Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

The Associations of Two Novel Inflammation Biomarkers, SIRI and SII, with Mortality Risk in Patients with Chronic Heart Failure

Di Zhu[1,2,*], Chi Wang[1,*], You Zhou[3], Hebin Che[1], Ruiqing Wang[1,2], Liting Cheng[3], Chongyou Rao[1,2], Qin Zhong[1], Zongren Li[1], Yongjie Duan[1,2], Kunlun He[1]

[1]Medical Big Data Research Center, Medical Innovation Research Department of PLA General Hospital, Beijing, 100853, People's Republic of China; [2]Graduate School of PLA General Hospital, Beijing, 100853, People's Republic of China; [3]School of Medicine, Nankai University, Tianjin, 300071, People's Republic of China

*These authors contributed equally to this work

Correspondence: Kunlun He, Medical Big Data Research Center, Medical Innovation Research Department of PLA General Hospital, 28 Fuxing Road, Beijing, 100853, People's Republic of China, Tel +86-10-66939107, Email kunlunhe@plagh.org

Background: The associations of two novel inflammation biomarkers, systemic inflammation response index (SIRI) and systemic immune inflammation index (SII), with mortality risk in patients with chronic heart failure (CHF) are not well-characterized.

Methods: This retrospective cohort study included patients with CHF in two medical centers of Chinese People's Liberation Army General Hospital, Beijing, China. The outcomes of this study included in-hospital mortality and long-term mortality. Associations of SIRI and SII with mortality were assessed using multivariable regressions and receiver operating characteristic (ROC) analyses.

Results: A total of 6232 patients with CHF were included in the present study. We documented 97 cases of in-hospital mortality and 1738 cases of long-term mortality during an average 5.01-year follow-up. Compared with patients in the lowest quartile of SIRI, those in the highest quartile exhibited 134% higher risk of in-hospital mortality (adjusted odds ratio, 2.34; 95% confidence interval [CI], 1.16–4.72) and 45% higher risk of long-term mortality (adjusted hazard ratio, 1.45; 95% CI, 1.25–1.67). Compared with patients in the lowest quartile of SII, those in the highest quartile exhibited 27% higher risk of long-term mortality (adjusted hazard ratio, 1.27; 95% CI, 1.11–1.46). In ROC analyses, SIRI showed better prognostic discrimination than C-reactive protein (area under the curve: 69.39 vs 60.91, $P = 0.01$, for in-hospital mortality; 61.82 vs 58.67, $P = 0.03$, for 3-year mortality), whereas SII showed similar prognostic value with C-reactive protein.

Conclusion: SIRI and SII were significantly associated with mortality risk in patients with CHF. SIRI may provide better prognostic discrimination than C-reactive protein.

Keywords: systemic inflammation, systemic immune inflammation index, systemic inflammation response index, chronic heart failure, mortality risk

Introduction

Heart failure (HF) is a complex clinical syndrome caused by abnormal changes in heart structure and/or ventricular dysfunction,[1] with high readmission rates, disability rates, and mortality rates. Approximately 1–2% of the population had HF worldwide.[2] According to data from the China Hypertension Survey in 2012–2015, the prevalence of HF among Chinese population aged 35 years or greater was 1.3%.[3] With the increase in societal aging and the increasing prevalence of cardiovascular risk factors, HF will lead to a heavy burden on public health and socio-economic development.[4] Therefore, early identification of risk factors for adverse outcomes in patients with HF are crucial for early intervention and improving prognosis.

A number of evidences showed that chronic systemic inflammation plays an essential role in the development of atherosclerosis and cardiovascular diseases (CVD).[5,6] However, compared with traditional inflammation biomarkers

Received: 22 November 2023
Accepted: 16 February 2024
Published: 23 February 2024

such as C-reactive protein (CRP) and interleukin-6, some novel inflammation biomarkers composed of several easily obtainable and reliable indicators may have greater clinical significance. Recently, systemic inflammation response index (SIRI) and systemic immune inflammation index (SII), two novel inflammation biomarkers that were calculated using blood counts, have been demonstrated to have greater power in predicting cardiovascular outcomes compared with CRP.[7–9] Analyses from Kailuan cohort study found that higher SIRI and SII were associated with increased risks of CVD and all-cause mortality in general population.[10,11] SII was also observed to predict adverse outcomes in patients with acute myocardial infarction, hypertension, and CVD.[12–14] Although, the associations of SIRI and SII with poor cardiovascular outcomes have been reported, there were few studies exploring the predictive value of SIRI and SII in patients with chronic heart failure (CHF). Therefore, the aim of our study was to investigate the associations of SIRI and SII with the risks of in-hospital mortality and long-term mortality in patients with CHF.

Materials and Methods

Study Population

The present study is a retrospective cohort study conducted in Chinese People's Liberation Army General Hospital. Patients with CHF who were hospitalized in the First Medical Center from January 1, 2011, to June 30, 2019, and patients with CHF who were hospitalized in the Sixth Medical Center from January 1, 2016, to December 31, 2018, were included. Patients with CHF were identified by a panel of trained physicians reviewing medical records. The identification of CHF followed the diagnostic criteria recommended by 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.[15] Patients were excluded if they had one of the follows: 1) missing data on blood counts, 2) acute inflammation response (defined as white blood cell [WBC] counts $>10\times10^9$/L or CRP >10mg/L) or low WBC counts (WBC $< 4\times10^9$/L), 3) cancer or leukemia, 4) aplastic anemia, myelodysplastic syndrome, or platelet diseases, 5) autoimmune connective tissue diseases or oral use of steroids. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Chinese People's Liberation Army General Hospital (Number: S2018-269-02). All patients provided their informed consents.

Baseline Data Collection

Data on demographic characteristics, anthropometric measurements, laboratory tests, diagnosis, medication use during hospitalization, and medication use after discharge were abstracted from the hospital information system. For patients who underwent repeated laboratory tests, the first test result was included in our analyses. SIRI was defined as (neutrophil counts × monocyte counts)/lymphocyte counts. SII was defined as (platelet counts × neutrophil counts)/lymphocyte counts.[10,11] Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters). The calculation of estimated glomerular filtration rate (eGFR) was according to the Chronic Kidney Disease Epidemiology Collaboration equation.[16] According to the 2021 ESC Guidelines for CHF, study patients were divided into three categories based on left ventricular ejection fraction (LVEF): heart failure with reduced ejection fraction (HFrEF, LVEF $\leq$ 40%), heart failure with mildly reduced ejection fraction (HFmrEF, 40% < LVEF < 50%) and heart failure with preserved ejection fraction (HFpEF, LVEF $\geq$ 50%).[15]

Follow-up and Outcomes

The outcomes of this study included in-hospital mortality and long-term mortality. Information on in-hospital all-cause mortality and cardiovascular mortality was obtained by reviewing medical records. Information on long-term all-cause mortality and cardiovascular mortality was obtained by telephone interviews with patients or their relatives, or by reviewing medical records of rehospitalization.

Statistical Analyses

Continuous variables with a normal distribution were exhibited as mean ± standard deviation and compared using analysis of variance, continuous variables with a skewed distribution were exhibited as median (interquartile range) and

compared using Kruskal–Wallis test, categorical variables were described as n (percentage) and compared using chi-square test.

We used multivariable logistic regression analysis to estimate the odds ratios (OR) and 95% confidence intervals (CI) of in-hospital mortality according to the quartiles of SIRI and SII and used Cox proportional hazards regression model to estimate the hazard ratios (HR) and 95% CI of long-term mortality. Multivariate-adjusted model was adjusted for age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, HF phenotypes, BMI, hemoglobin, fasting blood glucose (FBG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), albumin, eGFR, uric acid (UA), N-terminal pro-brain natriuretic peptide (NT-proBNP), medical history of myocardial infarction, atrial fibrillation, valvular heart disease, hypertension, stroke, peripheral arterial disease, chronic pulmonary disease, medications for HF (including renin-angiotensin-aldosterone system inhibitors [RAASi], spironolactone, diuretics, beta-blockers, digitalis and nitrates), antiplatelet medications (including aspirin, clopidogrel, and ticagrelor), and anticoagulant medications (including warfarin, dabigatran, and rivaroxaban). Missing values of covariates were handled by multiple imputation. The proportional hazard assumption was checked using Schoenfeld residuals. We used restricted cubic spline to examine the associations of SIRI and SII as the continuous variables with the risks of in-hospital and long-term mortality. To minimize the potential impact of reverse causation, we conducted a sensitivity analysis excluding patients who died within six months after discharge. To further examine whether the associations of SIRI and SII with the risk of all-cause mortality were modified by age, sex, and HF phenotypes, stratified analysis by these factors were performed.

Prognostic values of SIRI, SII, NT-proBNP, and CRP for in-hospital mortality and 3-year mortality were assessed by area under the curve (AUC) in receiver operating characteristic (ROC) analyses.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) and R software version 4.2.2 (R core team). Two-sided P value <0.05 was considered statistically significant.

Results

Characteristics of the Study Population

In the present study, we identified 10,186 patients with CHF and 3954 patients who met the exclusion criteria were excluded. A total of 6232 patients were included in the in-hospital mortality analysis (Figure 1). Of these, the mean age was 62.46±14.22 years, 4281 (68.69%) were men, 97 (1.56%) had in-hospital mortality, and 897 (14.39%) lost to follow-up. Finally, there were 5238 patients included in the long-term mortality analysis (Figure 1). Patients who lost to follow-up were younger (mean, 59.80 vs 62.76, $P < 0.01$), but had comparable SIRI (median, 0.92 vs 0.95, $P = 0.69$) and SII (median, 426.56 vs 437.46, $P = 0.26$) level compared with those who had follow-up information. The baseline characteristics of the study patients according to quartiles of SIRI are shown in Table 1. Compared with patients in Quartile 1, patients in Quartile 4 were older and more likely to be men, to have higher SBP, heart rate, LVEF, FBG, UA, CRP, and NT-proBNP, to have lower BMI, hemoglobin, LDL-C, HDL-C, TG, albumin, and eGFR, to have atrial fibrillation, hypertension, stroke, and chronic pulmonary disease, to be on diuretics, nitrates, antiplatelet medications, and anticoagulant medications.

Risk of Outcomes

Of the 6232 study patients, we identified 97 cases of in-hospital mortality (including 71 cases of in-hospital cardiovascular mortality). During the mean 5.01-year follow-up, we documented 1738 cases of long-term mortality (including 936 cases of long-term cardiovascular mortality). As the quartiles of SIRI and SII increased, both the incidences of in-hospital mortality and long-term mortality in patients with CHF increased (Tables 2 and 3). After adjustment for potential confounders, patients in the highest quartile of SIRI showed 134% higher risk of in-hospital mortality (OR: 2.34; 95% CI: 1.16–4.72) and 45% higher risk of long-term mortality (HR: 1.45; 95% CI: 1.25–1.67) compared with those in the lowest quartile of SIRI (Table 2), patients in the highest quartile of SII showed 27% higher risk of long-term mortality (HR: 1.27; 95% CI: 1.11–1.46) compared with those in the lowest quartile of SII (Table 3). Similar results were also observed in cardiovascular mortality analysis and sensitivity analysis. Furthermore, we observed a dose–response

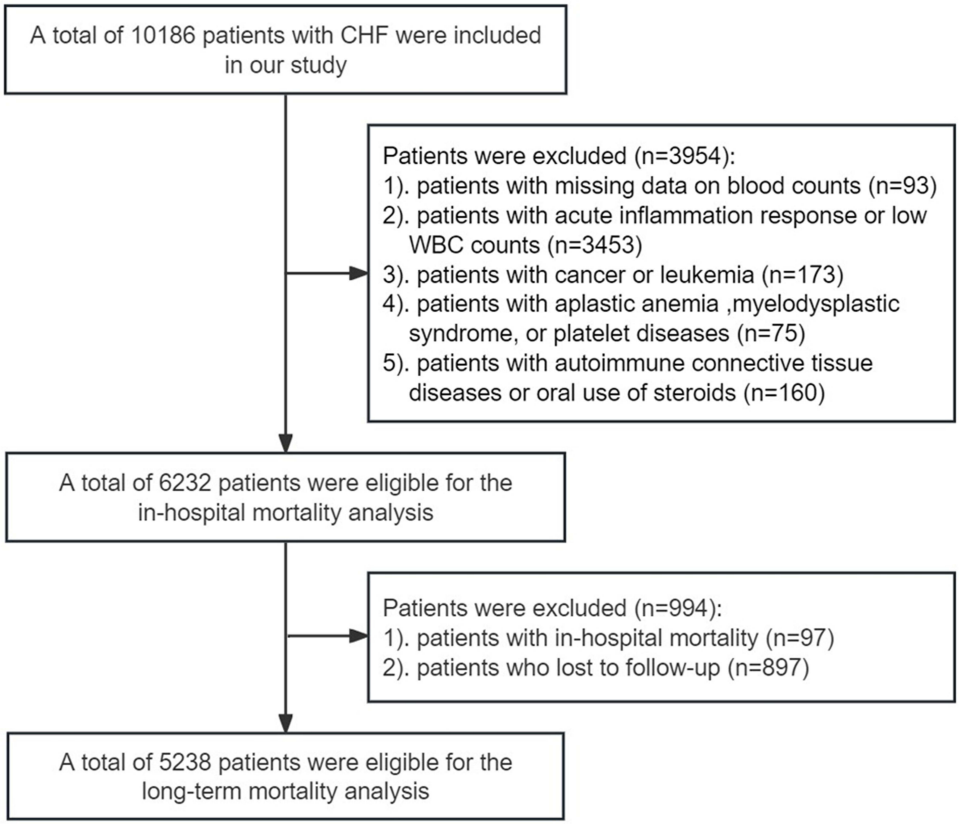

Figure 1 Eligibility of the study patients. The flowchart of the eligibility of 6232 patients included in the in-hospital mortality analysis, and 5238 patients included in the long-term mortality analysis.
Abbreviations: CHF, chronic heart failure; WBC, white blood cell; CRP, C-reactive protein.

relationship of SIRI and SII with the risk of all-cause mortality (P for trend <0.05), which was further supported by the restricted cubic spline regression analyses (Figure 2).

Stratified Analysis

We did not find significant interactions between SIRI, SII and age, sex, HF phenotypes in relation to the risk of in-hospital mortality (Online Tables 1 and 2). However, the associations of SIRI and SII with long-term mortality risk appeared to be more pronounced among patients with older age, relative to those aged younger than 60 years (Online Tables 1 and 2).

Table 1 Baseline Characteristics of the Patients According to the Quartiles of SIRI

Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
N	1553	1558	1556	1565	
Age (years)	58.79±13.58	61.63±13.46	63.43±14.19	65.97±14.66	<0.01
Male, No. (%)	933 (60.08)	1056 (67.78)	1136 (73.01)	1156 (73.87)	<0.01
BMI (kg/m^2)	25.30±4.02	25.39±3.82	25.49±4.04	25.13±4.18	<0.01
SBP (mmHg)	127.60±20.79	129.31±21.78	132.28±22.16	133.71±23.49	<0.01
DBP (mmHg)	75.17±13.46	75.97±13.12	76.55±14.07	76.29±14.49	0.06
Heart rate (beats per minute)	79.20±15.83	79.92±16.75	80.56±17.58	82.95±18.60	<0.01
LVEF (%)	45.65±13.44	44.70±13.20	44.85±13.01	45.96±13.00	<0.01
Hb (g/L)	137.04±19.13	136.12±20.61	134.15±23.03	128.90±25.64	<0.01
FBG (mmol/L)	5.12 (4.61, 6.15)	5.29 (4.68, 6.53)	5.34 (4.71, 6.66)	5.59 (4.85, 6.96)	<0.01

(*Continued*)

Table 1 (Continued).

Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
LDL-C (mmol/L)	2.49 (1.95, 3.11)	2.35 (1.83, 2.97)	2.29 (1.77, 2.94)	2.23 (1.68, 2.83)	<0.01
HDL-C (mmol/L)	1.09±0.31	1.07±0.29	1.06±0.30	1.05±0.33	<0.01
TG (mmol/L)	1.27 (0.92, 1.77)	1.24 (0.92, 1.74)	1.23 (0.89, 1.71)	1.16 (0.84, 1.64)	<0.01
Albumin (g/L)	40.60±4.21	40.23±4.18	39.94±4.34	38.75±4.74	
eGFR (mL/min/1.73m^2)	84.85 (68.21, 96.78)	79.81 (62.21, 93.28)	73.56 (53.38, 89.43)	64.88 (41.54, 85.46)	<0.01
UA (μmol/L)	365.20 (306.20, 440.00)	381.05 (308.80, 458.90)	390.20 (319.15, 472.90)	408.00 (325.60, 507.70)	<0.01
CRP (mg/L)	1.20 (0.98, 2.30)	1.33 (1.00, 3.00)	1.60 (1.00, 3.60)	2.57 (1.00, 5.35)	
NT-proBNP (pg/mL)	1147.00 (502.00, 3018.00)	1474.50 (639.58, 3789.60)	1969.00 (778.50, 4938.00)	2920.00 (1227.00, 7426.00)	<0.01
Myocardial infarction, No. (%)	506 (32.58)	580 (37.23)	622 (39.97)	620 (39.62)	<0.01
Atrial fibrillation, No. (%)	423 (27.24)	426 (27.34)	420 (26.99)	499 (31.88)	<0.01
VHD, No. (%)	378 (24.34)	314 (20.15)	297 (19.09)	286 (18.27)	<0.01
Hypertension, No. (%)	801 (51.58)	937 (60.14)	972 (62.47)	1081 (69.07)	<0.01
Stroke, No. (%)	221 (14.23)	286 (18.36)	307 (19.73)	368 (23.51)	<0.01
PAD, No. (%)	216 (13.91)	218 (13.99)	250 (16.07)	251 (16.04)	0.14
CPD, No. (%)	115 (7.41)	147 (9.44)	158 (10.15)	273 (17.44)	<0.01
RAASi, No. (%)	904 (58.21)	936 (60.08)	991 (63.69)	949 (60.64)	0.02
Spironolactone, No. (%)	1081 (69.61)	1096 (70.35)	1084 (69.67)	1092 (69.78)	0.97
Diuretics, No. (%)	1102 (70.96)	1150 (73.81)	1200 (77.12)	1313 (83.90)	<0.01
Beta-blockers, No. (%)	1272 (81.91)	1271 (81.58)	1275 (81.94)	1236 (78.98)	0.10
Digitalis, No. (%)	676 (44.53)	691 (44.35)	664 (42.67)	669 (42.75)	0.76
Nitrates, No. (%)	851 (54.80)	980 (62.90)	1054 (67.74)	1092 (69.78)	<0.01
Antiplatelet medications, No. (%)	1027 (66.13)	1114 (71.50)	1128 (72.49)	1141 (72.91)	<0.01
Anticoagulant medications, No. (%)	398 (25.63)	377 (24.20)	358 (23.01)	333 (21.28)	0.03

Notes: Data was presented as mean ± SD, median (25th, 75th percentiles), or percentage.
Abbreviations: BMI, body mass index; CPD, chronic pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; Hb, hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAD, peripheral arterial disease; RAASi, renin-angiotensin-aldosterone system inhibitors; SBP, systolic blood pressure; SIRI, system inflammation response index; TG, triglyceride; UA, uric acid; VHD, valvular heart disease.

Table 2 Risk of Mortality in Patients with CHF According to the Quartiles of SIRI

Mortality Risk	Quartile Groups of SIRI				*P*-trend
	Quartile 1 (<0.64)	Quartile 2 (0.64–0.94)	Quartile 3 (0.95–1.43)	Quartile 4 (≥1.44)	
In-hospital mortality, OR (95% CI)					
Case/Total	11/1553	10/1558	24/1556	52/1565	
Incident rate, %	0.71	0.64	1.54	3.32	
Model 1	1 (Reference)	0.91 (0.38–2.14)	2.20 (1.07–4.50)	4.82 (2.50–9.27)	<0.01
Model 2	1 (Reference)	0.85 (0.36–2.02)	1.99 (0.97–4.12)	4.15 (2.12–8.09)	<0.01
Model 3	1 (Reference)	0.75 (0.31–1.78)	1.53 (0.73–3.23)	2.34 (1.16–4.72)	<0.01
CV mortality	1 (Reference)	0.76 (0.29–1.99)	1.36 (0.58–3.16)	2.38 (1.08–5.23)	<0.01
Long-term mortality, HR (95% CI)					
Case/Total	326/1315	378/1306	466/1332	568/1285	
Incident rate, per 1000-person year	44.67	54.40	72.42	102.08	
Model 1	1 (Reference)	1.22 (1.05–1.41)	1.62 (1.41–1.87)	2.28 (1.99–2.61)	<0.01
Model 2	1 (Reference)	1.12 (0.96–1.30)	1.40 (1.21–1.61)	1.90 (1.65–2.18)	<0.01
Model 3	1 (Reference)	1.05 (0.90–1.22)	1.21 (1.05–1.41)	1.45 (1.25–1.67)	<0.01
CV mortality	1 (Reference)	1.07 (0.87–1.31)	1.24 (1.02–1.51)	1.59 (1.30–1.93)	<0.01
Sensitivity analysis	1 (Reference)	1.05 (0.90–1.23)	1.19 (1.02–1.39)	1.39 (1.20–1.62)	<0.01

Notes: Model 1 was non-adjusted model. Model 2 was adjusted for age and sex. Model 3 was further adjusted for SBP, DBP, heart rate, HF phenotypes, BMI, hemoglobin, FBG, LDL-C, HDL-C, TG, albumin, eGFR, UA, NT-proBNP, medical history of myocardial infarction, atrial fibrillation, valvular heart disease, hypertension, stroke, peripheral arterial disease, chronic pulmonary disease, and medication use of RAASi, spironolactone, diuretics, beta-blockers, digitalis, nitrates, antiplatelet medications and anticoagulant medications.
Abbreviations: CHF, chronic heart failure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; OR, odds ratio; SIRI, system inflammation response index.

Table 3 Risk of Mortality in Patients with CHF According to the Quartiles of SII

Mortality Risk	Quartile Groups of SII				*P*-trend
	Quartile 1 (<309.80)	Quartile 2 (309.80–437.45)	Quartile 3 (437.46–644.90)	Quartile 4 (≥644.91)	
In-hospital mortality, OR (95% CI)					
Case/Total	18/1558	12/1558	22/1558	45/1558	
Incident rate, %	1.52	1.16	1.74	4.52	
Model 1	1 (Reference)	0.66 (0.32–1.38)	1.23 (0.66–2.29)	2.55 (1.47–4.42)	<0.01
Model 2	1 (Reference)	0.64 (0.31–1.34)	1.14 (0.61–2.15)	2.20 (1.26–3.84)	<0.01
Model 3	1 (Reference)	0.64 (0.30–1.36)	0.97 (0.50–1.86)	1.51 (0.83–2.73)	0.05
CV mortality	1 (Reference)	0.70 (0.32–1.56)	0.88 (0.42–1.84)	1.28 (0.65–2.52)	0.31
Long-term mortality, HR (95% CI)					
Case/Total	368/1305	393/1314	446/1322	531/1297	
Incident rate, per 1000-person year	51.46	57.63	69.00	91.59	
Model 1	1 (Reference)	1.12 (0.97–1.29)	1.34 (1.17–1.54)	1.78 (1.55–2.03)	<0.01
Model 2	1 (Reference)	1.07 (0.93–1.23)	1.25 (1.09–1.44)	1.57 (1.38–1.80)	<0.01
Model 3	1 (Reference)	1.04 (0.90–1.20)	1.15 (1.00–1.32)	1.27 (1.11–1.46)	<0.01
CV mortality	1 (Reference)	1.15 (0.95–1.40)	1.29 (1.07–1.57)	1.41 (1.16–1.71)	<0.01
Sensitivity analysis	1 (Reference)	1.02 (0.88–1.18)	1.13 (0.97–1.30)	1.21 (1.05–1.40)	<0.01

Notes: Model 1 was non-adjusted model. Model 2 was adjusted for age and sex. Model 3 was further adjusted for SBP, DBP, heart rate, HF phenotypes, BMI, hemoglobin, FBG, LDL-C, HDL-C, TG, albumin, eGFR, UA, NT-proBNP, medical history of myocardial infarction, atrial fibrillation, valvular heart disease, hypertension, stroke, peripheral arterial disease, chronic pulmonary disease, and medication use of RAASi, spironolactone, diuretics, beta-blockers, digitalis, nitrates, antiplatelet medications, and anticoagulant medications.

Abbreviations: CHF, chronic heart failure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; OR, odds ratio; SII, systemic immune inflammation index.

ROC Analysis

Among 6232 study patients, 5066 had CRP data and were included in the ROC analyses. In the ROC analysis of in-hospital mortality (Figure 3A), the prognostic discrimination of SIRI was comparable to that of NT-proBNP (AUC, 69.39 vs 69.88, $P = 0.90$), but was larger than those of SII (AUC, 69.39 vs 63.16, $P < 0.01$) and CRP (AUC, 69.39 vs 60.91, $P = 0.01$); in the ROC analysis of 3-year mortality (Figure 3B), the prognostic discrimination of SIRI was smaller than that of NT-proBNP (AUC, 61.82 vs 70.40, $P < 0.01$), but was larger than those of SII (AUC, 61.82 vs 59.03, $P < 0.01$) and CRP (AUC, 61.82 vs 58.67, $P = 0.03$). SII showed similar prognostic discrimination with CRP in both in-hospital mortality (AUC, 63.16 vs 60.91, $P = 0.55$) and 3-year mortality (AUC, 59.03 vs 58.67, $P = 0.80$) (Figure 3).

Discussion

In this large-scale retrospective cohort study, we found that SIRI and SII were associated with the risks of both in-hospital mortality and long-term mortality in patients with CHF. These findings remained consistent in cardiovascular mortality analysis and sensitivity analysis. The significant associations of SIRI and SII with long-term mortality risk were observed to be more evident in patients aged ≥60 years compared with those aged <60 years. Moreover, according to the ROC analyses, SIRI had a similar prognostic value in predicting in-hospital mortality compared with NT-proBNP and had a higher prognostic value in predicting both in-hospital mortality and 3-year mortality compared with CRP.

Several studies have sought to investigate the associations of SIRI and SII with the prognosis of CHF. Findings from Medical Information Mart data for Intensive Care-III database showed that the risk of all-cause mortality rose with increasing SIRI[17] and SII.[18,19] However, these former studies only explored the outcome of short-term all-cause mortality and lacked data on cardiovascular mortality, while we had an average 5.01-year follow-up and examined the associations of SIRI and SII with both all-cause mortality and cardiovascular mortality. Moreover, the study design of these studies only included HF patients underwent critical care, which overlooked the SIRI/SII-mortality associations in CHF patients of general wards. Thus, the study patients in our study might be more representative. Additionally, Wang et al[20] found that elevated SII was significantly associated with higher risk of all-cause mortality and major cardiovascular adverse

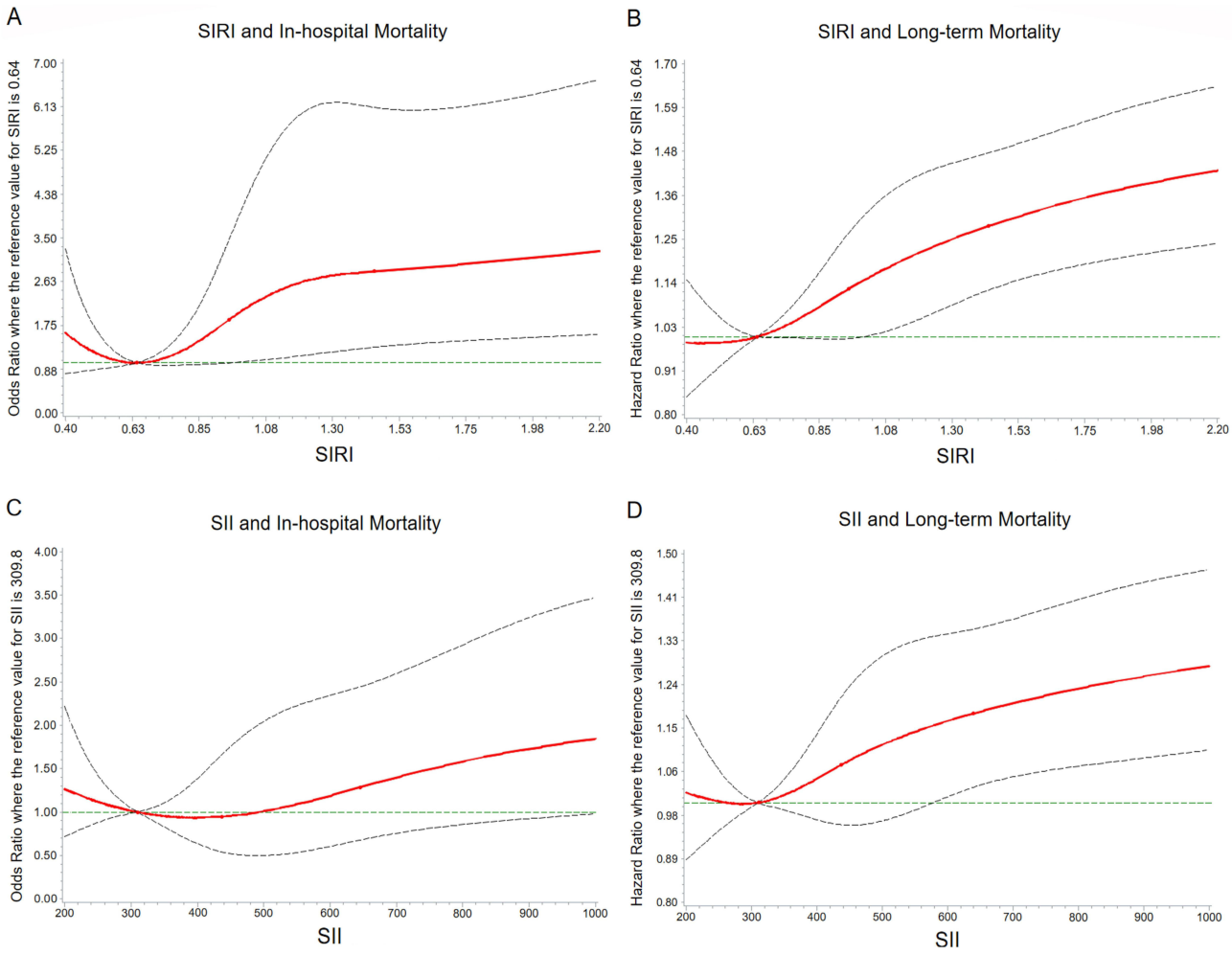

Figure 2 Restricted cubic spline regression analyses for the association of SIRI and SII with the mortality risk in patients with CHF. Odds ratios and 95% confidence intervals for SIRI (**A**) and SII (**C**) with in-hospital mortality and hazard ratios and 95% confidence intervals for SIRI (**B**) and SII (**D**) with long-term mortality by using restricted cubic spline regression with five knots placed at the 5th, 25th, 50th, 75th and 95th percentiles of SIRI and SII. The red solid line represented the odds ratio or hazard ratio, and the black dashed lines represented 95% confidence interval.

Abbreviations: CHF, chronic heart failure; SII, systemic immune inflammation index; SIRI, systemic inflammation response index.

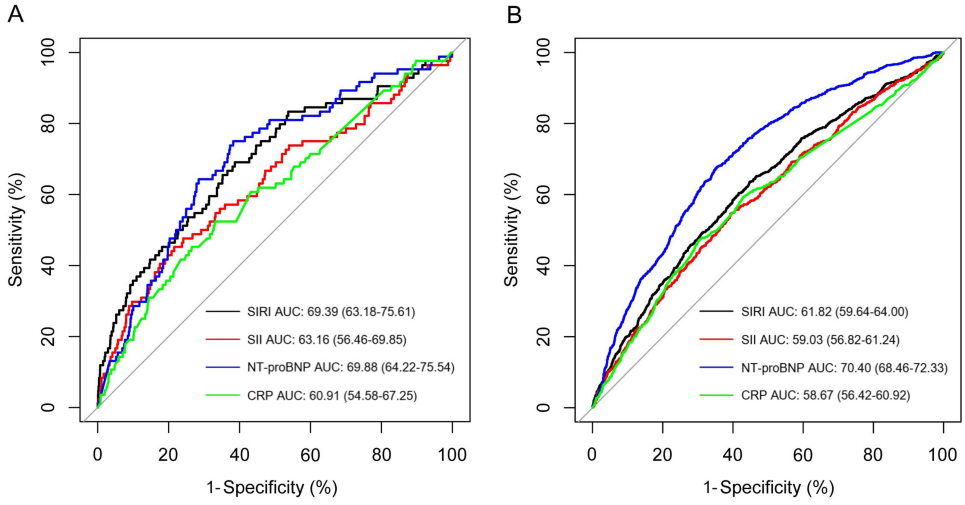

Figure 3 Receiver operating characteristic curves and AUCs (95% confidence interval) of SIRI, SII, NT-proBNP, and CRP as predictors for in-hospital mortality (**A**) and 3-year mortality (**B**).

Abbreviations: AUC, area under the curves; CRP, C-reactive protein; NT-proBNP, N-terminal pro-brain **natriuretic** peptide; SII, systemic immune inflammation index; SIRI, systemic inflammation response index.

events in patients with CHF and renal dysfunction, but the findings may not be generalized to general patients with CHF. None of these studies compared the prognostic value between SIRI, SII, and traditional prognostic markers, while we conducted ROC analyses among SIRI, SII, NT-proBNP, and CRP, and showed the superiority of SIRI as an inflammation marker in predicting mortality in patients with CHF. Taken together, our study comprehensively evaluated the relations of SIRI and SII with in-hospital and long-term mortality in a well-characterized CHF cohort, and provided further evidence that novel systemic inflammation biomarkers are of great value in predicting outcomes in patients with CHF and deserve prospective evaluation.

Inflammation has been demonstrated to be a key contributor in the development and deterioration of HF.[21–24] SIRI and SII, calculated by the counts of neutrophil, lymphocyte, monocyte, and platelet, have been previously reported that could reflect the systemic inflammation response of the body.[25–27] The underlying mechanisms of our findings are as follows. The release of various anti-inflammation cytokines could trigger immune suppression, leading to lymphocyte apoptosis.[28] A study had shown that in patients with HF, patients with lower absolute lymphocyte counts had a higher risk of mortality.[29] Another study found that neutrophil counts reflected the degree of deterioration of systemic inflammation response, and higher neutrophil counts indicated more severe myocardial damage, poorer left ventricular function, and poorer prognosis.[30] Additionally, several studies have demonstrated that monocyte and platelet play an important role in the association between inflammation and CHF outcomes. Activated monocytes differentiate into macrophages and trigger the release of various inflammatory cytokines.[31] Monocytes participate in the inflammatory response in myocardial damage and mediate cells apoptosis and necrosis, inflammation and immune cells activation, cardiomyocyte hypertrophy and myocardial interstitial fibrosis.[32] Increased platelet counts might be a consequence of megakaryocyte proliferation stimulated by pro-inflammation cytokines, thereby reflecting inflammation activation.[33] Meanwhile, increased platelet activity might be related to elevation of cytosolic-free calcium concentrations, elevated tumor necrosis factor, and enhanced sympathoadrenal activation and catecholamine release in patients with HF.[34]

Our study provides robust evidence that SIRI and SII are strong predictors of in-hospital mortality and long-term mortality in patients with CHF. These findings demonstrate that SIRI and SII could serve as readily available inflammation biomarkers in the risk assessment of patients with CHF and as alternative indicators when traditional inflammation biomarkers (eg, CRP) were not available. The results of our study also support the effort to highlight the assessment of SIRI and SII in future policies for CHF and provide further therapeutic target to improve the prognosis. The management of SIRI and SII and its beneficial effect on CHF outcomes deserves further exploration.

Strengths and Limitations

Our study has several strengths. We conducted this study in a large-scale multi-center retrospective cohort, and put great emphasis on data quality. The selection and review of patients with CHF were conducted by physicians following standard protocol, which avoided potential information bias. Additionally, we included wide spectrum of baseline characteristics in multivariable analysis to reduce the confounding of these factors. However, there are still several limitations in our study. First, the observational design of our study cannot determine causality. The effect of SIRI and SII on CHF outcomes still need to be confirmed in future randomized clinical trial. Second, the blood counts test was conducted only at baseline and lack of long-term assessment. The dynamic change of SIRI and SII may further modify their associations with CHF outcomes. Third, the patients of our study were only enrolled from China, thus the findings of our study may not be completely generalized to other regions. Fourth, 14.52% of the study patients lost to long-term follow-up, which may introduce bias into the results. However, the SIRI and SII levels between those who were included in the long-term mortality analysis and those who lost to follow-up were comparable. Therefore, we believe that the bias could be small. Fifth, 18.71% of the study patients were lack of data on CRP and were not included in the ROC analyses. The results may need to be further confirmed by prospective studies.

Conclusion

In conclusion, increased SIRI and SII were significantly associated with higher risks of in-hospital mortality and long-term mortality in patients with CHF. These associations persisted after adjusting for various confounding factors and the associations with long-term mortality were more evident in patients aged ≥60 years. SIRI had a similar prognostic

discrimination with NT-proBNP in predicting in-hospital mortality and had a higher prognostic value than CRP in both in-hospital mortality and 3-year mortality predictions. Our findings highlight the value of SIRI and SII in inflammation assessment, and emphasize the importance of SIRI and SII in the outcome prediction of patients with CHF.

Data Sharing Statement

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author upon reasonable request.

Acknowledgments

We thank the staff of the Medical Big Data Research Center, Medical Innovation Research Department of PLA General Hospital for their contributions.

Funding

The study was supported by the Project from Ministry of Science and Technology of China (No. 2021ZD0140406).

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Heidenreich PA, Bozkurt B, Aguilar D, et al. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145(18):e895–e1032. doi:10.1161/CIR.0000000000001063
2. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014;63(12):1123–1133. doi:10.1016/j.jacc.2013.11.053
3. Hao G, Wang X, Chen Z, et al. Prevalence of heart failure and left ventricular dysfunction in China: the China Hypertension Survey, 2012–2015. *Eur J Heart Fail*. 2019;21(11):1329–1337. doi:10.1002/ejhf.1629
4. Keşkek Ş, Sağlıker Y, Kırım S, Içen YK, Yıldırım A. Low serum phosphorus level in Massry's Phosphate Depletion Syndrome may be one of the causes of acute heart failure. *J Nutr Sci Vitaminol*. 2015;61(6):460–464. doi:10.3177/jnsv.61.460
5. Kaptoge S, Di Angelantonio E, Pennells L, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med*. 2012;367(14):1310–1320.
6. Kaplan RC, Frishman WH. Systemic inflammation as a cardiovascular disease risk factor and as a potential target for drug therapy. *Heart Dis*. 2001;3(5):326–332. doi:10.1097/00132580-200109000-00009
7. Tian SY. Systemic immune-inflammation index predicts restenosis after interventions for lower extremity arteriosclerosis obliterans. *Heart Surg Forum*. 2023;26(3):E225–E233. doi:10.1532/hsf.5303
8. Lin K, Lan Y, Wang A, Yan Y, Ge J. The association between a novel inflammatory biomarker, systemic inflammatory response index and the risk of diabetic cardiovascular complications. *Nutr Metab Cardiovasc Dis*. 2023;33(7):1389–1397. doi:10.1016/j.numecd.2023.03.013
9. Aksakal E, Aksu U, Birdal O, et al. Role of systemic immune-inflammatory index in predicting the development of in-hospital malignant ventricular arrhythmia in patients with ST-elevated myocardial infarction. *Angiology*. 2023;74(9):881–888. doi:10.1177/00033197221121435
10. Jin Z, Wu Q, Chen S, et al. The associations of two novel inflammation indexes, SII and SIRI with the risks for cardiovascular diseases and all-cause mortality: a ten-year follow-up study in 85,154 individuals. *J Inflamm Res*. 2021;14:131–140. doi:10.2147/JIR.S283835
11. Li J, He D, Yu J, et al. Dynamic status of SII and SIRI alters the risk of cardiovascular diseases: evidence from Kailuan cohort study. *J Inflamm Res*. 2022;15:5945–5957. doi:10.2147/JIR.S378309
12. Esenboga K, Kurtul A, Yamanturk YY, Tan TS, Tutar DE. Systemic immune-inflammation index predicts no-reflow phenomenon after primary percutaneous coronary intervention. *Acta Cardiol*. 2022;77(1):59–65. doi:10.1080/00015385.2021.1884786
13. Cao Y, Li P, Zhang Y, et al. Association of systemic immune inflammatory index with all-cause and cause-specific mortality in hypertensive individuals: results from NHANES. *Front Immunol*. 2023;14:1087345. doi:10.3389/fimmu.2023.1087345
14. Xiao S, Wang Z, Zuo R, et al. Association of systemic immune inflammation index with all-cause, cardiovascular disease, and cancer-related mortality in patients with cardiovascular disease: a cross-sectional study. *J Inflamm Res*. 2023;16:941–961. doi:10.2147/JIR.S402227
15. McDonagh TA, Metra M, Adamo M, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726. doi:10.1093/eurheartj/ehab368
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612. doi:10.7326/0003-4819-150-9-200905050-00006
17. Wang X, Ni Q, Wang J, Wu S, Chen P, Xing D. Systemic inflammation response index is a promising prognostic marker in elderly patients with heart failure: a retrospective cohort study. *Front Cardiovasc Med*. 2022;9:871031. doi:10.3389/fcvm.2022.871031
18. Yuan M, Ren F, Gao D. The value of SII in predicting the mortality of patients with heart failure. *Dis Markers*. 2022;2022:3455372. doi:10.1155/2022/3455372
19. Tang Y, Zeng X, Feng Y, et al. Association of systemic immune-inflammation index with short-term mortality of congestive heart failure: a retrospective cohort study. *Front Cardiovasc Med*. 2021;8:753133. doi:10.3389/fcvm.2021.753133

20. Wang Z, Qin Z, Yuan R, et al. Systemic immune-inflammation index as a prognostic marker for advanced chronic heart failure with renal dysfunction. *ESC Heart Fail*. 2023;10(1):478–491. doi:10.1002/ehf2.14217
21. Dick SA, Epelman S. Chronic heart failure and inflammation: what do we really know? *Circ Res*. 2016;119(1):159–176. doi:10.1161/CIRCRESAHA.116.308030
22. Van Linthout S, Tschope C. Inflammation - cause or consequence of heart failure or both? *Curr Heart Fail Rep*. 2017;14(4):251–265. doi:10.1007/s11897-017-0337-9
23. Adamo L, Rocha-Resende C, Prabhu SD, Mann DL. Reappraising the role of inflammation in heart failure. *Nat Rev Cardiol*. 2020;17(5):269–285. doi:10.1038/s41569-019-0315-x
24. Kan H, Finkel MS. Interactions between cytokines and neurohormonal systems in the failing heart. *Heart Fail Rev*. 2001;6(2):119–127. doi:10.1023/A:1011405926588
25. Chen JH, Zhai ET, Yuan YJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. *World J Gastroenterol*. 2017;23(34):6261–6272. doi:10.3748/wjg.v23.i34.6261
26. Fu H, Zheng J, Cai J, et al. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients after liver transplantation for hepatocellular carcinoma within Hangzhou criteria. *Cell Physiol Biochem*. 2018;47(1):293–301. doi:10.1159/000489807
27. Geng Y, Zhu D, Wu C, et al. A novel systemic inflammation response index (SIRI) for predicting postoperative survival of patients with esophageal squamous cell carcinoma. *Int Immunopharmacol*. 2018;65:503–510. doi:10.1016/j.intimp.2018.10.002
28. Liu X, Zhou K, Hua Y, et al. Prospective evaluation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for intravenous immunoglobulin resistance in a large cohort of Kawasaki disease patients. *Pediatr Infect Dis J*. 2020;39(3):229–231. doi:10.1097/INF.0000000000002566
29. Majmundar M, Kansara T, Park H, et al. Absolute lymphocyte count as a predictor of mortality and readmission in heart failure hospitalization. *Int J Cardiol Heart Vasc*. 2022;39:100981.
30. Fu S, Xie L, Li D, Ye P, Luo L. The predictive capacity and additional prognostic power of N-terminal pro-B-type natriuretic peptide in Chinese elderly with chronic heart failure. *Clin Interv Aging*. 2015;10:359–365. doi:10.2147/CIA.S77417
31. Li Q, Lin X, Bo X, et al. Monocyte to high-density lipoprotein cholesterol ratio predicts poor outcomes in ischaemic heart failure patients combined with diabetes: a retrospective study. *Eur J Med Res*. 2023;28(1):493. doi:10.1186/s40001-023-01451-6
32. Chen Q, Yin Q, Song J, Liu C, Chen H, Li S. Identification of monocyte-associated genes as predictive biomarkers of heart failure after acute myocardial infarction. *BMC Med Genomics*. 2021;14(1):44. doi:10.1186/s12920-021-00890-6
33. Hwang SY, Shin TG, Jo IJ, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in critically-ill septic patients. *Am J Emerg Med*. 2017;35(2):234–239. doi:10.1016/j.ajem.2016.10.055
34. Chung I, Choudhury A, Patel J, Lip GY. Soluble, platelet-bound, and total P-selectin as indices of platelet activation in congestive heart failure. *Ann Med*. 2009;41(1):45–51. doi:10.1080/07853890802227089