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ORIGINAL RESEARCH

Association Between Systemic Inflammation Response Index, Worsening of Left Ventricular Systolic Function and Prognosis in Patients with Coronary Artery Disease

Huangtao Ruan[1,2,*], Xiaozhao Lu[2,3,*], Huan Lu[2–4,*], Haozhang Huang[2,3,*], Zuxian Huang[1,2], Shangyi Tang[2,3], Ziyao Yuan[2,5], Rengui Jiang[2,3,6], Jiazhen Xin[6], Tao Tang[6], Jin Liu[1,2], Yong Liu[1,2], Ning Tan[1,2]

[1]Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, People's Republic of China; [2]Department of Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, People's Republic of China; [3]Department of Cardiology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, People's Republic of China; [4]Department of Cardiology and Centre of Cardiovascular Disease, People's Hospital of Yangjiang, Yangjiang, People's Republic of China; [5]Department of Cardiology, Shantou University Medical College, Shantou University, Shantou, People's Republic of China; [6]Department of Cardiology, Ganzhou Hospital of Guangdong Provincial People's Hospital, Ganzhou Municipal Hospital (Gannan Medical University Affiliated Municipal Hospital), Ganzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yong Liu; Ning Tan, Email liuyong@gdph.org.cn; tanning100@126.com

Background: Inflammation contributes substantially to the progression and adverse prognosis of coronary artery disease (CAD). Worsening of left ventricular (LV) systolic function is a key contributor to poor prognosis in CAD patients. However, whether inflammation influences prognosis through worsening of left ventricular systolic function remains uncertain.

Methods: This retrospective study enrolled patients from Cardiorenal Improvement-II who were initially hospitalised between 2007 and 2020 and had both baseline and follow-up echocardiographic information. Participants were stratified by systemic inflammation response index (SIRI) into 4 quartiles (Q1–Q4) for comparison. Worsening of LV systolic function served as the primary endpoint and was identified by an absolute decrease of 10% or more in LV ejection fraction from baseline to 12 months following hospital discharge. Secondary outcomes included cardiovascular and all-cause mortality. Logistic regression models were utilized to evaluate the association of SIRI with worsening of left ventricular systolic function. Mediation analysis was used to investigate the proportion of fatalities mediated by worsening of left ventricular systolic function.

Results: Among the 6307 enrolled participants with CAD (62.0 ±10.7 years, 20.6% female), a total of 521 (8.3%) worsening of left ventricular systolic function occurred in 1 year, and 523 (8.3%) cardiovascular deaths and 1022 (16.2%) all-cause deaths were recorded with a median observation period of 4.2 years. After fully adjusting, the logistic regression analysis revealed that Q4 group patients (with SIRI ≥2.61) were associated with a higher risk of worsening of LV systolic function (adjusted odds ratio: 1.52, 95% confidence intervals: 1.15–2.01, P =0.003). Approximately 4.0% and 2.0% of the overall association of SIRI with cardiovascular and all-cause mortality were mediated by worsening of left ventricular systolic function (P <0.05), respectively.

Conclusion: SIRI serve as a potential risk factor for worsening of LV systolic function in CAD patients, and further contributes to poor prognosis, indicating that anti-inflammatory treatment represents a viable approach to improve the prognosis for CAD patients.

Keywords: inflammation, systemic inflammation response index, left ventricular function, coronary artery disease, prognosis

Introduction

Coronary artery disease (CAD) is still a major contributor to global mortality and exerts substantial economic pressure on society.[1] Heart failure is recognized as a serious complication and strongly associated with adverse prognosis in CAD patients.[2]

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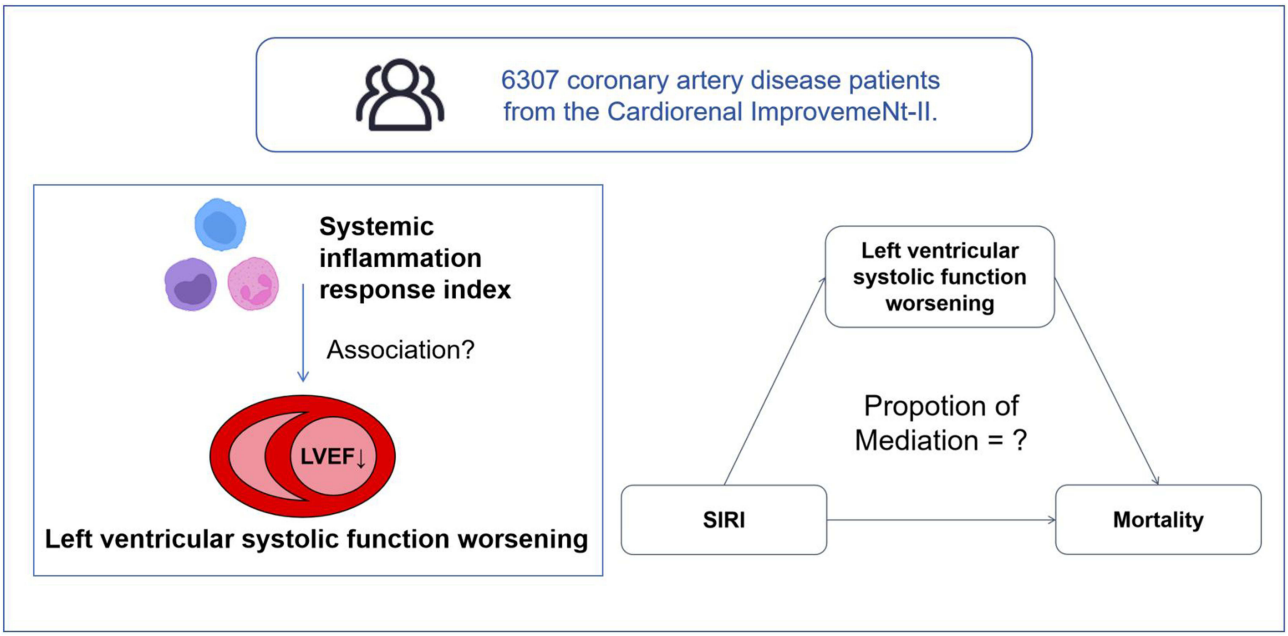
Graphical Abstract



Left ventricular (LV) remodeling, which commonly occurs in CAD patients and progresses to heart failure, is a critical phenotype for assessing ventricular dysfunction; this process is driven by activation of the neuroendocrine system, oxidative stress, and inflammatory processes.[3] A thorough understanding of factors driving worsening of LV systolic function is critical to improving prognosis in individuals with CAD.

Inflammation contributes substantially to the progression of CAD.[4] Longitudinal studies had further confirmed that elevated circulating inflammatory markers following myocardial infarction are significantly correlated with worse LV function.[5,6] The systemic inflammation response index (SIRI) exhibits a close correlation with proinflammatory cytokines and is commonly used as a surrogate marker for systemic inflammation.[7] Previous studies have established that its association with coronary atherosclerosis severity, future risk of acute coronary syndromes, and mortality in CAD patient.[8–10] Furthermore, the SIRI was a valuable indicator for identifying high risk of adverse outcomes in heart failure patients.[11,12] However, the association between inflammation and LV function has only been examined in small-scale studies.[13] The association between SIRI, worsening of LV systolic function and adverse prognosis in the broader CAD population was uncertain.

Therefore, this study was designed to evaluate the association between SIRI and worsening of LV systolic function and to clarify the extent to which worsening of LV systolic function serves as a mediator in the relationship between SIRI and prognosis among CAD patients.

Methods and Materials

Study Population

The study population was mainly drawn from the multicenter cohort Cardiorenal ImprovemeNt II (CIN-II, NCT05050877), with enrollment from 2007 to 2020. 6749 CAD patients with baseline and 1-year follow-up echocardiographic data were enrolled. After excluding patients without SIRI data (n = 422) or mortality information (n = 20), the final analysis comprised 6307 patients. (Figure 1). Approval was obtained from the Ethics Committee of Guangdong Provincial People's Hospital, and the study was carried out in compliance with the Declaration of Helsinki. (Approval no. GDREC2019-555H-2). The ethics committee waived

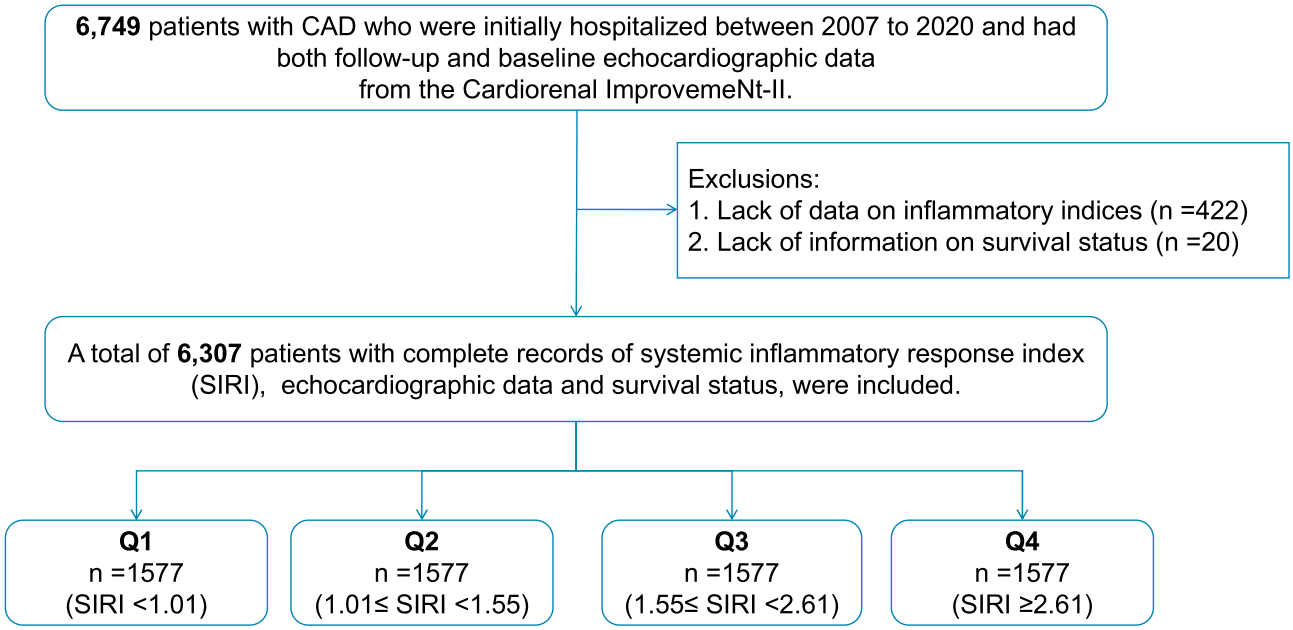


Figure 1 Flowchart of the enrolled population.
Abbreviation: CAD, Coronary artery disease.

the requirement for written informed consent, additional ethical review and approval owing to the retrospective secondary analysis design and use of fully anonymized data.

Data Collection and Definitions

Demographic, laboratory testing, and medication data for the study population were obtained from electronic clinical management systems. Renal function was assessed by estimated glomerular filtration rate (eGFR) which was estimated by applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[14] SIRI was calculated as (neutrophil count × monocyte count) / lymphocyte count. Transthoracic echocardiography was used to obtain left ventricular ejection fraction (LVEF) value by the quantitative two-dimensional biplane from end-diastolic and end-systolic apical 4-chamber and 2-chamber views. Individuals with systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or those on antihypertensive drugs were considered hypertensive. CKD was defined as an eGFR < 60 mL/min/1.73 m^2.[14] Patients who had a glycated hemoglobin level of ≥ 6.5% or were currently using hypoglycemic medications were diagnosed with diabetes mellitus.[15] Acute myocardial infarction (AMI) was diagnosed in accordance with the 4th Universal Definition of Acute Myocardial Infarction. Atrial fibrillation (AF) and valvular heart disease (VHD) were identified using the International Classification of Diseases, 10th Revision (ICD-10) codes I48 and I34.2, respectively.

Outcomes

Worsening of LV systolic function served as the primary endpoint and was identified by an absolute decrease of 10% or more in LVEF from baseline to 12 months following hospital discharge.[16] All-cause mortality was determined from death registry databases, and cardiovascular mortality was determined from primary and secondary causes of death listed in the ICD-10 codes I00–I99. LV remodeling was defined as an increase of LV end-diastolic volume (LVEDV) greater than or equal to 20% as a sensitivity analysis outcome.[17,18] LVEDV at baseline and at follow-up were calculated with the use of left ventricular end-diastolic diameter (LVEDD) and the Teichholz formula (LVEDV = [7 / (2.4 + LVEDD)] × $LVEDD^3$).[19]

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Statistical Analysis

Normally distributed continuous variables are shown as mean ± SD, non-normally distributed variables as median (IQR), and categorical variables as n (%). Group comparisons were performed using the Student's *t*-test, Mann–Whitney-*U* test, and Pearson chi-square test, respectively.

Participants were divided into 4 groups based on SIRI quartiles and compared: Q1 (SIRI < 1.0, n = 1577), Q2 group (1.0 ≤ SIRI < 1.5, n = 1576), Q3 group (1.5 ≤ SIRI < 2.6, n = 1577), Q4 group (SIRI ≥ 2.6, n = 1577). Multivariate logistic regression was used to evaluate the association between SIRI and worsening of left ventricular systolic function. The association of SIRI, worsening of LV systolic function and mortality was examined using multivariable Cox regression analyses. The potential nonlinear relationships between SIRI and study outcomes were assessed using 3 knots restricted cubic splines. The adjusted models accounted for common potential confounders and imbalanced variables at baseline, incorporating age, sex, hypertension, CKD, diabetes mellitus, procedure of percutaneous coronary intervention (PCI), AF, VHD, anemia, LVEF at baseline, and renin-angiotensin-aldosterone system inhibitor (RAASi) use. The missing variables in the model were only caused by RAASi (n=28). The missing data rate in the adjusted model was only 0.4% relative to the total sample size; therefore, no special handling of missing values was performed during the analyses. The mediating effect of worsening of LV systolic function in mortality was tested using a mediation analysis. Sensitivity analysis comprised subgroup analyses and interaction-effect analyses. Statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-sided *P* value < 0.05.

Results

Baseline Characteristics

The study cohort comprised 6307 participants (mean age: 62.0 ± 10.7 years, 20.6% female). In the higher inflammation group, participants were older, had a higher prevalence of hypertension, AMI, AF, CKD, and anaemia, and had a lower proportion of females and lower baseline eGFR and LVEF. Baseline characteristics of the study population are shown in Table 1.

Table 1 Baseline Characteristics of the Study Populations

	Overall	Q1	Q2	Q3	Q4	*P*
	N =6307	n =1577	n =1576	n =1577	n =1577	
Demographic						
Age, years	62.0 (10.7)	61.2 (10.4)	61.5 (10.4)	62.7 (10.4)	62.7 (11.5)	<0.001
Female (%)	1299 (20.6)	474 (30.1)	319 (20.2)	264 (16.7)	242 (15.3)	<0.001
Smoke, n (%)	2198 (37.3)	461 (31.6)	538 (36.4)	576 (39.1)	623 (42.3)	<0.001
Medical history						
Hypertension, n (%)	3577 (56.7)	824 (52.3)	889 (56.4)	924 (58.6)	940 (59.6)	<0.001
AMI, n (%)	1547 (24.5)	151 (9.6)	238 (15.1)	395 (25.0)	763 (48.4)	<0.001
ACS, n (%)	2892 (45.9)	558 (35.4)	612 (38.8)	745 (47.2)	977 (62.0)	<0.001
VHD, n (%)	520 (8.2)	131 (8.3)	132 (8.4)	129 (8.2)	128 (8.1)	0.993
AF, n (%)	316 (5.0)	81 (5.1)	70 (4.4)	65 (4.1)	100 (6.3)	0.022
Diabetes mellitus, n (%)	2457 (39.0)	624 (39.6)	605 (38.4)	616 (39.1)	612 (38.8)	0.922
CKD, n (%)	1405 (22.3)	201 (12.7)	291 (18.5)	384 (24.4)	529 (33.5)	<0.001
Anemia, n (%)	1113 (17.6)	170 (10.8)	224 (14.2)	274 (17.4)	445 (28.2)	<0.001
Procedure of PCI, n (%)	5268 (83.5)	1293 (82.0)	1282 (81.3)	1307 (82.9)	1386 (87.9)	<0.001
Laboratory tests						
WBC, 10^9/L	7.6 [6.3, 9.3]	6.2 [5.3, 7.2]	7.1 [6.1, 8.1]	7.9 [6.8, 9.1]	10.0 [8.3, 12.3]	<0.001
Monocyte, 10^9/L	0.7 (0.3)	0.5 (0.1)	0.6 (0.1)	0.7 (0.2)	0.9 (0.3)	<0.001
Neutrophil, 10^9/L	5.3 (2.6)	3.4 (1.0)	4.3 (1.0)	5.3 (1.4)	8.1 (3.1)	<0.001
Lymphocyte, 10^9/L	1.9 (0.7)	2.2 (0.7)	2.0 (0.7)	1.8 (0.6)	1.5 (0.6)	<0.001
Albumin, g/L	36.8 (4.3)	38.0 (3.7)	37.5 (3.9)	36.6 (4.4)	35.0 (4.7)	<0.001

(*Continued*)

Table 1 (Continued).

	Overall	Q1	Q2	Q3	Q4	*P*
	N =6307	**n =1577**	**n =1576**	**n =1577**	**n =1577**	
HS-CRP, mg/L	3.5 [1.1, 10.5]	1.4 [0.6, 3.7]	2.6 [0.8, 6.0]	4.3 [1.5, 11.3]	14.2 [4.6, 47.5]	<0.001
SIRI	1.5 [1.0, 2.6]	0.8 [0.6, 0.9]	1.3 [1.1, 1.4]	2.0 [1.7, 2.2]	4.0 [3.1, 6.0]	<0.001
HbA1c, %	6.6 (1.4)	6.6 (1.4)	6.6 (1.4)	6.6 (1.5)	6.6 (1.5)	0.712
LDL-C, mmol/L	2.9 (1.0)	2.9 (1.0)	2.9 (1.0)	2.9 (1.0)	2.9 (0.9)	0.364
eGFR, (mL/(min*1.73m^2))	78.1 (28.9)	83.5 (25.7)	80.3 (29.6)	76.9 (29.5)	71.7 (29.1)	<0.001
NT-proBNP, pg/mL	422.9 [94.5, 1514.5]	169.6 [59.1, 712.7]	324.9 [77.6, 1014.2]	455.7 [113.1, 1471.0]	1328.0 [406.6, 3608.0]	<0.001
LVEF, %	55.7 (13.4)	58.5 (12.7)	57.0 (13.1)	55.2 (13.5)	52.0 (13.5)	<0.001
Prescriptions						
RAASi, n (%)	4471 (71.2)	1059 (67.3)	1122 (71.4)	1178 (75.0)	1112 (71.1)	<0.001
β-blocker, n (%)	5216 (83.1)	1286 (81.7)	1298 (82.6)	1317 (83.9)	1315 (84.1)	0.236
CCB, n (%)	1143 (18.2)	288 (18.3)	304 (19.3)	293 (18.7)	258 (16.5)	0.199
DAPT, n (%)	5302 (84.4)	1323 (84.1)	1322 (84.1)	1334 (85.0)	1323 (84.6)	0.878
Statins, n (%)	5904 (94.0)	1479 (94.0)	1481 (94.2)	1492 (95.0)	1452 (92.8)	0.077

Abbreviations: AMI, Acute Myocardial Infarction; ACS, Acute coronary syndrome; VHD, Valvular heart disease; AF, Atrial fibrillation; CKD, Chronic Kidney Disease;PCI, percutaneous coronary intervention; WBC, White Blood Cells; HS-CRP, Hypersensitive C-Reactive Protein; SIRI, Systemic Inflammation Response Index; HbA1c, Hemoglobin A1c; LDLC, Low-Density Lipoprotein Cholesterol; eGFR, estimated Glomerular Filtration Rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, Left Ventricular Ejection Fraction; RAASi, Renin-Angiotensin-Aldosterone System inhibitor; CCB,Calcium Channel Blocker; DAPT, Dual-Anti Platelet-Therapy.

Association Between SIRI, worsening of Left Ventricular Systolic Function and Mortality

After a follow-up of 1 year, a total of 521 (8.3%) worsening of LV systolic function occurred. Over a median follow-up period of 4.2 years, 523 (8.3%) cardiovascular mortality and 1,022 (16.2%) all-cause mortality were recorded. Compared with patients without worsening of LV systolic function, those with worsening of LV systolic function had a higher SIRI level (2.4 vs 3.1; $P = 0.006$).

Participants in elevated SIRI level groups had a significantly increased risk of cardiovascular and all-cause mortality compared to the Q1 group (P for Log-rank < 0.05; Figure 2). Similarly, worsening of LV systolic function was associated with a higher cumulative risk of cardiovascular and all-cause mortality (P for Log-rank < 0.05; Supplementary Figure 1).

Multivariate logistics regression was performed to assess the association between SIRI groups and worsening of LV systolic function. After fully adjusting, the extreme SIRI level group exhibited a significant association with worsening of LV systolic function (adjusted odds ratio: 1.52, 95% confidence intervals [CI]: 1.15–2.01; $p = 0.003$). Cox regressions were conducted to evaluate SIRI levels and mortality. A robust association between extreme SIRI levels and cardiovascular mortality (adjusted Hazard Ratio[aHR]: 1.45, 95% CI: 1.10–1.91; $P = 0.008$) and all-cause mortality (aHR: 1.35, 95% CI: 1.12–1.63; $P = 0.001$) were presented (Table 2). The unadjusted results are presented in Supplementary Table 1. Furthermore, the occurrence of worsening of LV systolic function was also significantly associated with cardiovascular death (aHR: 1.77, 95% CI: 1.35–2.32; $P < 0.001$) and all-cause death (aHR: 1.38, 95% CI: 1.12–1.69; $P = 0.002$; Supplementary Figure 1).

Multivariate restricted cubic spline curves showed a nonlinear increasing relationship in worsening of LV systolic function (P for nonlinear < 0.05; Figure 3) and mortality (P for nonlinear < 0.05; Supplementary Figure 2) with rising SIRI values. Although the curves exhibited a nonlinear pattern, the overall trend remained monotonically increasing. Mediation analyses indicated that worsening of LV systolic function mediated 4% of the total effect of the SIRI on cardiovascular mortality ($P < 0.001$) and 2% of the overall effect on all-cause mortality ($P < 0.001$; Figure 4).

Sensitivity Analysis

The subgroup analysis of worsening of LV systolic function was conducted according to predefined strata: age (≥ 60 years vs. < 60 years), gender (Male vs. Female), hypertension (Present vs. Absent), CKD (present vs. absent), AMI at baseline (present vs. absent) and procedure of PCI (With vs. Without) (Table 3). SIRI showed a significant association with worsening of LV systolic function across all subgroups, except in females and those with CKD. No significant

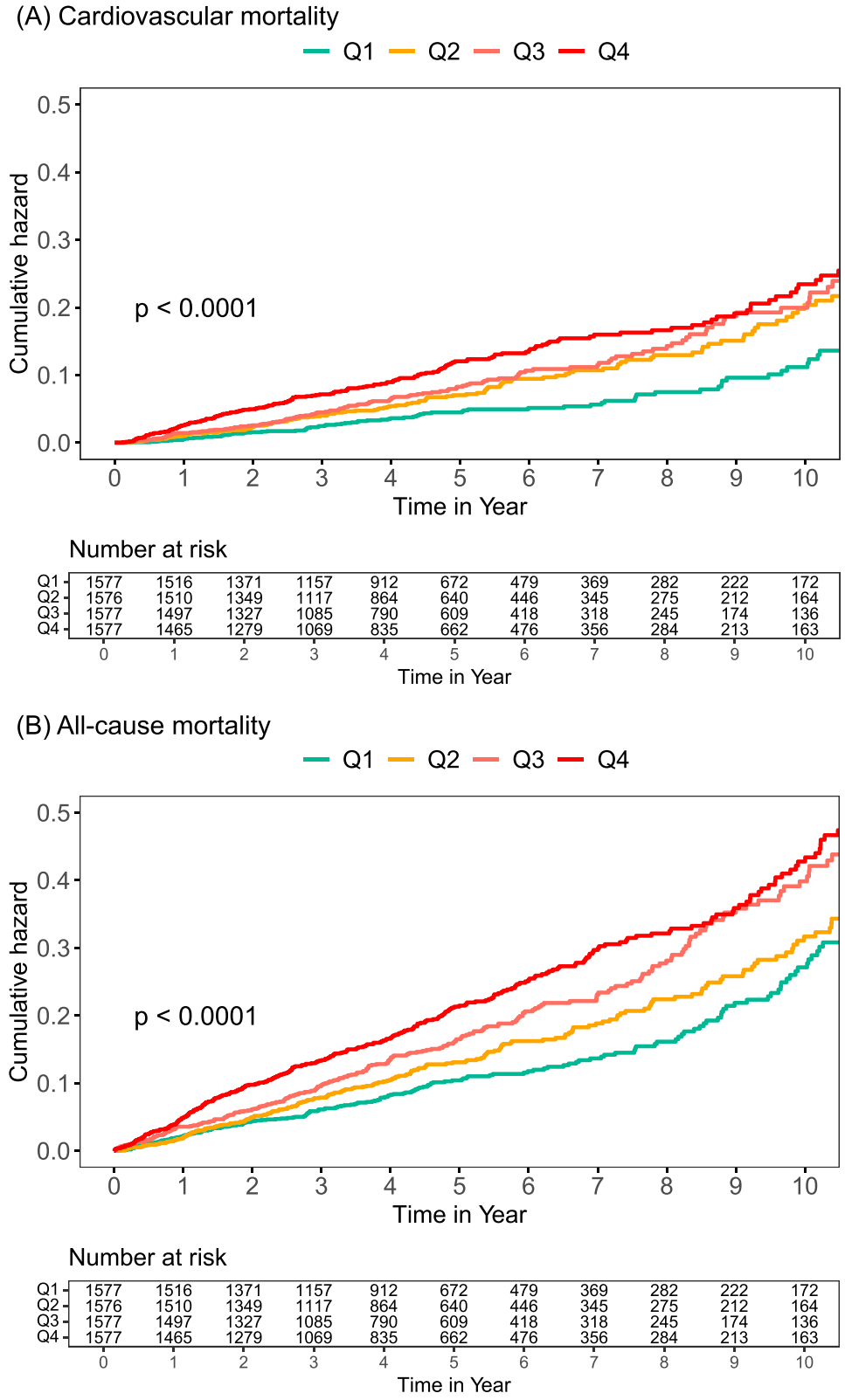

Figure 2 Kaplan-Meier curve of cardiovascular and all-cause death cumulative hazard for different SIRI levels groups. (**A**) Cumulative risk of cardiovascular death in groups with different levels of SIRI; (**B**) Cumulative risk of all-cause death in groups with different levels of SIRI.

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Table 2 The Association Between SIRI, Worsening of LV Systolic Function and Poor Prognosis

Groups	Worsening of LV Systolic Function			Cardiovascular Mortality			All-Cause Mortality		
	Events, n (%)	aOR (95% CIs)	*P*	Events, n (%)	aHR (95% CIs)	*P*	Events, n (%)	aHR (95% CIs)	*P*
Q1 (SIRI <1.0)	117 (1.9%)	Reference	—	117 (1.3%)	Reference	—	189 (3.0%)	Reference	—
Q2 (1.5>SIRI≥1.0)	131 (2.1%)	1.21 (0.93–1.58)	0.163	127 (2.0%)	1.47 (1.11–1.95)	0.008	227 (3.6%)	1.15 (0.95–1.40)	0.153
Q3 (2.6>SIRI≥1.5)	139 (2.2%)	1.37 (1.05–1.80)	0.021	134 (2.1%)	1.39 (1.05–1.84)	0.022	265 (4.2%)	1.25 (1.04–1.52)	0.020
Q4 (SIRI ≥2.6)	134 (2.1%)	1.52 (1.15–2.01)	0.003	180 (2.9%)	1.45 (1.10–1.91)	0.008	341 (5.4%)	1.35 (1.12–1.63)	0.001

Note: Adjusted model: age, sex, hypertension, chronic kidney disease, diabetes mellitus, procedure of percutaneous coronary intervention, atrial fibrillation, valvular heart disease, anemia, left ventricular ejection fraction at baseline, and renin-angiotensin-aldosterone system inhibitor use.
Abbreviations: LV, left ventricular; aOR, adjusted Odd Ratio; aHR, adjusted Hazard Ratio; CIs, Confidence Intervals.

statistical differences were observed across any subgroup interactions (P for interaction > 0.05). In the final adjusted models that included AMI and HS-CRP respectively, the significant association between SIRI and worsening of LV systolic function still existed ($P < 0.05$). SIRI was associated with LV remodeling obtained using the Teichholz formula ($P < 0.05$). The specific details are presented in Supplementary Table 2.

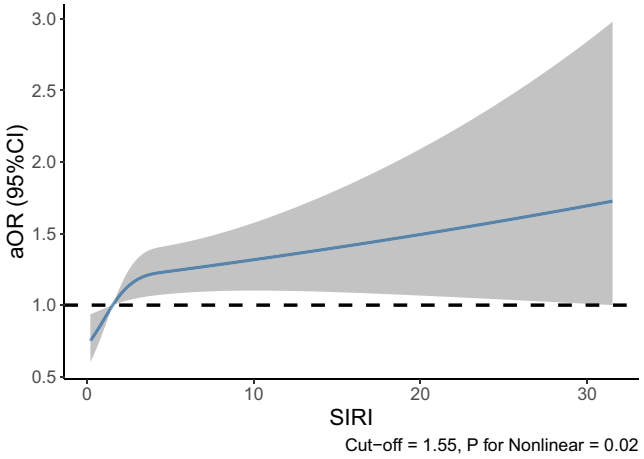

Figure 3 RCS curves of the SIRI for worsening of LV systolic function.
Notes: Adjusted model: age, sex, hypertension, chronic kidney disease, diabetes mellitus, procedure of percutaneous coronary intervention, atrial fibrillation, valvular heart disease, anemia, left ventricular ejection fraction at baseline, and renin-angiotensin-aldosterone system inhibitor use.
Abbreviations: aOR, adjusted odd ratio; CIs, Confidence Intervals; SIRI, Systemic Inflammation Response Index.

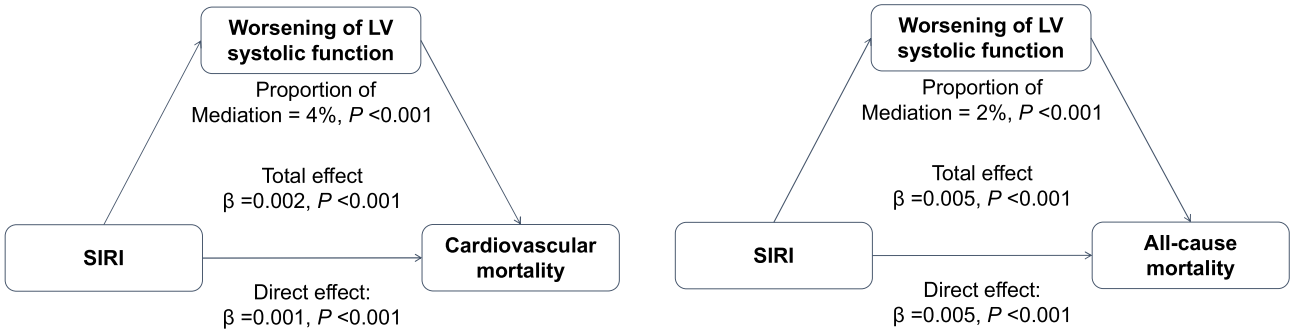

Figure 4 Mediation effort between SIRI, worsening of LV systolic function, cardiovascular and all-cause death.
Notes: Adjusted model: age, sex, hypertension, chronic kidney disease, diabetes mellitus, procedure of percutaneous coronary intervention, atrial fibrillation, valvular heart disease, anemia, left ventricular ejection fraction at baseline, and renin-angiotensin-aldosterone system inhibitor use.
Abbreviation: SIRI, Systemic Inflammation Response Index.

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Table 3 Subgroup Analysis

Subgroups	aOR (95% CIs)	*P*	*aOR (95% CIs)*	*P*	*P* for interaction	Subgroups	aOR (95% CIs)	*P*	aOR (95% CIs)	*P*	*P* for interaction
Age	**≥60, n =3841**		**<60, n =2466**		0.479	**Gender**	**Male, n =5008**		**Female, n =1299**		0.753
Q1	Reference	—	Reference	—		Q1	Reference	—	Reference	—	
Q2	1.40 (0.98–1.94)	0.065	0.97 (0.63–1.50)	0.900		Q2	1.31 (0.95–1.80)	0.100	1.06 (0.64–1.78)	0.782	
Q3	1.46 (1.04–2.06)	0.031	1.25 (0.81–1.94)	0.312		Q3	1.53 (1.12–2.11)	0.008	1.02 (0.57–1.77)	0.948	
Q4	1.48 (1.03–2.11)	0.034	1.58 (1.02–2.45)	0.040		Q4	1.65 (1.20–2.29)	0.002	1.33 (0.73–2.37)	0.343	
Hypertension	**Present, n =3577**		**Absent, n =2730**		0.537	**CKD**	**Present, n =1405**		**Absent, n =4902**		0.356
Q1	Reference	—	Reference	—		Q1	Reference	—	Reference	—	
Q2	1.28 (0.90–1.82)	0.176	1.14 (0.75–1.72)	0.538		Q2	1.42 (0.79–2.61)	0.244	1.15 (0.85–1.56)	0.354	
Q3	1.30 (0.91–1.87)	0.154	1.51 (1.00–2.26)	0.048		Q3	0.77 (0.41–1.43)	0.398	1.65 (1.23–2.23)	0.001	
Q4	1.55 (1.07–2.24)	0.020	1.51 (0.99–2.03)	0.057		Q4	1.19 (0.69–2.17)	0.549	1.69 (1.22–2.34)	0.001	
AMI	**Present, n =1547**		**Absent, n =4760**		0.356	**PCI**	**With, n =5268**		**Without, n =1039**		0.520
Q1	Reference	—	Reference	—		Q1	Reference	—	Reference	—	
Q2	1.31 (0.58–3.17)	0.163	1.18 (0.89–1.57)	0.246		Q2	1.13 (0.84–1.53)	0.413	1.66 (0.92–3.05)	0.098	
Q3	2.24 (1.08–5.13)	0.040	1.16 (0.85–1.56)	0.347		Q3	1.27 (0.94–1.72)	0.118	1.98 (1.08–3.71)	0.029	
Q4	1.62 (0.80–3.63)	0.207	1.44 (1.03–2.00)	0.033		Q4	1.47 (1.07–1.98)	0.016	2.08 (1.06–4.11)	0.032	

Notes: Adjusted model: age, sex, hypertension, chronic kidney disease, diabetes mellitus, procedure of percutaneous coronary intervention, atrial fibrillation, valvular heart disease, anemia, left ventricular ejection fraction at baseline, and renin-angiotensin-aldosterone system inhibitor use.

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Discussion

In our previous studies, we investigated the association between malnutrition and left ventricular functional deterioration.[20] In the present study, the relationship between systemic inflammatory status and worsening of LV systolic function and their associations with mortality were further evaluated in patients with CAD. The results identified a high SIRI level as an independent risk factor for worsening of LV systolic function in CAD patients, conferring a 1.52-fold risk. Moreover, worsening of LV systolic function serves as a significant mediator linking systemic inflammation to increased mortality.

In sensitivity analysis, the relationship between SIRI and worsening of left ventricular function in sensitivity analyses was independent of AMI and high-sensitivity C-reactive protein at baseline, respectively, providing partial support for the notion that this association is not entirely driven by prior myocardial infarction and for the uniqueness of SIRI relative to other inflammatory measures.

The finding that 95% of the effect was not mediated by worsening of LV systolic function strongly suggests that inflammation affects prognosis mainly through other equally important or even more important pathways, such as directly inducing arrhythmias, atherosclerosis and others.[21,22]

Although the proportion was low, worsening of LV systolic function had a statistically significant mediating effect, still establishing the existence of a chain of "inflammation-LV systolic function-death". This implies that in those patients with high levels of inflammation who are at an early, interventionable pathophysiological stage, targeted anti-inflammation has the value of improving outcomes, broadening the intervention perspective to address systemic inflammation.

In our previous study, Inflammatory markers were recognized as valuable indicators associated with adverse prognosis in patients with different clinical statuses.[23,24] Inflammation is also associated with worsening cardiac function. Supporting this notion, several cross-sectional studies had confirmed a link between inflammation markers and heart failure.[25–27] Analyses from NHANES database revealed a strong association between SIRI and heart failure and that SIRI was linearly associated with heart failure.[26,28]

Furthermore, in another cross-sectional study focusing on patients with CAD, those with high levels of the multi-inflammatory index had a 1.25-fold higher probability of having heart failure compared to those with low levels.[27] In patients with atrial fibrillation, prior research has demonstrated a significant correlation between SIRI and LV remodeling as well as systolic dysfunction.[13] Existing evidence confirms that circulating inflammatory cells or markers were associated with ventricular remodeling in post-myocardial infarction patients.[6,29] However, direct clinical evidence regarding the association between systemic inflammation and LV function in the broader population of patients with CAD remains scarce. To address this gap, our study is the first to specifically investigate the association between systemic inflammation, assessed by SIRI, and worsening of LV systolic function in CAD patients. Our findings highlight the clinical significance of early intervention targeting inflammation, which may help attenuate the progression of worsening of left ventricular systolic function and heart failure and improve long-term outcomes.

Ventricular remodeling is a complex pathological process driven by dysregulated interactions across multiple cardiac components. A central driver of this pathology is the inflammatory response, which orchestrates both its initiation and progression.[30] At the cellular level, macrophages may polarize to a pro-inflammatory M1 phenotype by cardiac extracellular matrix proteins, contributing to the acceleration of ventricular remodeling.[31] Alongside neutrophils, their cytotoxic products directly contribute to LV fibrosis and remodeling.[32] Lymphocytes further modulate this inflammatory milieu, with their depletion being linked to adverse outcomes.[33] Molecularly, key pro-inflammatory cytokines such as IL-6 and TNF-α are elevated in heart failure patients and may drive remodeling.[34–37] Concurrently, TNF-mediated alterations to the extracellular matrix create a permissive environment for adverse structural changes.[38] These established, multi-faceted role of inflammation in ventricular function and remodeling provides a strong mechanistic rationale for our study, which utilises SIRI to integrate these cellular and cytokine-level phenomena into a clinically measurable risk profile for patients with CAD.

Colchicine is classified as a class IIA recommendation for secondary prevention in patients with coronary artery disease. Previous studies have demonstrated that colchicine may reduce the risk of ventricular remodeling and cardiovascular events through inhibition of monocytes and neutrophils activity and the NLRP3 inflammasome.[39] Evidence from one study showed that dapagliflozin administration reduced inflammatory biomarkers and improved cardiac longitudinal strain capacity.[40] Meanwhile, tesiparatide could also attenuate LPS-induced LV remodeling and dysfunction by inhibiting inflammatory

pathway.[41] In addition, renin-angiotensin-aldosterone system Inhibitors, theophylline, inhaled corticosteroids and statings also showed anti-inflammatory effects, meaning that patients who meet the indications for these drugs may gain additional benefit from them.[42] These findings collectively suggest that anti-inflammatory therapies may attenuate ventricular remodeling and support the development of anti-inflammatory treatment strategies in patients with CAD. Whether there are potential treatment strategies can effectively modify the progression of ventricular remodeling and improve the poor prognosis remains an essential focus for future research.

This study is not without limitations. Firstly, owing to its retrospective design, despite adequate adjustment, residual confounding cannot be entirely ruled out, warranting further research to elucidate the causal relationship between SIRI and worsening of LV systolic function. Second, although LVEF serves as a reliable surrogate marker for assessing ventricular function, future studies should incorporate additional parameters to provide a more comprehensive evaluation. Furthermore, longitudinal monitoring of inflammatory markers in subsequent investigations may enable the calculation of annual rates of change, thereby offering a more accurate reflection of disease progression. Finally, although the study population was drawn from multiple study centres, it was predominantly derived from southern China, and the findings lack external validation in independent cohorts, which may restrict the generalizability of the findings.

Conclusions

SIRI serve as a potential risk factor for worsening of LV systolic function in CAD patients, and further contributes to poor prognosis, indicating that anti-inflammatory treatment represents a viable approach to improve the prognosis for CAD patients.

Data Sharing Statement

To protect participant privacy, all patient data were kept strictly confidential and were used solely for the purposes of research, in accordance with the ethical approval and data protection regulations. The datasets and statistical analysis code used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

Huangtao Ruan: Data curation; Formal analysis; Writing – original draft; Writing – review & editing. Xiaozhao Lu: Data curation; Investigation; Writing – original draft; Writing – review & editing. Huan Lu: Data curation; Investigation; Methodology; Software; Writing – original draft. Haozhang Huang: Formal analysis; Validation; Writing – review & editing. Zuxian Huang: Visualization; Writing – review & editing. Shangyi Tang: Visualization; Writing – review & editing. Ziyao Yuan: Investigation, Writing – review & editing. Rengui Jiang: Investigation, Writing – review & editing. Jiazhen Xin: Investigation, Writing – review & editing. Tao Tang: Validation, Writing – review & editing. Jin Liu: Conceptualization; Data curation; Methodology; Writing – review & editing. Yong Liu: Conceptualization; Funding acquisition; Methodology; Resources; Writing – review & editing. Ning Tan: Conceptualization; Resources; Project administration; Supervision; Writing – review & editing.

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Disclosure

The authors declare that they have no competing interests.

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