

Association of Systemic Inflammation Level on Admission with Total and Cardiovascular-Specific Death in Heart Failure with Preserved Ejection Fraction: A Large Multi-Center Retrospective Longitudinal Study

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Purpose: Heart failure with preserved ejection fraction (HFpEF) is inherently a complex inflammatory syndrome, and heightened inflammation is strongly associated with an increased risk of death. However, the association of systemic inflammation levels with total and cardiovascular death among patients with HFpEF remains unknown. We aimed to investigate the prognostic impact of systemic inflammation on all-cause and cardiovascular death among patients with HFpEF.

Patients and Methods: Patients with HFpEF were included in this study. Systemic inflammation response index (SIRI) is defined as the multiplication of neutrophil and monocyte divided by lymphocyte count, and patients were divided into four groups based on SIRI quartiles. Cox regression models and competing risk models were used to examine the relationships between SIRI and total and cardiovascular-specific mortality, respectively.

Results: 9,986 patients with HFpEF were included in five tertiary hospitals. During a median follow-up period of 4.4 years, a total of 2004 patients died, of which 965 were cardiovascular deaths. After fully adjusting for confounders, elevated SIRI level was significantly related to the increased risk of all-cause death (Q2, Q3, Q4: adjusted hazard ratio (aHR) [95 confidence interval (CI)%] = 1.17[1.01–1.35], 1.31[1.13–1.52], 1.51[1.30–1.76], respectively; P for trend <0.001). The elevated quartile of SIRI showed higher risks of cardiovascular death, but there was no statistically significant increased risk of cardiovascular death across the lower SIRI quartile (model 3: Q2, Q3, Q4: aHR [95CI%] = 1.22[0.99–1.51], 1.50[1.20–1.86], 1.73[1.37–2.18], respectively; P for trend <0.001).

Conclusion: Elevated systemic inflammation level on admission was correlated with an increased risk of all-cause and cardiovascular death among patients with HFpEF. The SIRI may serve as a promising marker of risk stratification for patients with HFpEF.

Keywords: heart failure with preserved ejection fraction, systemic inflammatory response index, all-cause death, cardiovascular death

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is the most common form of HF in the older population, and the prevalence has been more than 50% of HF cases in the community, and the five-year mortality rate is more than

50%.^{1,2} However, few currently available treatment strategies have shown clinical benefit in HFpEF.³ Accordingly, early identification of at-risk patients with HFpEF is significant for clinicians.

The long-term prognostic model based on traditional risk factors showed limited discrimination for predicting long-term mortality, and promising tools for risk stratification still need to be developed.⁴ HFpEF is a complex clinical syndrome mediated by a complex mechanism, of which, elevated inflammation may contribute to the progression of disease.⁵ The chronic inflammatory state can predispose to adverse cardiac remodeling such as left ventricular hypertrophy that can eventually lead to HFpEF.⁶ Moreover, proinflammatory cytokines may contribute to endothelial dysfunction and reduced vascular compliance and subsequent concentric LV remodeling, reduced left ventricular compliance.⁷ Together, these mechanisms can significantly increase the risk of death. Previous studies have also found that inflammatory biomarkers added to traditional risk factors could help to identify high-risk populations with HFpEF.⁸ A growing body of research indicated that various inflammatory cells are involved in the development of HFpEF and were related to long-term poor prognosis.^{9,10} Recently, a novel inflammatory indicator called systemic inflammatory response index (SIRI) that integrates inflammatory cells including neutrophil, lymphocyte, and monocyte counts into one variable, has been advocated to play an important role in the prognostic assessment of cancer, hyperuricemia, and stroke.^{11–13} However, the relationship between SIRI and long-term prognosis in the HFpEF population is not yet clear.

Consequently, this research was undertaken to explore the prognostic impact of systemic inflammation on all-cause and cardiovascular death among patients with HFpEF in a large multicenter cohort, which could provide clinicians with valuable information and prompt them to administer appropriate therapies for prevention.

Method

Study Population

This was a multi-center, retrospective observational research based on the registry of Cardiorenal Improvement II (CIN-II, ClinicalTrials.gov NCT05050877), and patients enrolled at five large tertiary hospitals in China from January 2007 to December 2020. Patients diagnosed with HFpEF (HF patients with left ventricular ejection fraction (LVEF) $\geq 50\%$) undergoing coronary angiography (CAG) on initial admission, and aged at least 18 years were included in the analysis. HF was diagnosed when meeting one of these criteria: i. New York Heart Association (NYHA) class $> II$ or Killip class $> I$,¹⁴ ii. LVEF $\leq 40\%$, iii. NT-proBNP > 450 pg/mL (age < 50 years); NT-proBNP > 900 pg/mL (age 50 to 75 years); NT-proBNP $> 1,800$ pg/mL (age > 75 years).^{15,16} The exclusion criteria were as follows: a) missing following data – monocyte count, lymphocyte count, and neutrophil count; b) patients lack of information on death and duration of follow-up ([Supplemental Figure 1](#)). The Ethics Committee of the Guangdong Provincial People's Hospital approved the research (No.GDREC2019-555H-2). All participating sites received institutional review board approval from their own ethics committees. This research was conducted in accordance with the principles of the Declaration of Helsinki.

Baseline Data Collection

The information of 9,988 subjects was extracted from the electronic clinical management system. LVEF value was obtained by using quantitative two-dimensional Simpson's biplane method using transthoracic echocardiography. Biochemistry data including monocytes, neutrophils, and lymphocytes upon admission were tested by an automatic biochemical analyzer. Patients' inflammation levels on admission were evaluated within 24 hours after admission and before the coronary angiography procedure. Survival information was obtained by cause-specific surveillance data from the Public Security System and Centers for Disease Control and Prevention.

Clinical Definition and Outcomes

The outcomes were all-cause, and cardiovascular death. SIRI was calculated as neutrophil count \times (monocyte count)/(lymphocyte count). Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m².¹⁷ Acute myocardial infarction (AMI), diabetes mellitus (DM), and hypertension (HT) were defined according to the 10th Revision Codes of the International Classification of Diseases (ICD-10).

Statistical Analysis

All patients were stratified into four groups by SIRI quartiles. Continuous variables were shown as mean \pm standard deviation or median, and normally distributed continuous variables were compared using Student's *t*-test with unequal variances, and continuous non-parametric variables by Kruskal–Wallis. Categorical variables were described as numbers (percentages) and compared using the χ^2 test. To establish a dose-response between SIRI and long-term death, we performed restricted cubic splines (RCS) analyses. Survival analysis for all-cause death was performed by Kaplan-Meier curves using the Log rank test. Cumulative incidence function (CIF) curves for cardiovascular death were used to depict the influence of the competing risk, and Gray's tests were used to assess differences between groups. Multivariate Cox regression models and competing risk Fine and Gray models were used to examine the relationships between SIRI level and total and cardiovascular-specific death, respectively. To fully analyze the relationship between SIRI and prognosis, three models were built: 1) model 1, unadjusted for covariates; 2) model 2, adjusted for age and gender; 3) model 3, further fully adjusted for age, gender, anemia, atrial fibrillation (AF), AMI, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), DM, HT, stroke, percutaneous coronary intervention (PCI), LVEF, eGFR, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), statins, β -blocker, low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C). A variance inflation factor of more than 5 means a multicollinearity criterion, indicating that there is no collinearity problem between variables for model 3.¹⁸ We further explored the relationship between SIRI and long-term prognosis in different subgroups according to age, AMI, CKD, and CAD. Stratification and interaction analyses were carried out to verify the robustness of our main results. To assess the predictability of SIRI for outcomes, we added SIRI to the traditional model (age, gender, anemia, AMI, CAD, COPD, CKD, DM, HT, stroke, LDL-C), and the C-index was calculated. All statistical analyses were performed using the software R version 4.0.3. A P-value < 0.05 was considered significant.

Results

Baseline Characteristics

9,988 patients with HFpEF were enrolled in our research. The mean age of the patients was 69.4 ± 13.2 years, with females accounting for approximately 62.7%. All subjects were classified into four groups based on the SIRI quartile: Q1 group (n=2527), Q2 group (n=2485), Q3 group (n=2483), and Q4 group (n=2493). Patients with high baseline SIRI levels were older, with a higher level of WBC, LDL-C, HGB, and eGFR, and tended to combine with AMI, HT, DM, CKD, and anemia. However, they are more likely to have a lower LVEF (Table 1).

Table 1 Baseline Characteristics of the Study Population According to Systemic Inflammation Response Index Levels

Characteristic	Q1 N=2527	Q2 N=2485	Q3 N=2483	Q4 N=2493	P
Demographic characteristics					
Age, years	61.22 (10.12)	62.79 (10.89)	63.85 (11.25)	64.62 (12.17)	<0.001
Age > 60, n (%)	1314 (52.0)	1427 (57.5)	1577 (63.6)	1607 (64.6)	<0.001
Female, n (%)	1438 (56.9)	939 (37.8)	713 (28.7)	562 (22.6)	<0.001
Complication					
AMI, n (%)	396 (15.8)	740 (29.9)	1134 (45.9)	1645 (66.2)	<0.001
HT, n (%)	907 (36.3)	1177 (47.6)	1294 (52.3)	1344 (54.1)	<0.001
DM, n (%)	684 (27.1)	809 (32.6)	849 (34.2)	814 (32.7)	<0.001
CAD, n (%)	1198 (47.9)	1678 (67.9)	1997 (80.8)	2161 (87.0)	<0.001
CKD, n (%)	445 (17.6)	676 (27.2)	786 (31.7)	960 (38.5)	<0.001
COPD, n (%)	50 (2.0)	77 (3.1)	93 (3.8)	109 (4.4)	<0.001
Cancer	32 (1.3)	29 (1.2)	40 (1.6)	43 (1.7)	0.298
Anemia, n (%)	799 (31.6)	915 (36.8)	1034 (41.6)	1110 (44.6)	<0.001

(Continued)

Table 1 (Continued).

Characteristic	Q1 N=2527	Q2 N=2485	Q3 N=2483	Q4 N=2493	P
Procedure					
IABP, n (%)	16 (0.6)	21 (0.8)	19 (0.8)	68 (2.7)	<0.001
PCI, n (%)	905 (35.8)	1343 (54.0)	1641 (66.1)	1883 (75.6)	<0.001
Laboratory tests					
WBC, 10 ⁹ /L	6.46 (8.64)	7.69 (14.41)	8.90 (4.56)	14.07 (58.02)	<0.001
LDL-C, mmol/L	2.88 (0.96)	2.87 (1.02)	2.95 (1.06)	2.99 (1.08)	<0.001
HDL-C, mmol/L	1.10 (0.30)	1.03 (0.29)	1.01 (0.30)	1.05 (0.31)	<0.001
HGB, g/L	130.17 (17.72)	130.46 (18.37)	129.52 (20.15)	128.69 (21.89)	0.008
eGFR, mL/min/1.73m ²	79.29 (23.95)	74.24 (26.94)	70.95 (27.70)	67.54 (28.02)	<0.001
LVEF, %	62.08 (6.66)	61.68 (6.59)	61.02 (6.48)	60.16 (6.33)	<0.001
Lymphocyte, 10 ⁹ /L	2.15 (1.31)	1.95 (0.69)	1.76 (0.71)	1.44 (0.65)	<0.001
Platelet, 10 ⁹ /L	201.02 (63.99)	219.96 (68.58)	233.58 (78.27)	239.90 (87.28)	<0.001
Neutrophil, 10 ⁹ /L	3.32 (1.08)	4.61 (1.22)	6.09 (1.86)	9.70 (3.64)	<0.001
Monocyte, 10 ⁹ /L	0.45 (0.14)	0.59 (0.16)	0.71 (0.22)	0.95 (0.39)	<0.001
Medications					
Statins, n (%)	1293 (51.7)	1717 (70.3)	2001 (82.2)	2076 (87.0)	<0.001
CCB, n (%)	366 (14.6)	422 (17.3)	432 (17.7)	398 (16.7)	0.018
ACEI/ARB, n (%)	1148 (45.9)	1462 (59.9)	1531 (62.9)	1457 (61.1)	<0.001
Diuretics, n (%)	1357 (54.3)	992 (40.6)	900 (37.0)	960 (40.2)	<0.001
β-blocker, n (%)	1426 (57.0)	1682 (68.9)	1809 (74.3)	1744 (73.1)	<0.001
Endpoints					
Cardiovascular mortality, n (%)	199 (7.9)	228 (9.2)	264 (10.6)	274 (11.0)	0.001
All-cause mortality, n (%)	429 (17.0)	490 (19.7)	520 (20.9)	565 (22.7)	<0.001

Abbreviations: AMI, acute myocardial infarction; HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; PCI, percutaneous interventions; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; IABP, intra-aortic balloon pump; WBC, white blood cell; LDL-C, low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein; HGB, hemoglobin; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; CCB, calcium channel blocker. ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

With a median follow-up period was 4.4 years ([interquartile range: 2.3–7.3]), there were 2004 and 965 patients who died from all-cause and cardiovascular mortality, respectively. Correspondingly, the total and cardiovascular mortality of Q1 group vs Q2 group vs Q3 group vs Q4 group was 17.0% vs 19.7% vs 20.9% vs 22.7% (p for trend <0.001) and 7.9% vs 9.2% vs 10.6% vs 11.0% (p for trend <0.001) (Table 1).

Systemic Inflammation Level and Clinical Outcomes

Multivariate analysis with different models was conducted to gain hazard ratio (HR) for all-cause and cardiovascular death with SIRI as a continuous and categorical variable. When SIRI as a continuous variable, a higher SIRI was related to an increased risk of all-cause and cardiovascular death after adjusting for confounding factors in model 3 (all-cause death: adjusted hazard ratio [aHR], 1.03, 95% confidence interval (CI):1.01–1.04, P<0.001; cardiovascular death: aHR, 1.03, 95% CI:1.01–1.05, P=0.004) (Table 2). In addition, restricted cubic splines indicated an approximately linear increase in the risk of total death (nonlinear P=0.083), while there is a non-linear relationship between SIRI levels and cardiovascular death (nonlinear P=0.019): SIRI at high levels were closely linked with increased cardiovascular mortality (Figure 1).

Subsequently, the univariate and multivariate regression analysis as a categorical variable were performed to further confirm the relationship between systemic inflammation level and the risk of all-cause and cardiovascular mortality. After adjusting for confounders, all-cause death increased with higher levels of SIRI (model 3: Q2, Q3, Q4: aHR[95CI%] = 1.17[1.01–1.35], 1.31[1.13–1.52], 1.51[1.30–1.76], respectively; P for trend<0.001). While the higher SIRI quartile was associated with an increased risk of cardiovascular death, and there was no statistically significant for cardiovascular death across lower SIRI quartile (model 3: Q2, Q3, Q4: aHR[95CI%]=1.22[0.99–1.51], 1.50[1.20–1.86], 1.73[1.37–2.18], respectively; P for trend <0.001)(Table 2; Supplementary Tables 1 and 2). Consistently, Kaplan-Meier curves and

Table 2 Univariable and Multivariable Cox Regression Analysis of the Association Between SIRI Levels on Admission and Death

Groups	Model 1 ^a		Model 2 ^b		Model 3 ^c	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
All-cause death						
Continuous						
SIRI	1.04(1.03,1.06)	<0.001	1.03(1.02,1.04)	<0.001	1.03(1.01,1.04)	<0.001
Quartiles						
Q1	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Q2	1.27(1.12,1.45)	<0.001	1.16(1.01,1.32)	0.031	1.17(1.01,1.35)	0.031
Q3	1.5(1.32,1.71)	<0.001	1.27(1.12,1.45)	<0.001	1.31(1.13,1.52)	<0.001
Q4	1.81(1.59,2.05)	<0.001	1.49(1.31,1.7)	<0.001	1.51(1.30,1.76)	<0.001
P for trend		<0.001		<0.001		<0.001
Cardiovascular death						
Continuous						
SIRI	1.03(1.02,1.05)	<0.001	1.02(1.01,1.04)	0.007	1.03(1.01,1.05)	0.004
Quartiles						
Q1	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Q2	1.29(1.06,1.56)	0.009	1.20(0.99,1.46)	0.060	1.22(0.99,1.51)	0.065
Q3	1.62(1.35,1.95)	<0.001	1.43(1.18,1.73)	<0.001	1.50(1.20,1.86)	<0.001
Q4	1.81(1.51,2.17)	<0.001	1.56(1.28,1.90)	<0.001	1.73(1.37,2.18)	<0.001
P for trend		<0.001		<0.001		<0.001

Notes: ^aModel 1: unadjusted. ^bModel 2: adjusted for age, gender. ^cModel 3: adjusted for age, gender, atrial fibrillation, acute myocardial infarction, anemia, chronic obstructive pulmonary disease, coronary artery disease, diabetes, hypertension, stroke, left ventricular ejection fraction, estimated glomerular filtration rate, percutaneous interventions, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statins, β -blocker, low-density lipoprotein cholesterol, high-density lipoprotein.

Abbreviations: SIRI, systemic inflammation response index; Q, quartile; HR, hazard ratio; CI, confidence interval.

cumulative incidence function curves demonstrated that as the SIRI levels increased, the risk of all-cause and cardiovascular death was significantly elevated, particularly at relatively higher levels (Figure 2).

Clinical Outcome Risk Prediction in Inflammatory Index

The predictive value of the inflammation-related index on the risk of total and cardiovascular death was evaluated among HFpEF patients. The addition of the SIRI could improve the performance of the traditional risk factors models for predicting the total and cardiovascular death (C-index for total death: 0.722 to 0.726, $P=0.013$, C-index for cardiovascular death: 0.734 to 0.736, $P=0.043$). Further research also demonstrated that the predictive performance of SIRI was significantly higher than CRP (Table 3).

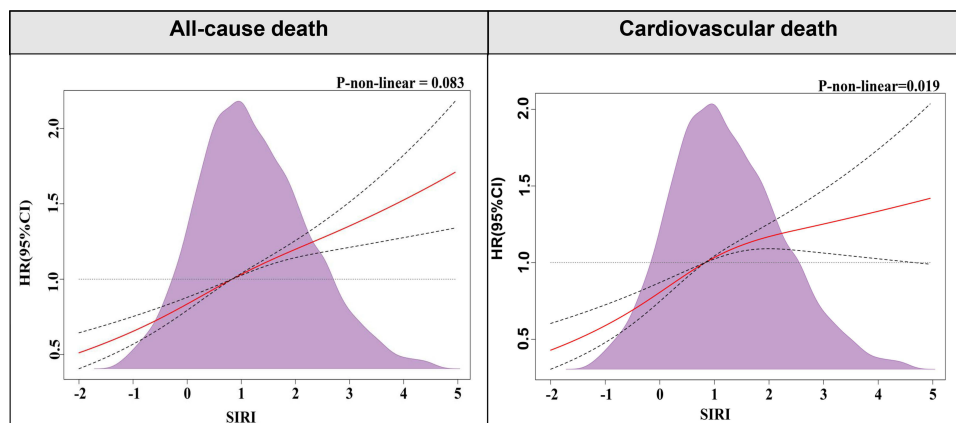


Figure 1 Hazard ratios for the all-cause, and cardiovascular death based on restricted cubic spline function for SIRI levels.

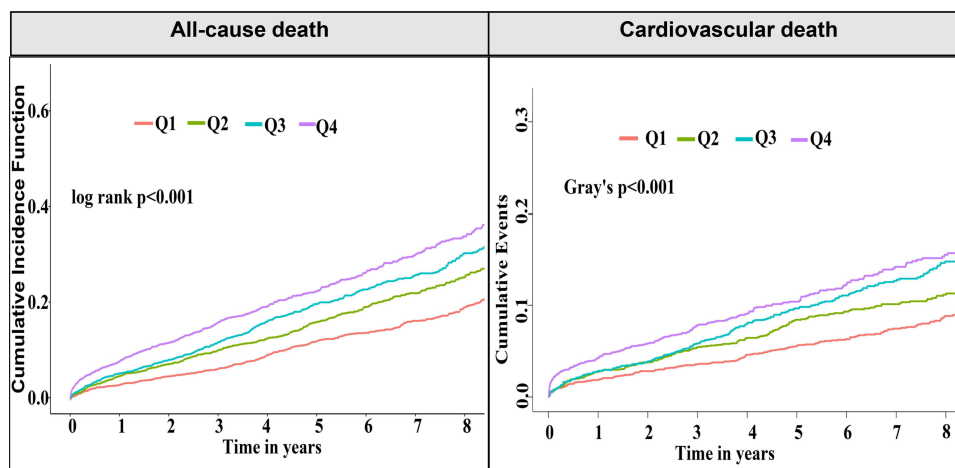


Figure 2 Kaplan–Meier analysis of all-cause and cardiovascular death according to different SIRI levels.

Subgroup Analysis

Our results remained consistent in our subgroup analyses (non-AMI, non-CKD, CAD, and regardless of age) for all-cause death, while a similar trend in cardiovascular death of different SIRI levels was observed in subjects with non-CKD according to quartile. Finally, the interactive analysis showed that there was a significant relationship between SIRI and all-cause death in CAD patients (P for interaction=0.005), and there were no significant interactions between the variables for cardiovascular mortality ([Supplemental Figures 2 and 3](#)).

Discussion

As far as we know, this is a large multicenter, retrospective, and longitudinal cohort research to explore the correlation between systemic inflammation level and long-term prognosis among patients with HFpEF. The findings of this research revealed that all-cause death significantly increased with elevated SIRI levels in a significant SIRI levels-dependent manner, while there was an increased risk of cardiovascular death when SIRI was at a relatively high level. We further found that adding SIRI to traditional risk factors models was able to improve the prediction for prognosis. Therefore, it is important to take into account systemic inflammation levels when assessing the risk of death.

HFpEF has become the main form of HF in the world and has a prevalence of more than 50% in the community, which is associated with high mortality, thus making it one of the greatest unmet needs in cardiology today.^{1,2} The causes of death in HFpEF patients are complex and involve multiple pathophysiological mechanisms, in which systemic inflammation plays an essential role in this process.¹⁰ Inflammatory cells are involved in the development of HFpEF and can be used as biomarkers for long-term prognosis. Neutrophils release significantly more cytokines among patients with DM and HFpEF, thereby increasing inflammation levels, which may explain the higher incidence of adverse events

Table 3 C-Index of Systemic Inflammation Response Index for Predicting Mortality in Patients with Heart Failure with Preserved Ejection Fraction

	All-Cause Death		Cardiovascular Death	
	C-Index	P-value	C-Index	P-value
Traditional risk factors ^a	0.722(0.700–0.743)		0.734(0.705–0.763)	
Traditional risk factors ^a +CRP	0.724(0.702–0.745)	0.036	0.735(0.705–0.766)	0.048
Traditional risk factors ^a +SIRI	0.726(0.704–0.749)	0.013	0.736(0.707–0.769)	0.043

Notes: ^aEstablished traditional risk factors include age, gender, anemia, acute myocardial infarction, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, diabetes, hypertension, stroke, and low-density lipoprotein cholesterol.

Abbreviations: C-index, concordance index; CRP, C-reactive protein; SIRI, systemic inflammation response index.

among HFpEF patients.¹⁹ In addition, a higher monocyte count is related to cardiac remodeling and carotid artery dilation, which may indicate a role for circulating monocytes in the pathophysiology of HFpEF.²⁰ Meanwhile, lymphocyte count is associated with an increased risk of mortality and readmission in patients with HF.²¹ SIRI, a new and widely available inflammatory indicator, exhibited relatively superior predictive ability for poor outcomes in patients with cancer, hyperuricemia, and stroke.^{11–13} However, it is unclear about the relationship between SIRI and long-term prognosis among the HFpEF population. Our research demonstrated that elevated SIRI is related to an increased risk of total and cardiovascular death among subjects with HFpEF, and further research also found that SIRI was able to improve the predictive performance of prognostic models. Therefore, monitoring SIRI levels may be helpful in predicting long-term outcomes among HFpEF patients.

Previous research has demonstrated that systemic inflammation is related to increased mortality among HFpEF patients, and immune-inflammatory activation releases inflammatory mediators which further augment pro-inflammatory and profibrotic processes.^{21,22} In the inflammation mechanism of HFpEF, cardiovascular risk factors could significantly increase the systemic inflammation level in patients with HFpEF, which may induce the dysfunction of endothelial cells, furtherly reducing the bioavailability of nitric oxide, and inhibiting protein-kinase G signaling, finally, leading to myocardial fibrosis, stiffening and hypertrophy.⁵ Recently, Muammer et al reported that SII level was independently associated with the existence of ischemia in the non-obstructive coronary artery.²³ In another study, SII was proved to be an independent predictor of newly diagnosed reverse-dipper hypertensive patients, which is a risk factor for cardiovascular mortality.²⁴ In addition, a novel index indicating nutritional status and systemic inflammation, the HALP (hemoglobin, albumin, lymphocyte, and platelet) score performed well in predicting in-hospital mortality in patients with ST-elevation myocardial infarction undergoing primary PCI, with an optimal HALP score cutoff value of <3.72 predicted in-hospital mortality with 95.56% sensitivity and 49.19% specificity.²⁵ Moreover, comorbidities also lead to microvascular inflammation, which adversely affects the adjacent cardiomyocyte through decreased nitric oxide bioavailability, reduced cyclic guanosine monophosphate availability, and altered phosphorylation of titin.⁵ Therefore, targeting inflammation may be an effective therapy to prevent HFpEF progression.

Cardiovascular mortality accounted for nearly 50% of total deaths in this study. Consistent with our study, previous research also showed that the majority of deaths in HFpEF are cardiovascular deaths, comprising more than 50% of deaths in many epidemiological studies and clinical randomized controlled trials.²⁶ The most common causes of cardiovascular deaths are sudden death and HF in HFpEF clinical trials. The difference in mortality rates appeared across research may be caused by a number of risk factors, including age, gender, body mass index, burden of comorbidities, and CAD.²⁶ In addition, the mortality burden of HFpEF is serious, ranging from 10% to 30% annually, and higher in epidemiological studies than in clinical trials. However, the 4.4-year all-cause death of HFpEF in this research was only approximately 20%, probably because of the high proportion of CAD in our population, and those patients receiving an optimized PCI and drug treatment.

Consistent with previous research, our results also demonstrated that DM and anemia were related to a significantly increased risk of poor outcomes in patients with HFpEF. Solomon et al reported that DM is an independent predictor of poorer outcomes among patients with HFpEF.²⁷ Meanwhile, DM mainly increases cardiomyocyte hypertrophy and stiffness, possibly due to hyperinsulinemia and microvascular endothelial inflammation, which exerts distinct effects on myocardial remodeling.²⁸ Anemia was significantly related to an increased risk of death among HF subjects.²⁹ With decreased oxygen-carrying capacity, anemia could cause an increase in compensatory mechanisms such as mitochondrial dysfunction of myocardial cells, increased anaerobic metabolism, and increased oxygen free radicals, which leads to cardiac remodeling.^{30–32}

SIRI can improve the predictive value of traditional risk factor models. Consequently, monitoring SIRI may be a useful tool for assessing the risk of long-term mortality and helping clinicians identify high-risk subjects with HFpEF. In addition, optimal therapy of inflammation-incident comorbidities like DM, anemia as well as stroke, could reduce the risk of poor prognosis for patients with HFpEF. What is more, the sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been shown to be an effective therapy in improving outcomes of patients with HFpEF,^{33,34} which not only reduce the plasma volume, but also be beneficial to reduce adipose tissue-mediated inflammation, pro-inflammatory cytokine

production, and oxidative stress.³⁵ Finally, further studies are vital to prospectively verify the prediction of SIRI for poor prognosis in patients with HFpEF.

Limitation

Firstly, as a retrospective observational analysis, a causal relationship between systemic inflammation and death may not be established. Secondly, despite adjusting for potential confounders, there are still residual confounding effects of indefinite factors that may contribute to the increased risk of death. Third, we failed to collect information on the history of autoimmune disease and other chronic inflammatory diseases, as well as information on medications such as SGLT2i, which probably led to residual confounding effects of increased risk of death. Fourth, we only recorded SIRI levels on admission, and did not assess the impact of dynamic changes in SIRI levels on long-term death risk. Finally, the causal association of systemic inflammation with all-cause and cardiovascular death, as well as the predictive value of SIRI for long-term mortality, need to be further validated by larger prospective studies. Despite the possible limitations of SIRI, the clinical significance of these findings deserves further investigation.

Conclusions

Elevated systemic inflammation level on admission is an independent risk factor for all-cause and cardiovascular death in the HFpEF population, and SIRI demonstrated a better ability to predict the risk of long-term death than CRP. Our research suggested that monitoring SIRI may provide an effective method for risk stratification and highlights the importance of systemic inflammation as a determinant of long-term prognosis among patients with HFpEF.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to the institution policy but are available from the corresponding author on reasonable request.

Statement of Ethics

This study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (No.GDREC2019-555H-2). All traceable personal identifiers were removed from the analytical dataset to protect patient privacy. All participating sites received approval from their respective institutional review boards and ethics committees. Our database is not open to the public to protect the privacy of the participants. The consent was exempted by the Ethics Committee of Guangdong Provincial People's Hospital. Because our research included retrospective cases, there was no additional intervention, and information on all patients was desensitized. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; 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

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