyG partially mediated the correlation between SIRI and both CVD and mortality. Specifically, the indirect effect of TyG on CVD was significant (β = 0.004, p <0.001), representing 5.3% of the total effect of SIRI on CVD (p = 0.006). This suggests that TyG mediates a small but significant portion of the relationship between SIRI and CVD, with the remaining portion of the effect being direct (β = 0.076, p <0.001). Similarly, TyG's indirect effect on mortality was also significant (β = 0.004, p <0.001), accounting for 2.9% of the total effect of SIRI on mortality (p = 0.003). The direct effect of SIRI on mortality was also significant (β = 0.128, p <0.001). To further explore the relationship among TyG, SIRI, and clinical outcomes, we examined the proportion of participants with low *vs*. high TyG and corresponding CVD/mortality risks across SIRI quartiles (Fig. 4C). The low TyG values increased slightly from 47.4% in SIRI Q1 to 51.6% in Q4. In parallel, CVD incidence rose from 16.0% to 18.8%, and mortality from 16.0% to 21.5% across SIRI quartiles. In contrast, PLT demonstrated no significant mediation for CVD (proportion mediated = 2.0%, p = 0.336) but showed a modest negative indirect effect for mortality (proportion mediated = -3.3%, p = 0.032). No significant mediation was observed for CVAI in relation to either outcome (all p >0.8) (Fig. S5).

Subgroup and sensitivity analyses

Subgroup analysis identified significant interactions between SIRI and all-cause mortality, influenced by gender and

Table 2. Associations between SIRI and risk of CVD and all-cause mortality in MASLD.

SIRI	Total N	No. of events (incident rate[a])	Model 1		Model 2		Model 3	
			HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
CVD								
Per IQR increase	24,340		1.10 (1.06-1.14)	<0.001	1.09 (1.05-1.13)	<0.001	1.09 (1.05-1.12)	<0.001
Quartiles								
Q1	6,098	972 (11.34)		Ref.		Ref.		Ref.
Q2	6,072	1,003 (11.79)	1.04 (0.96-1.14)	0.351	1.04 (0.95-1.13)	<0.001	1.05 (0.96-1.14)	0.317
Q3	6,126	1,058 (12.49)	1.11 (1.02-1.21)	0.017	1.10 (1.1-1.21)	0.027	1.10 (1.01-1.20)	0.031
Q4	6,044	1,138 (13.94)	**1.24 (1.14-1.35)**	**<0.001**	**1.22 (1.12-1.33)**	**<0.001**	**1.21 (1.10-1.31)**	**<0.001**
p for trend				<0.001		<0.001		0.001
MI								
Per IQR increase	24,340		1.11 (1.02-1.19)	0.012	1.09 (1.01-1.18)	0.028	1.08 (1.01-1.17)	0.040
Quartiles								
Q1	6,098	188 (2.08)		Ref.		Ref.		Ref.
Q2	6,072	199 (2.22)	1.05 (0.86-1.28)	0.658	1.05 (0.86-1.28)	0.656	1.06 (0.86-1.29)	0.596
Q3	6,126	205 (2.29)	1.08 (0.89-1.32)	0.451	1.07 (0.88-1.31)	0.487	1.07 (0.88-1.31)	0.494
Q4	6,044	234 (2.69)	**1.26 (1.04-1.53)**	**0.018**	**1.24 (1.02-1.50)**	**0.034**	**1.22 (1.01-1.48)**	**0.045**
p for trend				0.018		0.034		0.048
Total stroke								
Per IQR increase	24,340		1.06 (1.03-1.10)	0.001	1.06 (1.02-1.10)	0.001	1.05 (1.02-1.09)	0.003
Quartiles								
Q1	6,098	635 (7.22)		Ref.		Ref.		Ref.
Q2	6,072	661 (7.58)	1.04 (0.94-1.16)	0.439	1.04 (0.93-1.16)	0.519	1.04 (0.93-1.16)	0.457
Q3	6,126	684 (7.85)	1.08 (0.97-1.21)	0.152	1.07 (0.96-1.20)	0.197	1.07 (0.96-1.20)	0.203
Q4	6,044	739 (8.78)	**1.21 (1.08-1.34)**	**<0.001**	**1.19 (1.07-1.32)**	**0.002**	**1.18 (1.06-1.31)**	**0.003**
p for trend				<0.001		0.001		0.003
Ischemic stroke								
Per IQR increase	24,340		1.07 (1.02-1.12)	0.007	1.06 (1.01-1.11)	0.019	1.05 (1.01-1.10)	0.028
Quartiles								
Q1	6,098	568 (6.42)		Ref.		Ref.		Ref.
Q2	6,072	583 (6.64)	1.03 (0.92-1.16)	0.618	1.02 (0.91-1.15)	1.023	1.03 (0.92-1.16)	0.627
Q3	6,126	618 (7.06)	1.10 (0.98-1.23)	0.116	1.09 (0.97-1.22)	1.089	1.09 (0.97-1.22)	1.150
Q4	6,044	645 (7.61)	**1.18 (1.05-1.32)**	**0.004**	**1.16 (1.03-1.30)**	**0.011**	**1.15 (1.03-1.29)**	**0.017**
p for trend				0.002		0.005		0.009
Hemorrhagic stroke								
Per IQR increase	24,340		1.15 (1.03-1.28)	0.012	1.14 (1.02-1.27)	0.018	1.14 (1.02-1.27)	0.020
Quartiles								
Q1	6,098	87 (0.96)		Ref.		Ref.		Ref.
Q2	6,072	96 (1.06)	1.09 (0.82-1.46)	0.539	1.08 (0.81-1.45)	0.600	1.09 (0.81-1.46)	0.569
Q3	6,126	89 (0.99)	1.01 (0.75-1.36)	0.925	0.99 (0.74-1.34)	0.960	0.99 (0.74-1.34)	0.975
Q4	6,044	124 (1.42)	**1.44 (1.10-1.90)**	**0.009**	**1.42 (1.08-1.88)**	**0.014**	**1.41 (1.07-1.86)**	**0.016**
p for trend				0.016		0.024		0.028
All-cause mortality								
Per IQR increase	24,340		1.16 (1.12-1.19)	<0.001	1.15 (1.11-1.19)	<0.001	1.14 (1.11-1.18)	<0.001
Quartiles								
Q1	6,098	986 (10.78)		Ref.		Ref.		Ref.
Q2	6,072	1,044 (11.48)	1.07 (0.98-1.16)	0.140	1.06 (0.97-1.16)	0.170	1.07 (0.98-1.17)	0.136
Q3	6,126	1,178 (12.97)	1.22 (1.12-1.33)	<0.001	1.21 (1.12-1.32)	<0.001	1.21 (1.11-1.32)	<0.001
Q4	6,044	1,302 (14.73)	**1.38 (1.27-1.50)**	**<0.001**	**1.36 (1.25-1.48)**	**<0.001**	**1.34 (1.24-1.46)**	**<0.001**
p for trend				<0.001		<0.001		<0.001

HRs and 95% CIs for CVD, MI, stroke (total, ischemic, and hemorrhagic), and all-cause mortality were estimated across SIRI quartiles and per IQR increase using Cox proportional hazards models. Model 1 was adjusted for age and sex; Model 2 was further adjusted for education level, physical activity, current smoking status, marital status, hs-CRP, LDL-C, and ALT; Model 3 additionally adjusted for family history of CVD, antihypertensive treatment, antidiabetic treatment, and lipid-lowering treatment.

ALT, alanine aminotransferase; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease; MI, myocardial infarction; SIRI, systemic inflammation response index.

[a]Incident rate was calculated per 1,000 person-years of follow-up. Statistical significance was set at $p<0.05$.

physical activity. The association was stronger in women (*p* for interaction = 0.04, HR per IQR = 1.23, 95% CI 1.12–1.35). The association between SIRI and all-cause mortality was stronger in physically inactive individuals than in active ones (*p* for interaction <0.01, HR per IQR = 1.18, 95% CI 1.13–1.22). No significant interactions were identified between SIRI and the overall CVD risk (Fig. 5). Sensitivity analyses confirmed the primary findings, even after adjusting for covariates, excluding outcome events from the first 2 years of follow-up, and separately excluding participants on hypoglycemic or antihypertensive medications. The Fine–Gray hazard model, used to address competing risks from non-CVD-related deaths, yielded results consistent with the primary Cox regression (Table S4). Cumulative incidence of CVD remained significant by SIRI quartiles in the competing risk analysis (Gray's test, *p* <0.001; Fig. S6). These findings collectively affirm the robustness and stability of the observed associations.

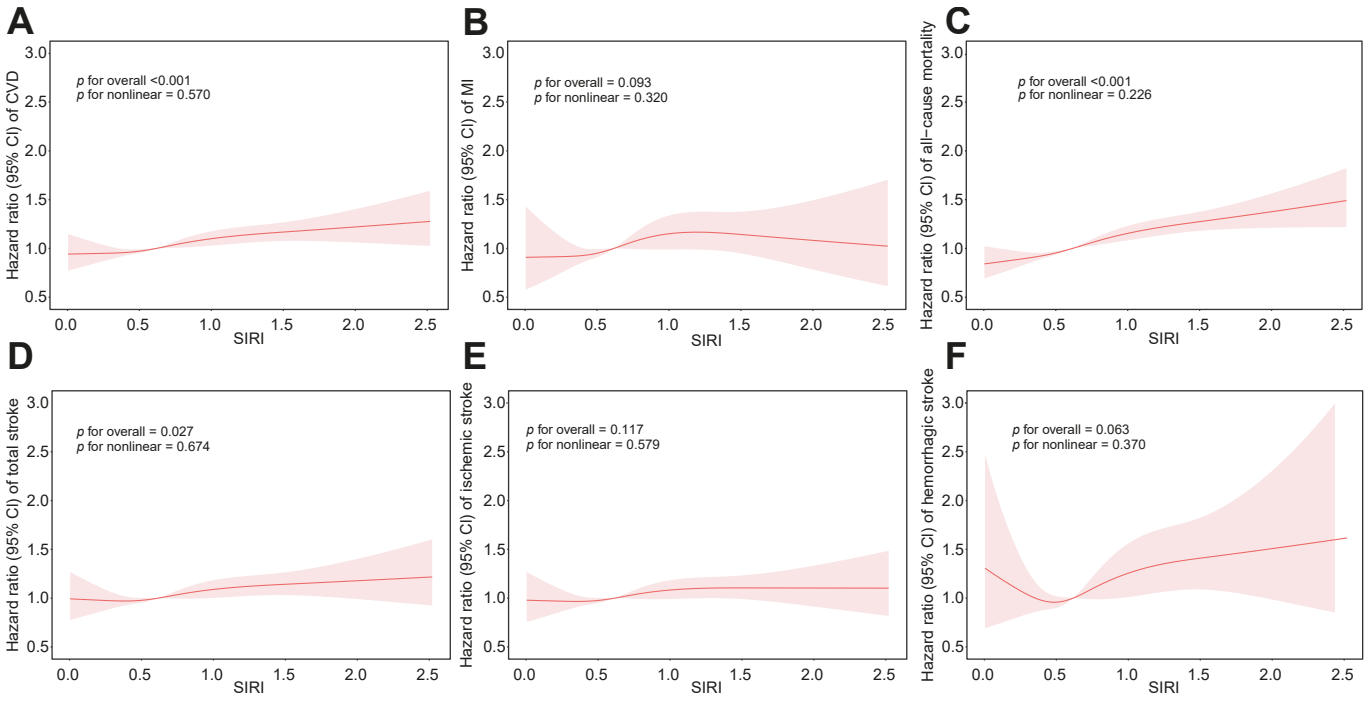


Fig. 3. Dose-response association between SIRI and CVD and mortality in patients with MASLD. Restricted cubic spline models were used to assess potential non-linear associations of SIRI with: (A) CVD; (B) MI; (C) all-cause death; (D) total stroke; (E) ischemic stroke; (F) hemorrhage stroke. The solid lines represent adjusted HRs, and the shaded areas indicate 95% CIs. Hazard ratios were adjusted for age, gender, education level, physical activity, current smoking, marital status, hs-CRP, LDL-c, ALT, family history of CVD, blood pressure-lowering treatment, hypoglycemic treatment and lipid-lowering treatment. *p* values for the overall association and for non-linearity were calculated using the likelihood ratio test. Significant overall associations were observed for CVD (p <0.001), all-cause mortality (p <0.001), and hemorrhagic stroke (p = 0.027). No statistically significant non-linear associations were found (all p for non-linearity >0.05). ALT, alanine aminotransferase; CVD, cardiovascular disease; hs-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease; MI, myocardial infarction; SIRI, systemic inflammation response index.

Table 3. Discrimination and reclassification analyses for cardiovascular disease risk prediction using NLR, SII, and SIRI.

	C-index estimate	IDI estimate (95% CI) %	*p*value	NRI (category free) estimate (95% CI) %	*p* value
Baseline model	0.6587	Ref.	Ref.	Ref.	Ref.
Baseline model+ NLR	0.6597	0.02 (0.00–0.04)	0.088	2.47 (-0.83 to 5.77)	0.146
Baseline model+ SII	0.6596	0.02 (0.00–0.04)	0.108	2.04 (-1.25 to 5.33)	0.230
Baseline model+ SIRI	**0.6599**	**0.04 (0.01–0.06)**	**0.012**	**5.84 (2.57–9.12)**	**<0.001**

C-statistics, IDI, and category-free NRI were calculated to assess the incremental value of adding NLR, SII, or SIRI to the baseline model in predicting CVD risk. Baseline model was adjusted for age, sex, education level, physical activity, current smoking, marital status, hs-CRP, LDL-c,
ALT, blood pressure-lowering treatment, hypoglycemic treatment, lipid-lowering treatment and family history of CVD. Statistical significance was set at p <0.05. ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; IDI, integrated discrimination improvement; LDL-c, low-density lipoprotein cholesterol; NLR, neutrophils to lymphocytes ratio; NRI, net reclassification index; Ref., reference; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

Discussion

In this extensive prospective analysis of the Kailuan Study, involving 24,340 participants with MASLD from a cohort of approximately 100,000 adults in northern China and followed for a median of 16.0 years, elevated SIRI levels were independently linked to a higher risk of CVD (including MI, total stroke, ischemic stroke, and hemorrhagic stroke) and all-cause mortality. These associations remained robust across extensive sensitivity and subgroup analyses, underscoring the stability of our findings. Notably, SIRI showed superior predictive performance over hs-CRP alone or other inflammatory indices, highlighting its value in cardiovascular risk stratification. Moreover, mediation analyses indicated that the TyG partially mediates the link between SIRI and the onset of CVD. PLT exhibited a slight inverse mediation effect on the association between SIRI and all-cause mortality.

Previous research has identified strong links between high SIRI levels and heightened risks of CVD and overall mortality in the general population. A 20-year cohort study of 42,875 US adults found that high SIRI levels independently correlated with increased risks of CVD and mortality.[28] Meanwhile, a large-scale prospective study using the UK Biobank cohort found a significant association between elevated SIRI and an increased risk of incident CVD in 423,701 individuals.[29] In addition, elevated SIRI has also been associated with adverse cardiovascular outcomes in individuals with chronic conditions like hypertension, diabetes mellitus, rheumatoid arthritis, and chronic kidney disease.[17–20] Our study is the first to show that elevated SIRI levels are linked to a higher risk of CVD and mortality in a Chinese cohort with MASLD, highlighting the role of chronic inflammation in MASLD pathogenesis and cardiovascular risk.

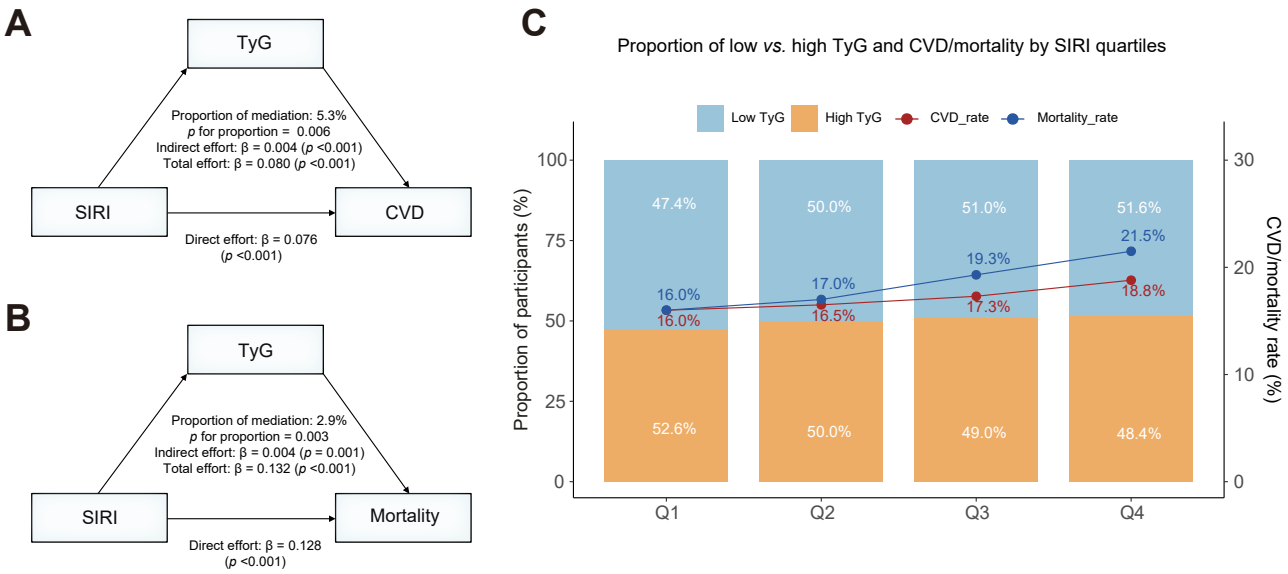


Fig. 4. Mediation analyses of the association between SIRI and CVD/mortality in MASLD. Mediation analysis was performed using the Cox proportional hazards model (survCox), with TyG as the mediator and SIRI as the exposure. Panels show the decomposition of total effects into direct and indirect (mediated) effects for: (A) CVD and (B) all-cause mortality. (C) Proportion of participants with low *vs*. high TyG and corresponding CVD/mortality risks across SIRI quartiles. For CVD, the indirect effect was β = 0.004 (*p* <0.001), direct effect β = 0.076 (*p* <0.001), and total effect β = 0.080 (*p* <0.001), with 5.3% of the total effect mediated by TyG (*p* for mediation = 0.006). For all-cause mortality, the indirect effect was β = 0.004 (*p* = 0.001), direct effect β = 0.128 (*p* <0.001), and total effect β = 0.132 (*p* <0.001), with 2.9% mediated by TyG (*p* for mediation = 0.003). All reported associations and mediation effects were statistically significant (*p* <0.05). An increasing trend in CVD/mortality was observed with higher SIRI quartiles and low TyG values, with low and high TyG groups defined by a median split. All models were adjusted for age, sex, education level, physical activity, current smoking, marital status, hs-CRP, LDL-c, ALT, family history of CVD, antihypertensive treatment, hypoglycemic treatment and lipid-lowering treatment. ALT, alanine aminotransferase; CVD, cardiovascular disease; hs-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease; SIRI, systemic inflammation response index; TyG, triglyceride-glucose index.

A cross-sectional study utilizing NHANES data found an independent association between SIRI and stroke history.[30] Moreover, a separate cohort study found that higher SIRI levels independently correlated with a greater risk of cardiovascular mortality in US adults with MASLD.[31] Additionally, a study in Northern Tuscany, Italy, involving 105 patients with ST-segment elevation MI, found that elevated SIRI levels significantly correlated with reduced survival rates and heightened mortality risk.[14] However, susceptibility to disease may vary across populations due to genetic, environmental, and lifestyle differences. Evidence derived from Western populations cannot be directly extrapolated to Eastern cohorts. Our study expands on existing evidence by showing that individuals in the highest SIRI quartile within the Chinese MASLD population face significantly elevated risks of CVD, its sub-outcomes, and all-cause mortality.

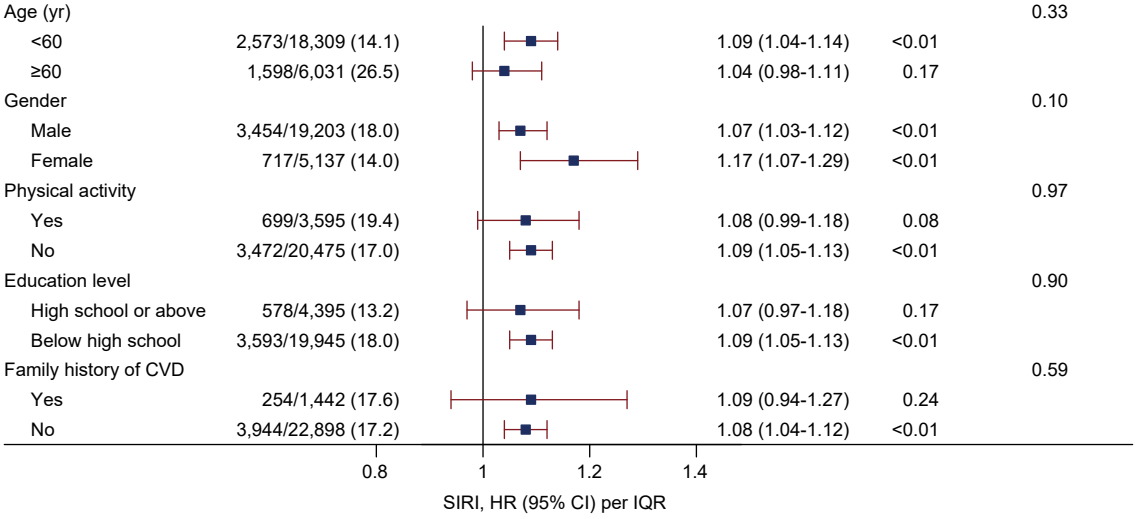
Our RCS analyses identified clear linear associations between SIRI and risks of CVD including total stroke, and all-cause mortality. No statistically significant associations were found between SIRI and CVD outcome subtypes, including MI, ischemic stroke, or hemorrhagic stroke. This discrepancy may stem from variations in underlying pathophysiological mechanisms: total stroke outcomes potentially aggregate heterogeneous etiologies, providing sufficient event numbers and power, while specific subtypes might have smaller event counts or more complex inflammatory pathways that dilute statistical significance.

Previous research within our cohort has established that a high SIRI correlates with a heightened risk of MI, stroke, and mortality.[25] The current analysis extends these findings specifically to patients with MASLD, providing additional evidence of these relationships in this particular population. Subgroup analyses indicated a stronger link between elevated SIRI levels and all-cause mortality in women and those with insufficient physical activity. These subgroups may represent particularly vulnerable populations, potentially due to less favorable lifestyle behaviors which may amplify inflammatory responses.[32] In women specifically, while estrogen is generally cardioprotective, this effect may be diminished in the presence of metabolic dysfunction and chronic low-grade inflammation. Evidence from the prior study suggests that younger women with MASLD are at elevated risk of heart failure, indicating a more adverse inflammatory-metabolic profile.[33] Combined with sex-related immune differences – such as heightened neutrophil and monocyte activity[34] – these factors may partly explain the stronger relationship between SIRI and mortality observed in women.

Systemic inflammation is a well-recognized hallmark of MASLD. Participants with MASLD show significantly higher circulating levels of pro-inflammatory cytokines such as interleukin-6, C–C motif chemokine ligand 19, and monocyte chemoattractant protein-1 compared to those without MASLD.[35] Elevated systemic inflammatory markers, including C-reactive protein, SII, and NLR, are consistently observed in MASLD populations. Importantly, this heightened systemic inflammatory state is believed to play a critical role in driving the histological progression of MASLD.[36] A recent study in patients with heart failure demonstrated that SIRI had a stronger predictive value for all-cause mortality than SII, suggesting its potential superiority as an inflammation-based

A

Subgroups	Case/total (%)	HR (95% CI)	*p* value	*p* for interaction
Age (yr)				0.33
<60	2,573/18,309 (14.1)	1.09 (1.04-1.14)	<0.01	
≥60	1,598/6,031 (26.5)	1.04 (0.98-1.11)	0.17	
Gender				0.10
Male	3,454/19,203 (18.0)	1.07 (1.03-1.12)	<0.01	
Female	717/5,137 (14.0)	1.17 (1.07-1.29)	<0.01	
Physical activity				0.97
Yes	699/3,595 (19.4)	1.08 (0.99-1.18)	0.08	
No	3,472/20,475 (17.0)	1.09 (1.05-1.13)	<0.01	
Education level				0.90
High school or above	578/4,395 (13.2)	1.07 (0.97-1.18)	0.17	
Below high school	3,593/19,945 (18.0)	1.09 (1.05-1.13)	<0.01	
Family history of CVD				0.59
Yes	254/1,442 (17.6)	1.09 (0.94-1.27)	0.24	
No	3,944/22,898 (17.2)	1.08 (1.04-1.12)	<0.01	



B

Subgroups	Case/total (%)	HR (95% CI)	*p* value	*p* for interaction
Age (yr)				0.47
<60	1,825/18,309 (10.0)	1.15 (1.10-1.21)	<0.01	
≥60	2,685/6,031 (44.5)	1.12 (1.08-1.17)	<0.01	
Gender				0.04
Male	3,916/19,203 (20.4)	1.13 (1.10-1.17)	<0.01	
Female	594/5,137 (11.6)	1.23 (1.12-1.35)	<0.01	
Physical activity				<0.01
Yes	915/3,595 (25.5)	1.03 (0.95-1.11)	0.48	
No	3,595/20,475 (17.6)	1.18 (1.13-1.22)	<0.01	
Education level				0.98
High school or above	572/4,395 (13.0)	1.13 (1.03-1.24)	<0.01	
Below high school	3,938/19,945 (19.7)	1.15 (1.11-1.19)	<0.01	
Family history of CVD				0.48
Yes	220/1,442 (15.3)	1.18 (1.02-1.37)	0.03	
No	4,290/22,898 (18.7)	1.13 (1.09-1.17)	<0.01	

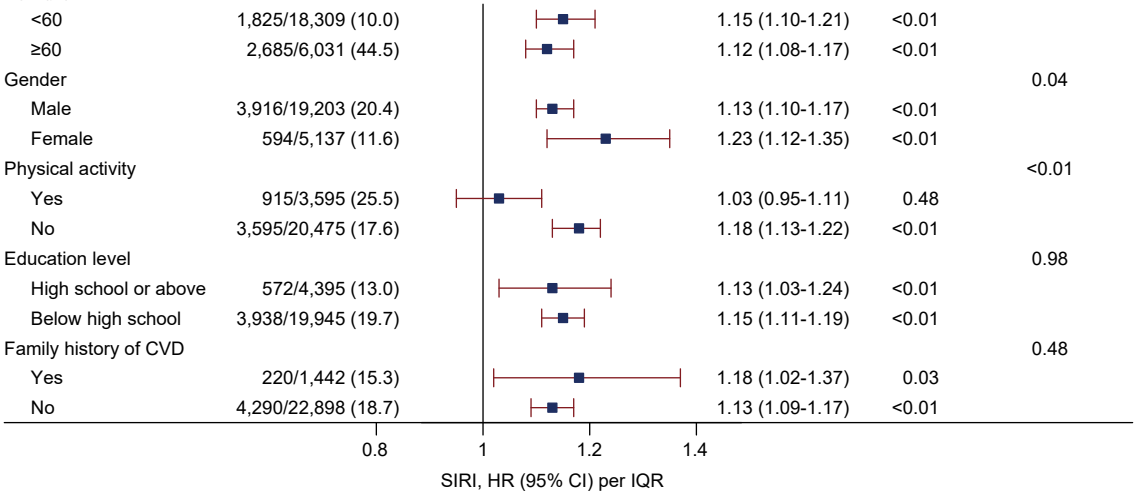


Fig. 5. Subgroup analyses of SIRI in relation to the risk of CVD and mortality in patients with MASLD. HRs and 95% CIs per IQR increase in SIRI were estimated using Cox proportional hazards models across subgroups defined by age, gender, physical activity, education level, and family history of CVD. All models were adjusted for age, sex, education level, physical activity, current smoking, marital status, hs-CRP, LDL-c, ALT, family history of CVD, blood pressure-lowering agents, hypoglycemic agents and lipid-lowering agents. (A) Results for incident CVD; (B) for all-cause mortality. Statistical significance was assessed using Wald tests. p <0.05 was considered statistically significant; p for interaction <0.05 indicated significant effect modification across subgroups. ALT, alanine aminotransferase; CVD, cardiovascular disease; HRs, hazard ratios; hs-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease; SIRI, systemic inflammation response index.

prognostic marker.[15] Similarly, SIRI demonstrated a stronger association with the severity of coronary atherosclerosis than NLR, underscoring its superiority in reflecting vascular inflammatory burden.[37] In line with these findings, our results further demonstrated that adding SIRI to a conventional risk model, including hs-CRP, modestly improved model discrimination and significantly enhanced risk reclassification. Compared with other inflammation-based indices, SIRI provided superior prognostic performance, underscoring its potential clinical relevance for cardiovascular risk stratification in individuals with MASLD. Although no standardized thresholds for SIRI have been established, our analysis suggests that it contributes incremental predictive value beyond traditional inflammatory markers. Given that SIRI is calculated from routine blood counts, it is inexpensive, widely accessible, and readily integrable into clinical workflows. These characteristics make it a promising candidate for risk stratification, especially in resource-limited settings. In the future, elevated SIRI levels could potentially serve as a trigger for intensified cardiovascular surveillance, lifestyle modification, or even consideration of anti-inflammatory or insulin-sensitizing therapies, pending validation in prospective trials.

The components of SIRI – neutrophils, monocytes, and lymphocytes – reflect immune processes central to both

hepatic and vascular pathology: Neutrophil extracellular trap formation, M1 macrophages polarization, and T-cell imbalance contribute to hepatic inflammation and fibrosis,[38] while the same mechanisms also drive vascular inflammation, foam cell formation, and plaque instability, linking systemic immune activation to elevated cardiovascular risk.[39] This study found no evidence of PLT mediating the relationship between SIRI and CVD risk. Notably, our mediation analysis identified a slight negative indirect effect of PLT on the association between SIRI and all-cause mortality in individuals with MASLD. This finding suggests that although higher SIRI levels were overall associated with increased mortality risk, part of this association was attenuated by pathways involving platelet activation. In MASLD, chronic low-grade inflammation and metabolic disturbances frequently coexist and can drive both prothrombotic states and vascular damage. Nevertheless, accumulating evidence indicates that platelets may also contribute to endothelial repair and help maintain vascular integrity, potentially counteracting some deleterious effects of inflammation.[40] This inconsistent mediation underscores the complex interplay between inflammation, hemostasis, and metabolic dysfunction in MASLD. In addition, chronic inflammation in MASLD may exacerbate insulin resistance and promote peripheral fat accumulation, further elevating cardiovascular risk.[41] Our mediation analyses supported this hypothesis by showing that the TyG partially mediated the relationship between SIRI and both CVD and all-cause mortality, while the CVAI did not exhibit a significant mediation effect. These findings imply that SIRI may increase cardiometabolic risk in patients with MASLD partly through mechanisms linked to insulin resistance. However, the proportion of effect mediated by TyG was relatively modest (5.3% for CVD and 2.9% for mortality), suggesting that other potential mediators may play a role. Future research should explore additional mechanistic pathways – such as pro-inflammatory cytokines (*e.g.* IL-6, TNF-α), adipokines (*e.g*. leptin, adiponectin), or oxidative stress markers – that may more fully account for the observed association between SIRI and cardiometabolic outcomes. Moreover, longitudinal studies incorporating these biomarkers are warranted to clarify the causal interplay between systemic inflammation and metabolic dysfunction.

This study has several notable strengths. The study utilizes a prospective cohort with an extensive sample size and prolonged follow-up duration. The number of documented CVD events was substantial, including major subtypes such as MI and stroke, which reduces potential misclassification and enhances the internal validity of our findings. Furthermore, although causal relationships could not be established, this study investigated the potential mediating role between SIRI and cardiovascular outcomes in individuals with MASLD, identifying insulin resistance as a possible mediator linked to chronic inflammation and providing a basis for future research. In addition, the consistent findings in both subgroup and sensitivity analyses demonstrate the robustness of the results. Nevertheless, some limitations should be noted. The information on lifestyle and other baseline characteristics was self-reported, which may lead to reporting bias. The selection of covariates was based on known associations with both exposure and outcomes, and multicollinearity tests confirmed no significant interdependence among included covariates. Nonetheless, residual confounding remains possible, particularly from unmeasured lifestyle and socioeconomic factors such as dietary intake, moderate alcohol use, income, or medication adherence, which may influence both inflammation and cardiovascular risk. Although all ultrasounds were performed using standardized equipment and protocols, potential inter-operator variability over time cannot be completely ruled out. Moreover, hepatic fibrosis is a key predictor of cardiovascular risk in MASLD and has greater prognostic relevance than steatosis alone. However, due to the absence of fibrosis staging or surrogate markers such as FIB-4 in our study, we were unable to evaluate the potential role of hepatic fibrosis as an effect modifier or confounder in the association between systemic inflammation and CVD outcomes. Future studies incorporating fibrosis assessments are warranted to further elucidate this relationship. Additionally, we only analyzed SIRI at baseline, despite the availability of repeated measures. Although systemic inflammation is a dynamic process, the current study focused on baseline inflammatory status to reflect early metabolic and cardiovascular risk. Investigating longitudinal changes in SIRI and their relationship with outcomes represents a valuable next direction, which we plan to address in future research. Finally, the predominance of male participants in this study, likely due to the occupational structure of the Kailuan cohort, may limit the external validity of our findings, as previous research suggests that systemic inflammation and cardiovascular risk pathways may differ by sex.[42] Furthermore, studies have shown that the Kailuan population exhibits relatively low adherence to ideal cardiovascular health behaviors compared to other populations,[43,44] which may influence baseline risk profiles and further limit the generalizability of our findings. Future studies with a more balanced sex distribution are warranted to confirm the generalizability of these associations across sexes.

In this extensive cohort study of Chinese adults with MASLD, elevated SIRI levels were independently linked to heightened risks of CVD and mortality. These associations remained robust in multiple sensitivity and subgroup analyses. Notably, SIRI outperformed hs-CRP alone or other inflammatory indices, highlighting its potential in cardiovascular risk stratification. Mediation analyses suggested that insulin resistance partly explained these relationships. These findings highlight the importance of systemic inflammation in cardiovascular risk among individuals with MASLD and the potential value of targeting inflammatory pathways in this population.

Affiliations

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Abbreviations

CVAI, Chinese visceral adiposity index; CVD, cardiovascular disease; HRs, hazard ratios; hs-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease; MI, myocardial infarction; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet count; RCS, restricted cubic spline; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; TyG, triglyceride-glucose index.

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Conflict of interest

The authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

HXZ, SLW, GV, and YRC conceptualized and designed the study. HXZ, KYW, HZ, GLC, and YLL performed the data analysis. HXZ drafted the initial manuscript. HXZ, KYW, HZ, GLC, YLL, and SHC interpreted the results. HXZ, KYW, YLL, SHC, GC, LAS, SLW, GV, and YRC critically revised the manuscript for important intellectual content. All authors reviewed the final manuscript and approved it for submission.

Data availability

Data supporting the findings of this study are available from the corresponding author on reasonable request.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101602.

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