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ORIGINAL RESEARCH

Chronic Inflammation in Patients with Chronic Coronary Syndrome Who Have Been Taking Lipid-Lowering Drugs as a Residual Risk Factor – a Bidirectional Synergistic Correlation with Epicardial Adipose Tissue

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Background: Patients with coronary heart disease on long-term lipid-lowering agents typically maintain relatively low lipid levels. However, an elevated systemic inflammatory state represents another major risk factor for poor prognosis in these individuals. This study aims to investigate the relationship between systemic inflammation and adverse outcomes in patients with chronic coronary syndrome(CCS), as well as its synergistic interaction with epicardial adipose tissue (EAT).

Methods: This is a double-center retrospective cohort study. From March 2017 to September 2023, We retrospectively included 278 patients with CCS from two medical institutions in China, all of whom had been receiving long-term statin therapy. Participants underwent cardiovascular magnetic resonance (CMR) imaging and blood testing. Systemic inflammatory response index (SIRI) were derived, and CMR parameters, including EAT volume, were measured. Cox regression analysis was used to evaluate the association between each variable and major adverse cardiovascular events (MACEs). Mediation analysis was applied to assess the interrelationships among systemic inflammatory markers, indexed EAT volume, and CMR parameters.

Results: Both the SIRI and indexed EAT volume were independently associated with MACEs. Combining SIRI and indexed EAT volume significantly improved the predictive capacity for MACEs. EAT volume partially mediated the relationship between SIRI and MACEs, and similarly, SIRI partially mediated the association between EAT volume and MACEs. Additionally, we observed analogous interrelationships among SIRI, indexed EAT volume, and extracellular volume (ECV).

Conclusion: In patients with CCS on long-term statin therapy, elevated SIRI and increased EAT volume represent more important risk factors than lipid levels. SIRI and EAT volume interact with each other and collectively contribute to a poor prognosis in these patients.

Keywords: chronic inflammation, chronic coronary syndrome, epicardial adipose tissue, systemic inflammatory response index, cardiovascular magnetic resonance

Introduction

Hyperlipidemia, particularly elevated low-density lipoprotein, has traditionally been an important predictor of future cardiovascular events in patients with chronic coronary syndrome(CCS).[1] With the widespread clinical use of lipid-lowering agents, especially statins, most patients now maintain relatively low blood lipid levels. However, the inflammatory state is often overlooked and is one of the important factors contributing to the residual risk of cardiovascular

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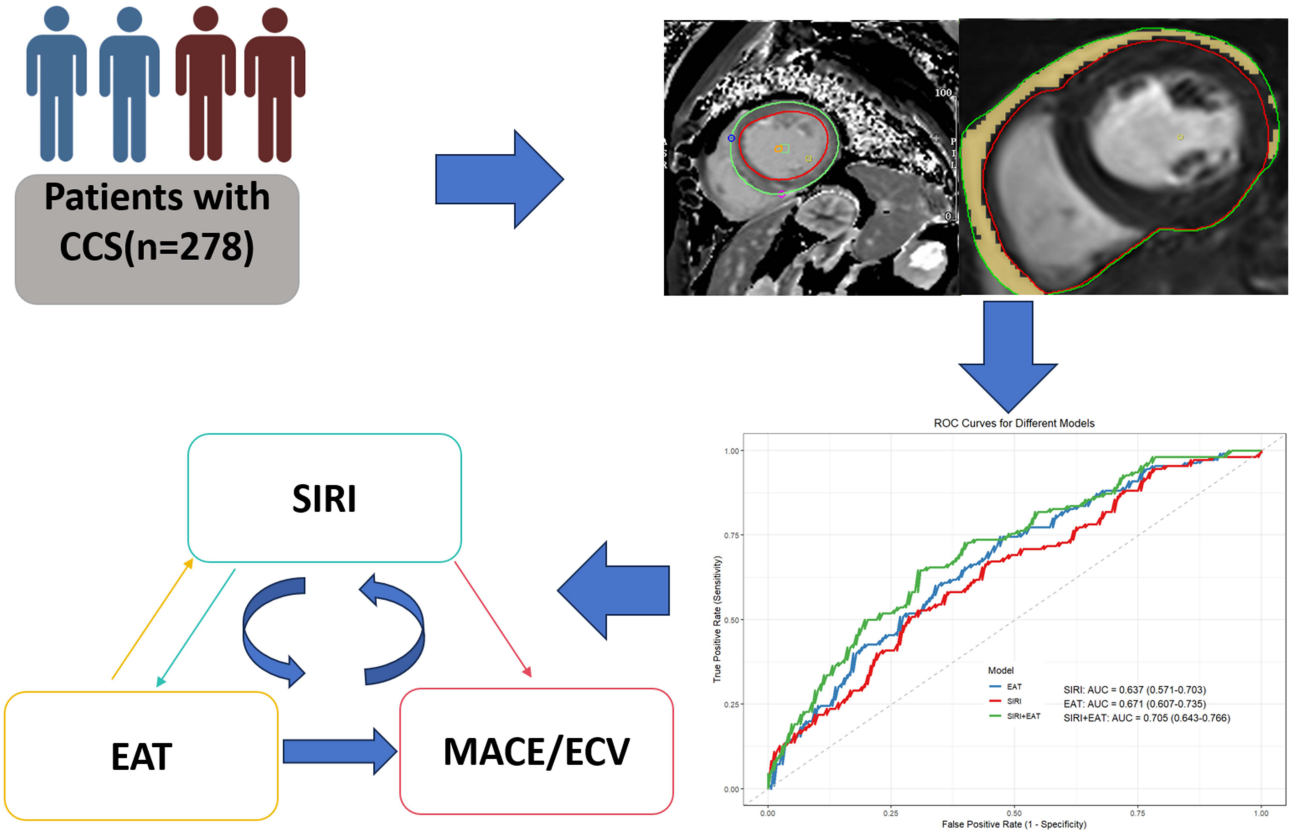
Graphical Abstract



diseases.[2] However, anti-inflammatory therapies have not yet been widely adopted in clinical practice. Relying solely on reducing low-density lipoprotein is unlikely to eliminate all vascular risks.

The Systemic Inflammatory Response Index (SIRI), as a comprehensive inflammatory marker, plays a significant role in assessing inflammatory status and prognosis in patients with CCS.[3] A chronic low-grade inflammatory state is central to the pathogenesis and progression of CCS. It accelerates the instability of atherosclerotic plaques and promotes myocardial interstitial fibrosis, thereby increasing the risk of adverse cardiovascular events. On one hand, inflammation drives the progression of atherosclerosis, often leading to plaque rupture and subsequent acute coronary syndrome (ACS). On the other hand, inflammation activates cardiac fibroblasts, resulting in diffuse myocardial fibrosis, which not only impairs cardiac systolic and diastolic function but also predisposes patients to malignant arrhythmias.[4] Therefore, a deeper investigation into the impact of systemic inflammation on the extent of myocardial fibrosis and myocardial strain in patients with CCS is crucial for identifying high-risk individuals and preventing adverse endpoint events such as heart failure and arrhythmias through clinical interventions.

Epicardial adipose tissue (EAT) is a fat depot located between the myocardium and the epicardium. Under normal physiological conditions, EAT can protect the adjacent myocardium through its dynamic brown-fat-like heat-producing function. However, in pathological conditions, its physiological function is altered, thereby causing damage to the myocardium.As a unique type of fat depot, EAT is closely associated with coronary heart disease. In general, inflammation, excessive innate immune responses, oxidative stress, endothelial injury, adipocyte stress, lipid accumulation, and glycation toxicity are all involved in the atherosclerotic process, and inflammation is the main feature of EAT in patients with coronary heart disease.[5] As an active endocrine organ,EAT can exacerbate the dense infiltration of macrophages,

mast cells and CD8+ T cells.[6,7] Similarly, an elevated systemic inflammatory state can disrupt the normal physiological functions of EAT, further promoting myocardial fibrosis and functional impairment through pro-inflammatory and pro-fibrotic mediators.[8] We hypothesize that in patients with CCS, EAT may exacerbate the inflammatory state, and the inflammatory state in turn may intensify the pro-inflammatory or pro-fibrotic effects of EAT, thereby jointly determining the myocardial fibrosis and poor prognosis of the patients.Therefore, this study aims to explore whether systemic inflammatory status represents a more significant risk factor than lipid parameters in patients on long-term lipid-lowering therapy, and whether it acts synergistically with epicardial fat to collectively determine poor clinical outcomes.

Methods

Study Population

This research was conducted strictly in accordance with the requirements of the Reporting of Studies Conducted using Observational Routinely-collected Data (RECORD) guideline.From March 2017 to September 2023, a total of 278 patients with coronary artery disease (CAD) were enrolled from two medical institutions in Shandong province. Eligible participants met the diagnostic criteria for CCS based on current guidelines. These included patients who had been hospitalized for ACS or coronary revascularization and were discharged after achieving clinical stability. Exclusion criteria were as follows: (1) patients with inadequately controlled lipid levels due to inconsistent use of lipid-lowering therapy; (2) those with non-ischemic cardiac conditions or in the acute phase of illness; (3) acute infections; (4) active malignancy or paraneoplastic syndromes; (5) severe liver failure; (6) known inflammatory or autoimmune diseases; and (7) active cerebrovascular disease (Figure 1). The study was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University and strictly follows the ethical guidelines of the Helsinki Declaration. The requirement for informed patient consent was waived.

Clinical Data Collection

Fasting blood samples were collected from the antecubital vein on the second morning after admission. Biochemical parameters, including complete blood count and lipid profiles, were measured. The SIRI was calculated as: [neutrophil count ($\times 10^9$/L) × monocyte count ($\times 10^9$/L)] / lymphocyte count ($\times 10^9$/L).[9] All patients underwent at least two complete blood count tests, with differences between results falling within one-third of the allowable measurement error.[10] In

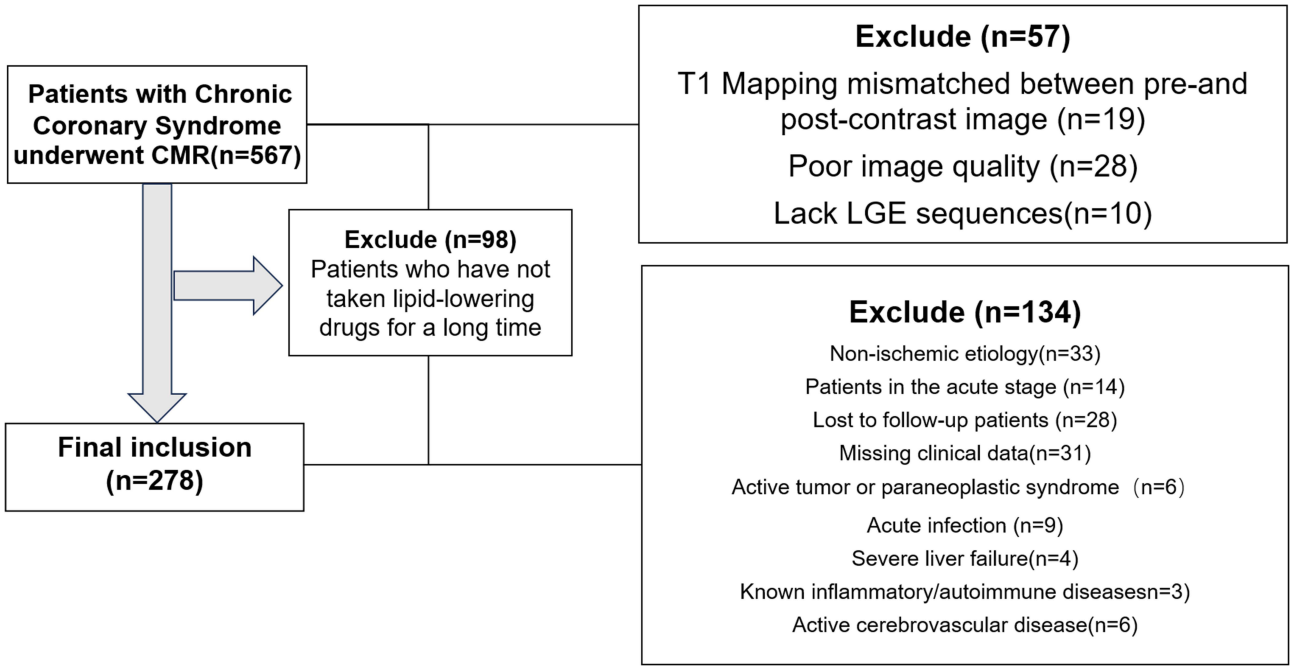


Figure 1 Flowchart shows the selection process of patients with chronic coronary syndrome based on inclusion and exclusion criteria.

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addition, we collected information on clinical history, health-related behaviors, family history, prior CCS, and medication use,which may serve as potential confounding factors. Relevant definitions are provided in Appendix S1. Major adverse cardiovascular events (MACEs) were defined as a composite of (1) cardiovascular death, myocardial infarction, and stroke (2) rehospitalization for unstable angina requiring hospitalization or revascularization, heart failure, and ventricular arrhythmias (VAs).[11] Based on the characteristics of our population, previous studies and the recommendations of the guidelines, we have included VAs.[12–14]Only the first event was counted when multiple events occurred in the same patient. All patients had the option to refuse follow-up contact throughout the study duration.

CMR Protocol and Image Analysis

All cardiovascular magnetic resonance (CMR) examinations were performed in accordance with a standardized protocol using a 3.0T MR scanner (MAGNETOM Prisma, Siemens Medical). The imaging protocol included T1 mapping before and after contrast administration, breath-hold cine imaging, and steady-state free precession (SSFP) sequences.[15,16] Detailed parameters for all sequences are provided in Appendix S2.

Image analysis was carried out independently by two experienced CMR physicians blinded to clinical data, using CVI42 post-processing software. Following American Heart Association guidelines, they manually delineated the endocardial and epicardial borders of the left ventricle at the basal, middle, and apical levels, carefully excluding papillary muscles and trabeculae. Myocardial T1 values were calculated for native and post-contrast scans based on the AHA 17-segment model. Extracellular volume (ECV) was derived after measuring hematocrit and segmenting the blood pool region.[17,18] The specific formula is included in Appendix S3.

Left ventricular global longitudinal strain, global circumferential strain, and global radial strain were automatically analyzed using feature-tracking technology applied to the SSFP cine sequences.

EAT volume was quantified on end-diastolic short-axis slices by manually tracing EAT contours using the tissue signal intensity module in CVI42. The tracing extended from the basal atrial level to the apical ventricular level, carefully excluding non-EAT regions. Before measurement, image quality was optimized and slice thickness was standardized; manual corrections were applied during segmentation as needed (Figure 2). All procedures followed standardized protocols to ensure reproducibility.[19,20] Further operational details are available in Appendix S3.

Statistical Analysis

Analyses were conducted using SPSS (version 26.0) and R (version 4.0.2). A two-tailed P-value < 0.05 was considered statistically significant. Normality of variables was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation or median with interquartile range, and were compared using Welch's t-test or the Mann–Whitney U-test, as appropriate. Categorical variables are expressed as numbers and percentages and were compared with the chi-square test. To determine the appropriate sample size, we performed a priori power analysis using GPower 3.1.The associations of EAT and inflammatory indicators with MACEs were visualized using restricted cubic spline (RCS) curves and Kaplan–Meier analysis. Univariate Cox proportional hazards regression was used to identify potential risk factors associated with endpoint events. The proportional hazards assumption was verified using log-log survival plots and Schoenfeld residuals.

Receiver operating characteristic (ROC) analysis was conducted to evaluate the predictive performance of EAT, SIRI and the interaction term (EAT × SIRI) for MACEs.

A pre-specified mediation analysis was designed to explore potential mechanistic pathways, without presuming temporal precedence or inferring causality. First, we examined whether EAT mediates the relationship between inflammatory indicators and MACEs. Second, we assessed whether inflammatory indicators mediate the association between EAT and MACEs. To further investigate underlying mechanisms, ECV was additionally analyzed as a dependent variable. All confidence intervals were estimated via bootstrap resampling with 1000 iterations.

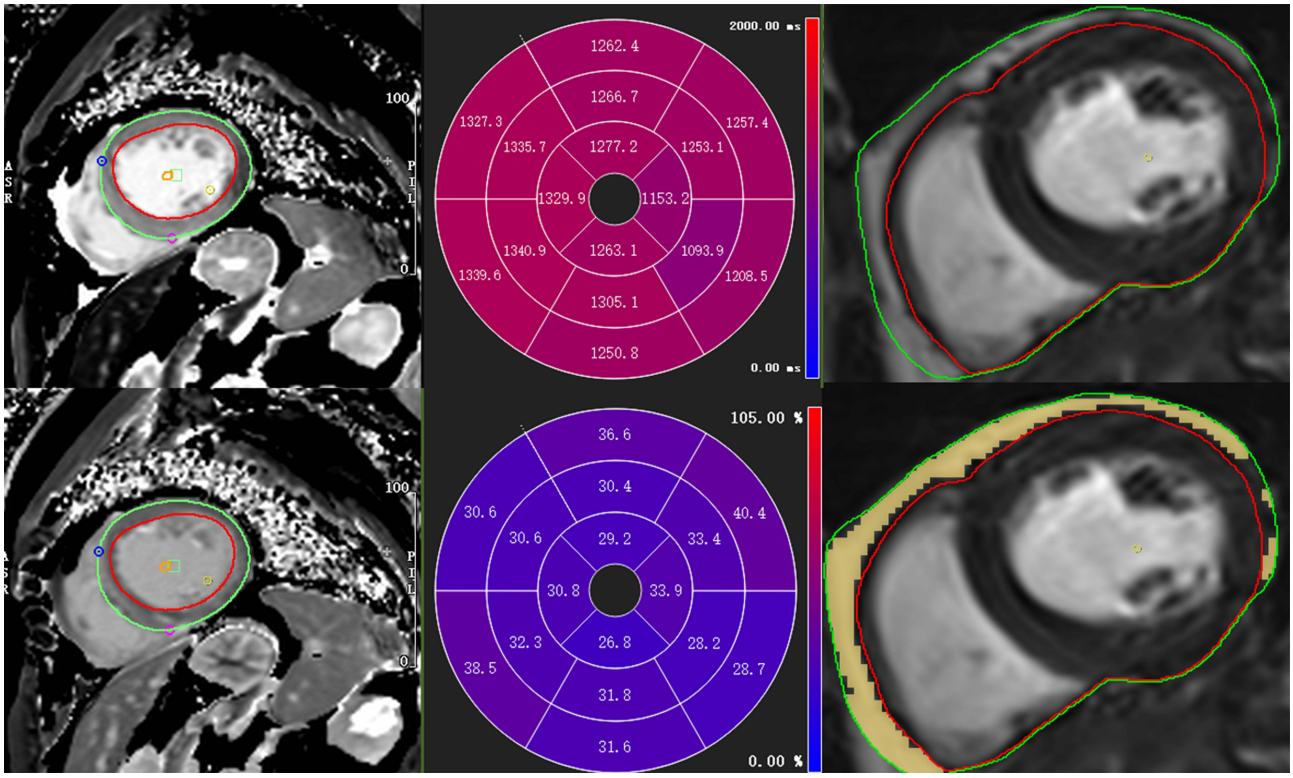

Figure 2 A schematic diagram for measuring native T1, ECV and EAT using commercial software. Red represents the inner membrane outline of the heart, while green represents the outer membrane outline of the heart.

Results

Patient Characteristics

Table 1 summarizes the clinical characteristics of the patients with CAD. The median age was 59 [52, 67] years, and 71% of the cohort were male. Older age, female sex, hypertension, diabetes, and a family history of cardiovascular disease were associated with a higher incidence of MACEs ($P < 0.05$), whereas differences related to health-related behaviors

Table 1 Baseline Characteristics According to Major Adverse Cardiac Events

Variable	All Patients (n = 410)	No MACE (n=255)	MACE (n=155)	p
Age (years)	59.00[52.00,67.00]	59.00[51.00,65.00]	62.00[54.00,70.00]	0.007
Male sex, n (%)	197(70.86)	127(75.60)	70(63.64)	0.032
BMI (kg/m2)	27.34[25.18,29.22]	27.34[24.97,29.02]	27.68[25.52,30.37]	0.101
SBP (mm Hg)	123.00[114.00,135.00]	123.00[113.44,137.00]	124.00[114.17,132.00]	0.996
DBP (mm Hg)	78.00[71.00,86.00]	78.00[70.00,85.34]	77.37[71.00,86.00]	0.714
Diabetes, n (%)	82(29.50)	42(25.00)	40(36.36)	0.042
Drinking, n (%)	92(33.09)	55(32.74)	37(33.64)	0.876
Smoking, n (%)	156(56.12)	88(52.38)	68(61.82)	0.121
Family history of CAD, n (%)	55(19.78)	25(14.88)	30(27.27)	0.011
History of PCI, n (%)	156(56.12)	89(52.98)	67(60.91)	0.192
History of heart failure, n (%)	155(55.76)	90(53.57)	65(59.09)	0.365
ACE inhibitor/ARB, n (%)	145(52.16)	89(52.98)	56(50.91)	0.736
Betablocker, n (%)	194(69.78)	113(67.26)	81(73.64)	0.258
Diuretics, n (%)	147(52.88)	89(52.98)	58(52.73)	0.968

(*Continued*)

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Table 1 (Continued).

Variable	All Patients (n = 410)	No MACE (n=255)	MACE (n=155)	p
Aspirin, n (%)	223(80.22)	135(80.36)	88(80.00)	0.942
Glyceryl trinitrate, n (%)	64(23.02)	35(20.83)	29(26.36)	0.284
Antidiabetic drugs, n (%)	61(21.94)	32(19.05)	29(26.36)	0.15
Hypertension, n (%)	162(58.27)	86(51.19)	76(69.09)	0.003
Plasma triglycerides (mmol/L)	1.49[1.06,2.08]	1.56[1.11,2.22]	1.36[0.99,1.88]	0.104
Total cholesterol (mmol/L)	3.78±1.09	3.66±1.18	3.97±0.92	0.015
HDL (mmol/L)	1.03[0.90,1.26]	1.04[0.90,1.24]	1.02[0.90,1.26]	0.497
LDL (mmol/L)	2.51±0.90	2.49±0.93	2.54±0.86	0.715
SIRI	0.91[0.53,1.79]	0.80[0.40,1.48]	1.26[0.66,2.14]	<0.001

Abbreviations: BMI, body mass index; BP, blood pressure.

were less pronounced. As all patients had been on long-term lipid-lowering therapy, lipid profiles were generally comparable between groups, except for total cholesterol, which was significantly higher in patients who experienced MACEs ($P = 0.015$). In contrast, the SIRI showed a marked difference between groups ($P < 0.001$). No significant differences were observed in the use of other cardiovascular medications.Patients with missing interest variables were obtained through phone calls or questionnaires, while those who could not be obtained were excluded from this study.

Table 2 compares CMR parameters between patients with and without MACEs. Those who experienced MACEs demonstrated lower left ventricular and atrial ejection fractions, larger atrial volumes, elevated native T1 and ECV, indicating more severe diffuse myocardial fibrosis, a greater extent of late gadolinium enhancement (LGE), and more

Table 2 CMR Parameters According to Major Adverse Cardiac Events

Variable	All Patients (n = 410)	No MACE (n=255)	MACE (n=155)	p
Nativet1	1305.35±49.97	1299.60±44.40	1314.14±56.32	0.024
ECV	31.66±4.28	30.76±3.31	33.02±5.14	<0.001
LGE	6.00[2.00,9.00]	5.00[0.00,8.00]	9.00[4.00,13.00]	<0.001
LVGLS	−11.88±4.13	−12.87±3.73	−10.37±4.25	<0.001
LVGCS	−11.89±4.17	−12.34±4.14	−11.19±4.12	0.025
LVGRS	14.70[11.70,17.50]	15.30[11.90,18.50]	14.00[11.50,16.30]	0.035
LVEDVi	92.61±27.01	90.52±27.00	95.80±26.71	0.112
LVESVi	54.84[35.29,75.60]	49.81[31.25,69.15]	65.59[47.99,79.25]	<0.001
CO	3.60[2.64,4.80]	3.90[2.70,5.00]	3.10[2.40,4.40]	0.014
LVMassi	77.00[57.50,116.19]	83.42[56.26,119.00]	73.30[61.08,105.00]	0.511
LVEF	39.88±14.83	43.75±14.70	33.95±12.94	<0.001
EAT	70.19[57.69,80.78]	66.22[54.82,76.58]	75.03[65.33,84.53]	<0.001
Nativet1	1305.35±49.97	1299.60±44.40	1314.14±56.32	0.024
ECV	31.66±4.28	30.76±3.31	33.02±5.14	<0.001
LGE	6.00[2.00,9.00]	5.00[0.00,8.00]	9.00[4.00,13.00]	<0.001
LVGLS	−11.88±4.13	−12.87±3.73	−10.37±4.25	<0.001
LVGCS	−11.89±4.17	−12.34±4.14	−11.19±4.12	0.025
LVGRS	14.70[11.70,17.50]	15.30[11.90,18.50]	14.00[11.50,16.30]	0.035
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CO	3.60[2.64,4.80]	3.90[2.70,5.00]	3.10[2.40,4.40]	0.014
LVMassi	77.00[57.50,116.19]	83.42[56.26,119.00]	73.30[61.08,105.00]	0.511
LVEF	39.88±14.83	43.75±14.70	33.95±12.94	<0.001
EAT	70.19[57.69,80.78]	66.22[54.82,76.58]	75.03[65.33,84.53]	<0.001

(*Continued*)

Table 2 (Continued).

Variable	All Patients (n = 410)	No MACE (n=255)	MACE (n=155)	p
Nativet1	1305.35±49.97	1299.60±44.40	1314.14±56.32	0.024
ECV	31.66±4.28	30.76±3.31	33.02±5.14	<0.001
LGE	6.00[2.00,9.00]	5.00[0.00,8.00]	9.00[4.00,13.00]	<0.001
LVGLS	−11.88±4.13	−12.87±3.73	−10.37±4.25	<0.001
LVGCS	−11.89±4.17	−12.34±4.14	−11.19±4.12	0.025
LVGRS	14.70[11.70,17.50]	15.30[11.90,18.50]	14.00[11.50,16.30]	0.035
LVEDVi	92.61±27.01	90.52±27.00	95.80±26.71	0.112
LVESVi	54.84[35.29,75.60]	49.81[31.25,69.15]	65.59[47.99,79.25]	<0.001
CO	3.60[2.64,4.80]	3.90[2.70,5.00]	3.10[2.40,4.40]	0.014
LVMassi	77.00[57.50,116.19]	83.42[56.26,119.00]	73.30[61.08,105.00]	0.511

Abbreviations: ECV, Extracellular volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVi, LV end-diastolic volume index; LVESVi, LV end-systolic volume index; LVEF, LV ejection fraction; LVMI, left ventricular mass index; CO, cardiac output; LVGCS, LV global circumferential strain; LVGLS, LV global longitudinal strain; LVGRS, LV global radial strain.

impaired ventricular and atrial strain ($P < 0.05$). In addition, EAT volume was significantly higher in the MACEs group ($P < 0.001$).The reproducibility of native T1 values (intra: ICC = 0.96,inter: ICC = 0.98), ECV (intra: ICC = 0.93, inter: ICC = 0.96), and indexed EAT volume (intra: ICC = 0.94,inter: ICC = 0.97) demonstrated excellent intra- and inter-observer agreement (Supplementary Table S1).

Association of EAT and SIRI with MACE

Over a median follow-up of 31 (19, 41) months, a total of 110 patients experienced MACEs. These included 12 cardiovascular deaths, 48 hospitalizations for heart failure or recurrent myocardial infarction, 22 cases of ventricular arrhythmia, and 28 late revascularization procedures.During the follow-up period, no patient was recorded for having experienced a stroke for the first time.

Restricted cubic spline models were used to assess potential nonlinear relationships of SIRI and EAT with MACEs risk. As shown in Figure 3A, SIRI exhibited a nonlinear association with MACEs (P for non-linearity = 0.025), with the hazard ratio increasing progressively and at an accelerating rate as SIRI rose. In contrast, EAT demonstrated a predominantly linear relationship with MACEs risk (P for nonlinearity = 0.188). Based on optimal cutoff values for SIRI and EAT, patients were divided into two groups. Kaplan–Meier analysis revealed that patients with SIRI and EAT above these thresholds had a significantly higher cumulative incidence of MACEs (log-rank $P < 0.001$; Figure 3B).

ROC analysis assessed the predictive performance of SIRI, EAT, and their product (EAT × SIRI) for MACEs (Figure 4). The EAT × SIRI index yielded a C-index of 0.705 (95% CI: 0.643–0.766), outperforming both SIRI alone (0.637, 95% CI: 0.571–0.703) and EAT alone (0.671, 95% CI: 0.607–0.735).

Univariate Cox regression (Table 3) indicated that age, gender, hypertension, diabetes, family history of CCS, total cholesterol, and several CMR-derived parameters were associated with MACEs. Notably, both EAT and SIRI were significantly associated with MACEs ($P < 0.001$).

Variables with $P < 0.05$ in univariate analysis were entered into a multivariate Cox model with backward selection. The power analysis indicates that a sample size of 276 individuals is capable of detecting a moderate main effect of MACEs in CCS patients at a significance level (α) of 0.05 or lower, and has a statistical power (1 - β) of 0.8.The final model retained 11 variables, all free from multicollinearity (VIF < 5) (Supplementary Table S2). Both EAT and SIRI remained independently associated with MACE ($P < 0.001$; Table 4).

Mediation Analysis

Figure 5A illustrates the potential bidirectional mediation between SIRI and EAT in relation to MACEs risk. The indirect effect of EAT (HR 1.034, 95% CI: 1.019–1.052) enhanced the direct effect of SIRI on MACEs (HR 1.221, 95% CI: 1.079–1.421), leading to a greater total effect (HR 1.262, 95% CI: 1.113–1.473). Similarly, the indirect effect of SIRI (HR

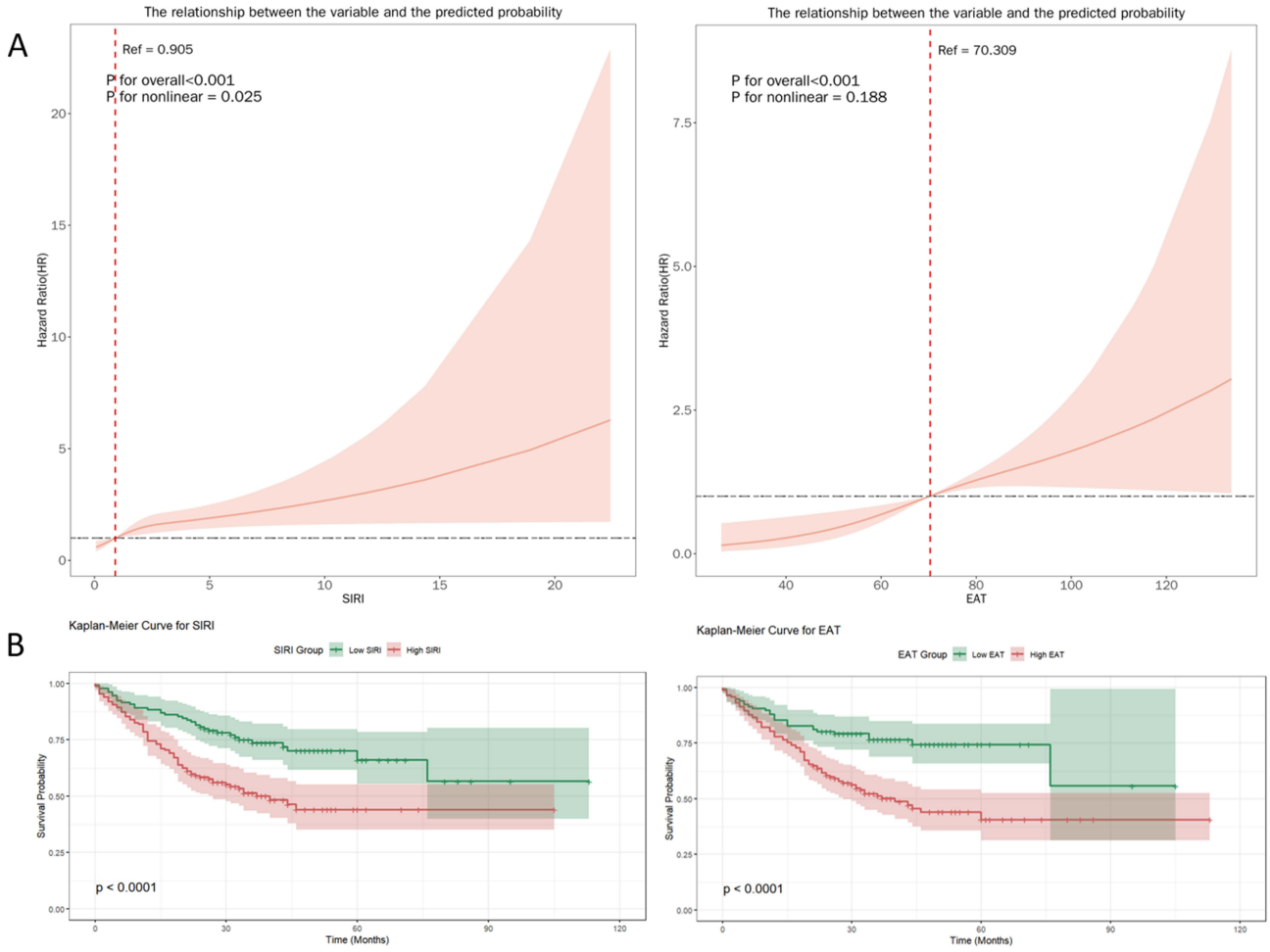

Figure 3 RCS curves (**A**) and time-to-event curves (**B**) of the relationship between SIRI, EAT and the risk of MACE events.

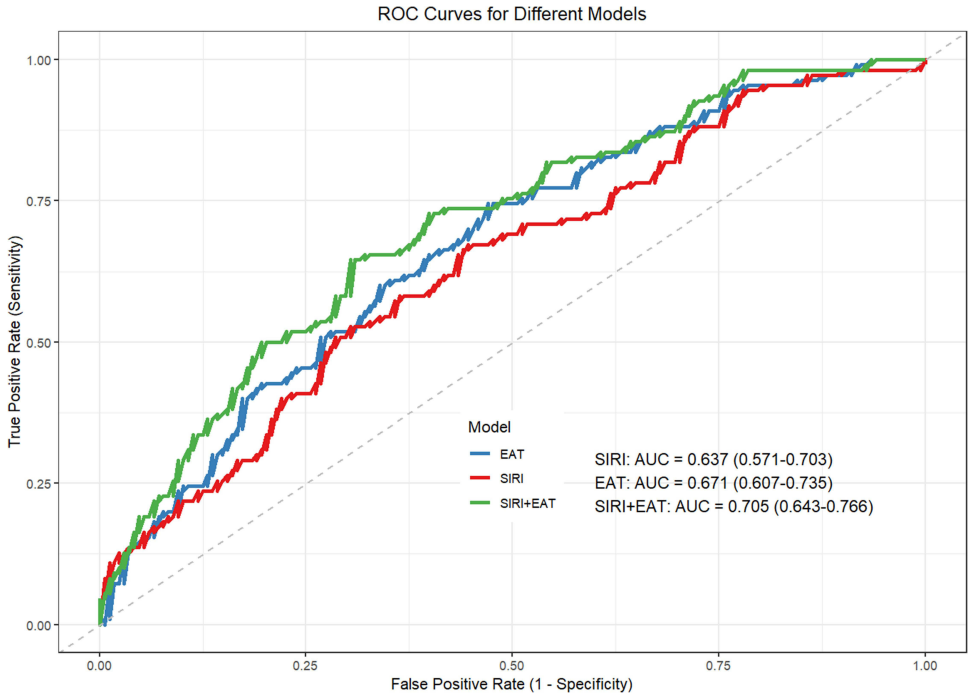

Figure 4 The ROC curve showing the association between Siri and EAT and the risk of major adverse cardiovascular events (MACEs) in CAD patients.

Table 3 Univariable Cox Proportional Hazards Analyses for the Association of CMR Parameters with Major Adverse Cardiac Events in Training Set

Variable	HR	95% CI	P-value
Age	1.03	[1.01,1.05]	**<0.01**
Sex	0.63	[0.42,0.93]	**0.02**
BMI	1.03	[0.98,1.09]	0.20
SBP	1.00	[0.99,1.01]	0.83
DBP	1.00	[0.99,1.02]	0.60
Smoking	1.30	[0.88,1.91]	0.19
Drinking	0.95	[0.64,1.42]	0.82
Family history of CAD	1.77	[1.16,2.70]	**0.01**
Diabetes	1.49	[1.01,2.20]	**0.04**
Hypertension	1.69	[1.13,2.53]	**0.01**
History of PCI	1.13	[0.77,1.66]	0.53
History_of_heart_failure	1.13	[0.77,1.65]	0.53
ACEinhibitor/ARB	0.92	[0.63,1.33]	0.65
Betablocker	1.17	[0.76,1.78]	0.48
Diuretics	0.91	[0.63,1.33]	0.64
Aspirin	0.95	[0.59,1.51]	0.81
Glyceryl trinitrate	1.28	[0.83,1.95]	0.26
Antidiabetic drugs	1.39	[0.91,2.12]	0.13
Plasma triglycerides	0.91	[0.74,1.12]	0.36
Total cholesterol	1.21	[1.02,1.42]	**0.03**
HDL	0.77	[0.45,1.31]	0.33
LDL	1.04	[0.84,1.27]	0.74
Native T1	1.00	[1.00,1.01]	**0.01**
ECV	1.11	[1.07,1.16]	**<0.01**
LGE	1.13	[1.09,1.16]	**<0.01**
LVGLS	1.14	[1.08,1.19]	**<0.01**
LVGCS	1.06	[1.01,1.11]	**<0.01**
LVGRS	0.96	[0.92,0.99]	**0.02**
LVEDVi	1.01	[1.00,1.01]	**0.07**
LVESVi	1.01	[1.01,1.02]	**<0.01**
CO	0.81	[0.71,0.92]	**<0.01**
LVMassi	1.00	[0.99,1.00]	0.50
LVEF	0.96	[0.95,0.98]	**<0.01**
SIRI	1.12	[1.06,1.17]	**<0.01**
EAT	1.03	[1.02,1.04]	**<0.01**

Note: The bold numerals represent that P-value is less than 0.05.

Abbreviations: HR, hazard ratio; ECV, Extracellular volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVi, LV end-diastolic volume index; LVESVi, LV end-systolic volume index; LVEF, LV ejection fraction; LVMI, left ventricular mass index; CO, cardiac output; LVGCS, LV global circumferential strain; LVGLS, LV global longitudinal strain; LVGRS, LV global radial strain; RV, right ventricular; RVEDVi, RV end-diastolic volume index; RVEF, RV ejection fraction; RVESVi, RV end-systolic volume index; RVSVi, RV stroke volume index; RVGCS, RV global circumferential strain; RVGLS, RV global longitudinal strain; RVGRS, RV global radial strain; LA, left atrial; LAEF, LA emptying fraction; LAVmaxi, LA maximum volume index; LAVmini, LA minimum volume index; LAVpaci, LA preatrial contraction volume index; RA, right atrial; RAEF, RA emptying fraction; RAVmaxi, RA maximum volume index; RAVmini, RA minimum volume index; RAVpaci, RA preatrial contraction volume index.

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Table 4 Multivariable Cox Proportional Hazards Analyses for the Association of Variables with Primary End Points

Predictor	Hazard Ratio	Lower	Upper	p
Sex	0.60	0.39	0.91	0.02
Family history of CAD	1.52	0.97	2.38	0.07
Hypertension	1.70	1.09	2.64	0.02
Diabetes	1.42	0.95	2.12	0.08
LGE	1.08	1.04	1.12	<0.001
LVGLS	1.26	1.14	1.40	<0.001
LVGRS	1.20	1.10	1.31	<0.001
LVESVi	0.99	0.97	1.00	0.03
LVEF	0.93	0.91	0.96	<0.001
EAT	1.02	1.01	1.03	<0.001
SIRI	1.14	1.08	1.21	<0.001

Abbreviations: ECV, Extracellular volume; LGE, late gadolinium enhancement; LVGLS, LV global longitudinal strain; LVESVi, LV end-systolic volume index; LVEF, LV ejection fraction.

1.005, 95% CI: 1.003–1.008) strengthened the direct effect of EAT (HR 1.035, 95% CI: 1.019–1.052), resulting in an increased total effect (HR 1.045, 95% CI: 1.022–1.056). These findings suggest mutual interaction and cooperation between EAT and SIRI. The variables in the characteristics of the research participants that were significantly associated with the MACEs event were regarded as confounding factors.Results remained consistent after adjusting for MACEs-related confounders (Indirect effect of EAT (HR 1.028, 95% CI: 1.015–1.045;Indirect effect of SIRI (HR 1.004, 95% CI: 1.002–1.007).

To explore the underlying mechanisms, we examined correlations between predefined CMR parameters, SIRI, and indexed EAT volume. Replacing the outcome with CMR parameters that were significantly associated with both SIRI and EAT revealed that EAT partially mediated the relationship between SIRI and ECV. Similarly, SIRI partially mediated the association between EAT and ECV. These results remained robust after adjusting for ECV-related confounders (Figure 5B).

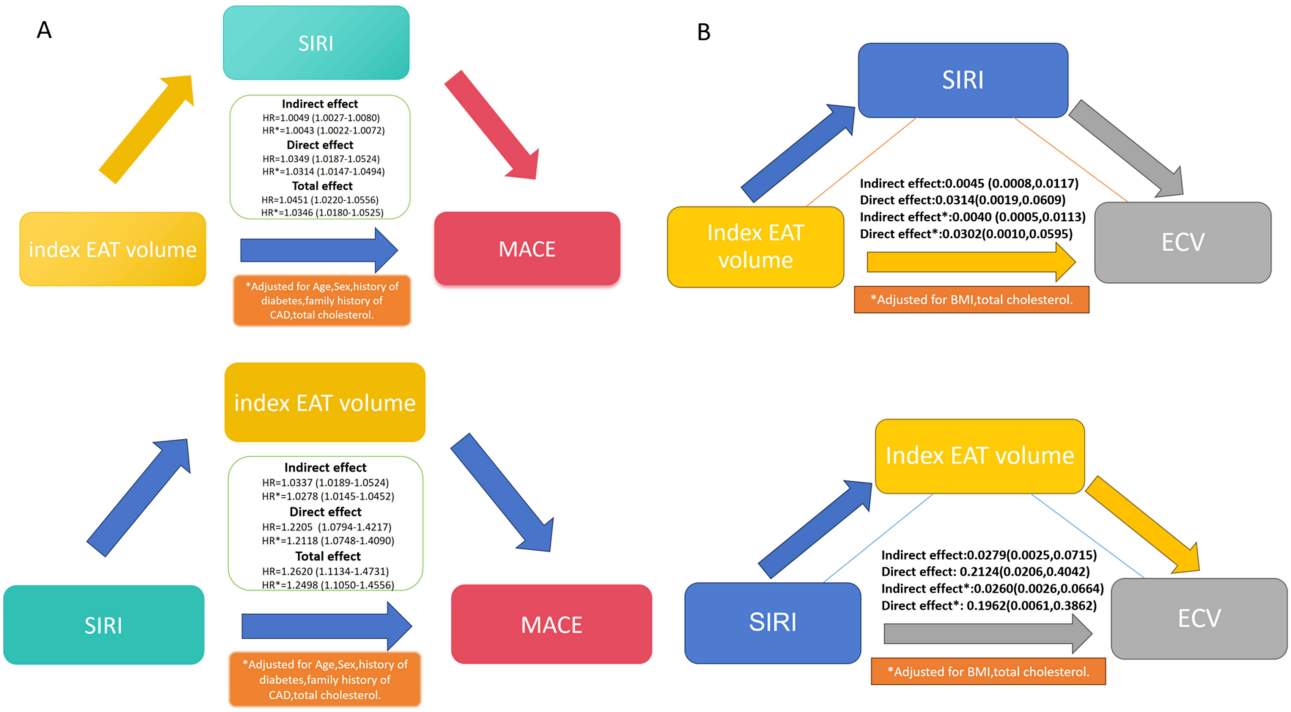

Figure 5 Mediation effects of SIRI and EAT in the incidence of MACE (**A**) or ECV (B).

Discussion

This study demonstrates that in patients with CCS and well-controlled lipid levels, the SIRI serves as an important marker of residual cardiovascular risk. Moreover, a notable interaction exists between EAT and chronic inflammation: chronic inflammation may stimulate EAT to promote myocardial fibrosis, while abnormal EAT accumulation in turn exacerbates the systemic inflammatory response, collectively increasing the risk of MACEs. In conclusion, both SIRI and EAT are not only important drivers of poor prognosis but also provide a key basis for risk stratification in this patient population, aiding in the identification of high-risk individuals and guiding precision secondary prevention strategies.

Lipid levels, especially low-density lipoprotein, are well-established risk factors in coronary heart disease, and lipid-lowering therapy, primarily with statins, constitutes a cornerstone of management.[21,22] Although most patients achieve relatively low lipid levels under treatment, coronary heart disease remains a leading cause of mortality worldwide. Thus, there is an urgent need to identify additional risk factors to enable more refined risk stratification. The immune system and inflammatory responses are key drivers of atherosclerosis. In patients with coronary heart disease, inflammatory markers such as white blood cell count and C-reactive protein are frequently elevated and correlate strongly with overall cardiovascular risk, severity of coronary lesions, impaired myocardial perfusion, plaque instability, and mortality. This underscores the central role of chronic low-grade inflammation in disease progression.[23] In ACS, inflammation is a major contributor to myocardial ischemia-reperfusion injury.[24] Consequently, therapeutic strategies targeting residual inflammatory risk are under extensive investigation. SIRI, as a composite indicator derived from routine blood cell counts, more directly reflects the cellular immune imbalance of the body in a diseased state, while C-reactive protein mainly indicates the level of systemic inflammation. Furthermore, compared to CRP which requires additional testing, SIRI is more cost-effective.Numerous studies have reported that elevated SIRI is associated with a significantly higher risk of adverse clinical events. However, the mechanisms linking elevated inflammatory markers to poor cardiovascular outcomes remain incompletely understood.

EAT contributes critically to the pathogenesis and progression of CAD through local inflammatory processes. In affected patients, EAT adopts a pronounced pro-inflammatory phenotype, characterized by enhanced macrophage infiltration, upregulation of pro-inflammatory cytokines and adipokines, and decreased expression of anti-inflammatory factors.[25,26] This distinct pro-atherosclerotic transcriptional profile acts on the myocardium and coronary vasculature through paracrine or vascular secretion pathways, promoting endothelial dysfunction, oxidative stress, and plaque instability. Systemic inflammation further disrupts the normal physiological functions of EAT, inducing an increased release of pro-inflammatory and pro-fibrotic factors that elevate cardiovascular risk.[8,27] As an independent cardiometabolic risk factor, EAT has been widely linked to inflammatory cell infiltration. Hirata et al reported that in EAT samples from patients with advanced CAD, the concentration of pro-inflammatory M1 macrophages exceeded that of anti-inflammatory M2 macrophages.[28] Similarly, Mazurek et al observed elevated levels of inflammatory mediators in human EAT.[6] Our research further reveals that as SIRI increases, the risk of adverse coronary events rises at an accelerating rate, possibly reflecting a vicious cycle of interaction–adipose tissue crosstalk. This was supported by mediation analysis, which indicated that EAT partially mediates the effect of SIRI on MACEs, and SIRI likewise partially mediates the effect of EAT on MACEs. Further analysis suggests that this process may involve EAT-driven myocardial fibrosis. Overall, within the ischemic and hypoxic milieu of coronary heart disease, often accompanied by metabolic disorders such as hypertension and insulin resistance, systemic or local inflammation may act as a triggering factor. Under sustained inflammatory stimulation, epicardial fat may undergo pathological remodeling, characterized by inflammatory cell infiltration and functional impairment. These changes can promote the secretion of pro-inflammatory and pro-fibrotic mediators, thereby accelerating myocardial fibrosis and atherosclerotic plaque formation, ultimately leading to poor clinical outcomes.

Owing to its modifiable nature, EAT is regarded as a potential target for therapeutic intervention. Studies indicate that medications such as GLP-1 receptor agonists and SGLT2 inhibitors can modestly reduce EAT volume or thickness.[29–31] However, our recent findings suggest that heightened systemic inflammation further alters EAT function, aggravating myocardial fibrosis and increasing the risk of adverse outcomes in patients with coronary heart disease. Therefore, while targeting EAT reduction, it is equally crucial to mitigate systemic inflammation. In recent years, agents such as semaglutide have shown pleiotropic benefits, including not only glycemic control but also multi-level anti-

inflammatory effects.[32] For patients with inflammatory risk who are intolerant to statins, colchicine offers a potential alternative for primary and secondary prevention.[2] Moreover, dietary interventions have been established as an important means of modulating chronic low-grade inflammation, with high-fiber foods and chia seeds among the reported anti-inflammatory options.[33,34] Our study is the first to reveal the interaction between SIRI and EAT, suggesting that metabolic dysregulation and hemodynamic imbalance are interrelated. Further analysis demonstrates that combining SIRI with EAT significantly enhances the prediction of MACEs. This finding emphasizes the importance of addressing not only visceral adiposity but also underlying metabolic disturbances to achieve more comprehensive control of chronic inflammatory processes and improve cardiovascular outcomes. In the future, through large-sample prospective studies or randomized controlled studies, the thresholds of SIRI and EAT volume can be further determined, and these thresholds can serve as an effective early warning system to help clinicians.

This study has several limitations. Firstly, although we demonstrated through mediation analysis that EAT and SIRI may have a possible association with myocardial fibrosis and cardiovascular risk, we were unable to determine the temporal sequence of their occurrence.Long-term follow-up studies are still needed to determine their relationship. Secondly, this study may introduce some biases. The relatively small sample size may lead to insufficient statistical power and the use of a composite endpoint indicator that includes ventricular arrhythmias, this may result in our statistical power being insufficient to detect the primary endpoint, introducing risks related to reporting biases of soft endpoints. Therefore, this study needs to be validated in future larger-scale randomized controlled trials and the main objective should be set as a hard metric. Additionally, the study protocol respects the patients' right to withdraw, but this also led to some patients being excluded from the analysis due to their refusal to cooperate. These patients' withdrawal behavior may be related to their health conditions, thereby introducing biases to the results.Thirdly, although common confounding factors were adjusted for in the analysis, the potential influence of unmeasured confounders cannot be ruled out. For instance, due to the retrospective nature of the study, we were unable to gather more information and thus were unable to conduct a detailed investigation into aspects such as the patients' lifestyles and psychosocial factors.This might limit the generalizability of the research.Fourthly,due to the limitations of spatial resolution and motion artifacts in conventional cardiac magnetic resonance imaging, we were unable to conduct quantitative measurements of the pericoronary adipose tissue. In the future, the relationship between pericoronary adipose tissue and inflammation can be explored through CT or more advanced magnetic resonance techniques.

In conclusion,this study demonstrates that in patients with CCS on long-term lipid-lowering therapy, the SIRI serves as an important residual risk factor. When combined with SIRI, EAT enhances the predictive ability for MACEs. Moreover, we reveals a synergistic association between the SIRI and EAT, whereby they jointly contribute to the occurrence of adverse outcomes, a process potentially mediated by myocardial fibrosis. This association finding provides an important assumption basis for future prospective studies to clarify its potential causal mechanism.

Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study protocol was in accordance with the Declaration of Helsinki of the World Medical Association. This retrospective study was approved by the institutional review board of Shandong Provincial Hospital Affiliated to Shandong First Medical University (SWYX:NO.2025207). Since the analysis of the de-identified data conducted in this study poses no greater privacy risk to patients than the minimum acceptable risk, the ethics committee has approved that the requirement for informed consent can be waived for this research. All the patient data collection plans have been approved in the main project.

Author Contributions

Runze Zhu: Investigation, Methodology, Writing – original draft, Writing – review & editing, Data curation
Wenxian Wang: Methodology, Software, Supervision, Writing – review & editing
Yan Gao: Data curation, Writing – review & editing
Bowen Li: Data Curation, Validation, Writing – review & editing

Wanting Wang: Data Curation, Writing – review & editing
Jie Liu, Data Curation, Writing – review & editing
Ling Wu: Conceptualization, Formal analysis, Investigation, Writing – review & editing
Shifeng Yang: Data curation, Project administration, Resources, Supervision, Writing – review & editing
Ximing Wang: Data curation, Project administration, Resources, Supervision, Writing – review & editing

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests to disclose.

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