

Systemic Immune-Inflammatory Index as a Prognostic Biomarker in Patients with Heart Failure: A Comprehensive Analysis

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Abstract

Objective: This study aimed to assess the prognostic significance of the Systemic Immune-Inflammatory Index (SII) in chronic heart failure (CHF) patients and evaluate its potential as a predictive biomarker.

Methods: A retrospective analysis was conducted on 2748 CHF patients from the First Affiliated Hospital of Xinjiang Medical University from 2012 to 2022. The primary outcome was all-cause mortality (ACM), with readmission rates as secondary endpoints. An optimal SII cutoff value of 916.68 was determined for predicting ACM.

Results: Elevated SII levels were significantly correlated with an increased risk of ACM in CHF patients across all left ventricular ejection fraction (LVEF) categories. The high SII group had a 43.8% increased risk of ACM compared to the low SII group.

Conclusion: SII is a significant prognostic biomarker in CHF, independent of traditional risk factors, highlighting its importance in risk stratification and clinical decision-making, and necessitating further investigation in prospective studies.

Keywords

systemic immune-inflammatory index, chronic heart failure, prognosis, all-cause mortality, inflammatory biomarkers

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Introduction

Over the past two decades, the prevalence of cardiovascular disease (CVD) has been on a relentless rise, and its mortality rates have surpassed those of cancer, posing a substantial threat to human health.¹ Chronic heart failure (CHF), the terminal stage of most cardiovascular diseases, is characterized by impaired systolic and/or diastolic functions of the heart due to various chronic factors, leading to venous congestion and inadequate arterial perfusion. This results in an inability to meet the body's circulatory demands, with typical clinical manifestations including dyspnea, fatigue, and tissue edema. Given the high incidence and mortality rates of CHF and its generally poor prognosis,² the use of reliable laboratory markers to predict the mortality risk in CHF patients is of crucial importance.

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Such markers can guide early treatment strategies and facilitate medical decision-making.³

Investigations have revealed numerous pathophysiological processes involved in the development and progression of CHF, among which inflammation plays a crucial role.^{4,5} The onset of CHF often triggers a series of inflammatory responses. Initially, the body's immune cells are activated, leading to increased levels of pro-inflammatory cytokines and activation of the complement system. Subsequently, numerous autoantibodies are generated and the expression of adhesion molecules increases, collectively exacerbating the systemic inflammatory environment characteristic of CHF. Therefore, biomarkers reflecting immune responses are beneficial for both clinical diagnosis and prognosis.⁶ Recognizing the limitations of traditional single serum markers in predicting the progression of CHF, Hu et al introduced a novel predictive index, the Systemic Immune-Inflammation Index (SII), through a prospective cohort study in 2014.⁷ The SII has been proven to be a valuable prognostic indicator in oncology and other inflammatory conditions, attracting significant attention and inspiring extensive research.^{8,9}

Extensive research on CVD has revealed associations between certain CVDs and the SII. For example, a study by Wang et al¹⁰ published in 2024 showed that elevated levels of SII are positively associated with an increased risk of heart failure. Huang et al¹¹ investigated the correlation between SII and the short-term and long-term prognoses of elderly patients with acute myocardial infarction (AMI) who underwent percutaneous coronary intervention (PCI). Their findings identified SII as a significant independent predictor of in-hospital mortality, as well as major adverse cardiovascular and cerebrovascular events (MACCE) during the hospital stay, and long-term mortality and MACCE in AMI patients. Peng et al¹² also explored this relationship in a retrospective study of 707 patients with cardiogenic shock (CS), suggesting that SII could be an independent predictor of poor short-term or long-term outcomes in CS patients.

Furthermore, recent research has highlighted the interaction between oxidative stress and inflammation in the context of cardiovascular diseases. For instance, a study by Chen et al¹³ demonstrated a significant negative correlation between the Oxidative Balance Score (OBS) and SII. This suggests that oxidative stress, as measured by OBS, may modulate the inflammatory state, which in turn is associated with an increased risk of cardiovascular diseases. This finding underlines the complexity of the relationship between inflammation, oxidative stress, and cardiovascular outcomes, providing a broader context for our investigation into the role of SII in CHF.

Although previous studies have explored various biomarkers in CHF, the introduction of the SII as a prognostic biomarker represents a significant advancement. Unlike

traditional markers such as NT-proBNP and CRP, which mainly reflect cardiac function and inflammation respectively, SII integrates multiple aspects of the immune-inflammatory response, providing a more comprehensive assessment of the disease state. Moreover, the stratification of patients by ejection fraction (EF) in our study offers detailed insights into different CHF subgroups, a feature often lacking in similar studies. This approach allows for a more in-depth understanding of disease progression and the differential impact of SII across various EF categories, thereby enhancing the clinical utility of SII as a prognostic tool.

Methods

Patient Cohort and Recruitment

A thorough examination of medical records was performed for 4442 patients with CHF admitted to the First Affiliated Hospital of Xinjiang Medical University, encompassing a decade from July 2012 to July 2022. This cohort study is part of a larger dataset that has been previously analyzed by our research team to investigate various aspects of heart failure. Notably, the dataset has been utilized to explore the role of high-density lipoprotein cholesterol (HDL-C) levels as a novel predictor of long-term adverse outcomes in HF patients, as detailed in a recent publication.¹⁴ The current analysis focuses on the prognostic significance of the SII in CHF, providing insights into disease management and prognosis. To enhance the robustness of our findings, we performed a detailed stratified analysis of patient characteristics and outcomes across different ejection fraction subgroups, revealing the prognostic value of SII in patients with varying disease severity and informing individualized clinical strategies for improved patient outcomes.

This extensive retrospective cohort study incorporated patients who fulfilled the predefined diagnostic criteria¹⁵ for CHF and possessed comprehensive clinical documentation. The study protocol was conducted in compliance with the Declaration of Helsinki and received ethical approval from the hospital's Ethics Committee (approval number 202207-019). Acknowledging the retrospective design of the study, informed consent from participants was waived by the Ethics Committee. Further details regarding the study's design can be accessed through the identifier NCT06092658 on the ClinicalTrials.gov registry. Eligibility for inclusion was determined based on participants being 18 years of age or older and fulfilling the diagnostic criteria for CHF as specified in the 2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure.¹⁵ To qualify for the study, individuals had to have been diagnosed with CHF for a minimum of three months. Informed consent was mandatory for participation. The study excluded candidates with advanced cancer,

substantial organ dysfunction, immune system disorders, blood-related conditions, a familial predisposition to psychiatric disorders, or a history of recent surgical intervention or severe injury within the past three months. Upon applying these criteria, 2748 individuals with complete SII-related indicator measurements (including PLT count, NEU count, Lym count, etc) were enrolled. The standard patient discharge process is illustrated in Figure 1.

Data Compilation and Laboratory Protocols

For this investigation, a thorough examination of clinical records was undertaken to retrospectively analyze the data of enrolled subjects. The dataset comprised demographic details, medical histories, physical examination outcomes, laboratory measurements, and diagnostic outcomes.

Laboratory measurements, including NEU count, PLT count, Lym count, white blood cell (WBC) count, creatinine levels, and triglyceride (TG) levels, were obtained from fasting peripheral venous blood samples taken either at admission or the following morning. Echocardiographic assessments were conducted during the patients' hospital stay. All blood samples were collected following a 12-h fast and were analyzed in the central laboratory of Xinjiang Medical University using established protocols. The SII was computed using the formula $SII = \text{PLT count} \times \text{NEU count} / \text{Lym count}$.⁷

Diagnostic Criteria

The diagnosis of CHF in this research aligns with the 2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure.¹⁵ The diagnostic criteria encompass: (1) clinical manifestations of CHF, such as dyspnea and fatigue; (2) physical signs suggestive of CHF, including elevated jugular venous pressure and pulmonary rales; (3) categorization of left ventricular ejection fraction (LVEF) into three groups: heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF)^{16,17}; (4) a stable or mildly reduced LVEF, in conjunction with relevant structural heart disease and/or diastolic dysfunction, but without left ventricular dilation, is defined as heart failure with preserved ejection fraction or diastolic heart failure.

Hypertension diagnosis in this study adheres to the latest clinical guidelines, specifically the International Society of Hypertension (ISH) Global Hypertension Practice Guidelines published in May 2020.¹⁸ According to these guidelines, hypertension is diagnosed when there is a consistent systolic blood pressure of ≥ 140 mm Hg and/or a diastolic blood pressure of ≥ 90 mm Hg (where 1 mm Hg equals 0.133 kPa), as confirmed by multiple clinical measurements.

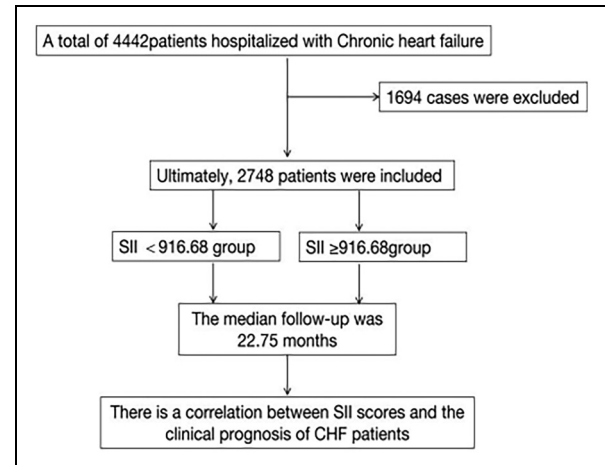


Figure 1. Flowchart of patient enrollment in the CHF study. This visual representation outlines the process of participant selection for the study, detailing the initial number of CHF patients assessed, the subsequent exclusions based on specific criteria, and the final enrollment figure. The study's focus was on examining the relationship between SII values and clinical outcomes, with a median follow-up period of 22.75 months.

Diagnosis of diabetes in this study is established by the presence of characteristic symptoms, including polydipsia, polyuria, polyphagia, and unintended weight loss, along with a random plasma glucose (RPG) level of ≥ 11.1 mmol/L at any time of the day, irrespective of the timing relative to the last meal, or a fasting plasma glucose (FPG) level of ≥ 7.0 mmol/L following a minimum of eight hours of fasting.¹⁹ In cases where the typical symptoms are not present, an RPG level of ≥ 11.1 mmol/L necessitates a repeat measurement on a different day to confirm the diagnosis definitively.

Defining and Quantifying SII Indicators

The SII index is determined using the formula: $SII = \text{PLT count} \times \text{NEU count} / \text{Lym count}$.⁷ On the second day of hospital admission, a 5 ml venous blood sample was collected from the peripheral vein in the early morning following an overnight fast, utilizing an EDTA blood collection tube, to establish baseline measurements. The blood samples were collected in a standardized manner and analyzed using the impedance method, a widely accepted technique for accurately quantifying PLT and WBC counts, including NEU and Lym. The Beckman LH750 and Beckman DXC800 automated hematology analyzers (Beckman Coulter, Brea, California, USA) were employed for the analysis. The testing kits, sourced from Fujian New Continent Biotechnology Co., Ltd, were utilized to guarantee the precision of the results. The testing protocols strictly complied with the instructions provided in the reagent kit's manual. The kit, which

contains quality control materials or standards, was used to conduct quality control checks throughout the testing process, ensuring the stability and consistency of the measurements.

Patient Surveillance Protocol

In this longitudinal observational study, we monitored individuals with a diagnosis of CHF, commencing our engagement at the study's inception and conducting follow-ups at intervals ranging from 6 to 36 months, with additional assessments as required. The principal aim was to monitor the health status of the participants for a minimum of one year, with a focus on all-cause mortality (ACM) and the possibility of hospital readmissions. Data collected throughout these intervals were systematically analyzed to support ongoing patient care post-discharge and to identify and monitor adverse health events. Comprehensive follow-up was achieved through diverse methods, such as in-person clinic visits, electronic communications, and other forms of contact, continuing until a significant event occurred or the study concluded. The median duration of the study was 22.75 months, with the interquartile range extending from 12.37 to 47.11 months.

Statistical Analysis

In conducting this investigation, we adopted a rigorous statistical approach to ensure the accuracy and reliability of our results. The data analysis was conducted utilizing SPSS version 25.0, a sophisticated tool designed for the analysis of complex datasets. Data that adhered to a normal distribution were summarized using the mean and standard deviation, providing a clear indication of the central tendency and dispersion of the data. For data that did not follow a normal distribution, non-parametric methods were applied, with the results presented in quartiles to accurately portray the distribution and range of the data, thus minimizing the effect of outliers.

Categorical variables, including gender and health status, were tabulated as counts and percentages and analyzed using the chi-square test, a conventional statistical method for assessing associations between categorical variables. The independent samples t-test was employed to compare the means of two groups, under the assumption of normal distribution and homogeneity of variances. In cases where data were not normally distributed, the Mann-Whitney U test was utilized, serving as a non-parametric alternative for comparing continuous or ordinal data that do not meet the criteria for a t-test.

The Kaplan-Meier method was utilized to conduct survival analysis, estimating the probability of survival over

time, which enabled us to measure the time until a specific event, such as death, occurred within the study population. Cox proportional hazards regression was applied to assess the impact of multiple variables on survival outcomes, offering a multivariate analysis that isolates the effect of each variable independently.

A *P*-value threshold of .05 was established to define statistical significance, a criterion widely accepted in the field of statistics to ascertain that the observed results are unlikely due to random variation.

Results

Baseline Data

In our study, we assembled a sample of 2748 patients with CHF, comprising 1773 males (64.52%) and 975 females (35.48%), with an average age of 65.05 years and a median follow-up duration of 22.75 months. As shown in Table 1, the sample was stratified into three distinct groups based on the patients' ejection fraction: HFrEF, *n* = 727, HFmrEF, *n* = 729, and HFpEF, *n* = 1292. The table provides a detailed breakdown of gender, age, comorbidities, ACM, and readmission rates for each subgroup. The HFrEF subgroup displayed a lower average age, a lower prevalence of hypertension (HTN), and lower readmission rates compared to the other two groups. In contrast, the HFrEF subgroup had a higher proportion of males, a higher incidence of cardiomyopathy (CMP), arrhythmia (AR), and ACM. The HFpEF subgroup showed a higher prevalence of coronary artery disease (CAD) and readmission rates than the other groups. All comparative analyses presented in Table 1 resulted in *P*-values less than .05, signifying statistical significance.

SII Level-Based Patient Profiles

Participants were divided into two cohorts based on whether their SII levels were above or below the median value. The median baseline SII value for the collective sample was established at 916.68. As indicated in Table 2, the chi-square test demonstrated that individuals with lower SII levels exhibited a reduced prevalence of CAD, HTN, valvular heart disease (VHD), diabetes mellitus (DM), CMP, and AR across all categories. T-tests indicated that those with lower SII levels were generally younger and presented with lower WBC counts, yet demonstrated higher triglyceride levels in comparison to all groups. The Mann-Whitney U test was applied to analyze NT-proBNP levels, revealing that patients with lower SII levels had diminished levels of this biomarker across all groups. All comparative analyses yielded statistically significant results, with *P*-values below .05.

Table 1. Baseline Profiles and Clinical Outcomes of CHF Patients Categorized by Ejection Fraction.

Variable	Total (n = 2748)	HFrEF (n = 727)	HFmrEF (n = 729)	HFpEF (n = 1292)	P-value
Age, years	65.05 ± 13.70	61.21 ± 13.55	64.69 ± 12.80	66.27 ± 13.87	<.001
Gender, male, n(%)	1773(64.52)	547(75.24)	499(68.45)	727(56.27)	<.001
CAD, n(%)	1597(58.11)	392(53.92)	482(66.12)	723(55.96)	.587
HTN, n(%)	1465(53.31)	327(44.98)	372(51.03)	766(59.29)	.019
VHD, n(%)	593(21.58)	155(21.32)	132(18.11)	306(23.68)	.180
CHD, n (%)	53(1.93)	12(1.65)	7(0.96)	34(2.63)	<.001
DM, n(%)	728(26.49)	171(23.52)	215(29.49)	342(26.47)	.187
CMP, n(%)	381(13.86)	237(32.60)	85(11.66)	59(4.57)	<.001
Tumor, n (%)	120(4.37)	20(2.75)	32(4.39)	68(5.26)	.058
AR, n(%)	1251(45.52)	394(54.20)	331(45.40)	526(40.71)	<.001
ACM, n(%)	1105(40.21)	313(43.05)	284(38.96)	508(39.32)	<.001
Readmission, n(%)	733(26.67)	179(24.62)	197(16.17)	357(27.63)	<.001

Note: The data are summarized as the mean ± standard deviation for continuous variables and as counts and percentages for categorical variables. ACM: All-cause mortality; HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mildly reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HTN: Hypertension; CMP: Cardiomyopathy; AR: Arrhythmia; CAD: Coronary artery disease. All reported comparisons achieved statistical significance at the $P < .05$ threshold. This table offers an in-depth analysis of gender distribution, age, comorbid conditions, all-cause mortality, and readmission frequencies across the subgroups.

SII Levels and Clinical Outcomes

The receiver operating characteristic (ROC) curve presented in Figure 2 demonstrates the predictive capability of SII levels in identifying patients at different risk levels for ACM. The area under the ROC curve (AUC) for the subgroup with elevated SII levels, which is set at ≥ 916.68 , is calculated to be 0.88, with a 95% confidence interval ranging from 0.82 to 0.95 ($P < .001$). This result signifies a robust capacity to differentiate patients who encountered all-cause mortality from those who did not. The AUC value, in conjunction with the P -value of less than .001, implies a strong correlation between elevated SII levels and an increased risk of mortality. The placement of the ROC curve above the non-discrimination line further validates the diagnostic utility of SII in this scenario.

Table 3 presents a comprehensive analysis of the incidence of ACM within the entire study population, revealing distinct patterns in mortality rates between patients with low and high SII levels. The low SII cohort exhibits a lower ACM rate of 683 occurrences among 1888 individuals, which corresponds to a rate of 36.20%, in contrast to the high SII cohort, which has a higher ACM rate of 422 out of 863 individuals, equating to 49.01%. This disparity is statistically significant ($P < .001$). This trend is consistently observed across all subgroups, including HFrEF with rates of 40.00% in the low SII group versus 50.99% in the high SII group ($P < .05$), HFmrEF with rates of 31.91% versus 53.59% ($P < .001$), and HFpEF with rates of 36.32% versus 45.50% ($P < .05$).

Conversely, the readmission rates reveal an inverse relationship, with the low SII group having a rate of 551 out of 1888 individuals (29.20%) and the high SII group having a rate of 182 out of 863 individuals (21.14%), indicating a significant difference between the groups ($P < .001$).

This inverse trend is also present within each subgroup, with HFrEF having rates of 26.29% versus 20.30% ($P < .05$), HFmrEF with rates of 30.69% versus 19.41% ($P < .05$), and HFpEF with rates of 30.11% versus 22.51% ($P < .05$).

The data suggests that despite the low SII group having a lower ACM rate, suggesting a potentially better survival prognosis, they paradoxically have a higher readmission rate. This could suggest that the low SII group may include patients who, while having a lower risk of dying from their condition, are more likely to experience events that necessitate hospital readmission. It is plausible that these patients have conditions that are more manageable or have access to superior post-discharge care, which may reduce the risk of death but not necessarily prevent readmissions. Further research is warranted to investigate the underlying reasons for these findings and to identify potential interventions that could enhance outcomes for this patient cohort.

The Kaplan-Meier survival curves for the SII in relation to adverse outcomes are presented in Figures 3 and 4. In general, the Kaplan-Meier analysis demonstrates that the low SII group, defined as SII values below 916.68, experienced superior cumulative survival rates over time (Figure 3) and demonstrated a reduced cumulative hazard rate when compared to the high SII group (Figure 4). These distinctions were observed uniformly across all subgroups examined, namely HFrEF, HFmrEF, and HFpEF, with all comparisons yielding statistically significant results ($P < .001$).

Following the adjustment for potential confounders, the predictive utility of the SII was evaluated using a multivariate analysis approach. During the extended follow-up period, within the entire study population, subjects in the high SII category exhibited a 43.8% heightened risk of

Table 2. Baseline Characteristics and Clinical Attributes Grouped by SII Threshold.

Variable	Tato (n = 2748)				HFpEF (n = 729)				HFpEF (n = 1292)			
	SII < 916.68 (n = 1887)	SII ≥ 916.68 (n = 861)	F _{1/2} /H value	P-value	SII < 916.68 (n = 525)	SII ≥ 916.68 (n = 202)	F _{1/2} /H value	P-value	SII < 916.68 (n = 492)	SII ≥ 916.68 (n = 237)	F _{1/2} /H value	P-value
Age, years	63.83 ± 13.79	66.27 ± 13.61	11.54	.02	60.58 ± 13.12	64.84 ± 13.98	12.68	.01	63.80 ± 12.86	65.57 ± 12.74	10.03	.007
Gender, male, n (%)	1221 (64.71)	552 (64.11)	0.005	.942	394 (75.05)	153 (75.74)	0.038	.846	341 (69.31)	158 (66.67)	0.517	.472
CAD, n (%)	1057 (56.01)	540 (62.72)	16.665	<.001	270 (51.43)	122 (60.40)	4.721	.03	312 (63.41)	170 (71.73)	4.937	.026
HTN, n (%)	830 (43.98)	635 (73.75)	18.51	<.001	202 (38.48)	125 (61.88)	17.75	<.001	213 (43.29)	159 (67.09)	19.04	<.001
VHD, n (%)	306 (16.22)	287 (33.33)	12.543	<.001	74 (14.10)	81 (40.09)	19.51	<.001	67 (13.62)	65 (27.43)	18.42	<.001
CHD, n (%)	38 (2.01)	15 (1.74)	0.5	.479	10 (1.90)	20 (9.9)	0.752	.386	5 (1.02)	2 (0.84)	0.05	.823
DM, n (%)	400 (21.20)	328 (38.10)	18.86	<.001	103 (19.62)	68 (33.66)	17.09	<.001	103 (20.93)	112 (47.26)	18.75	<.001
CMP, n (%)	201 (10.65)	180 (20.91)	17.648	<.001	124 (23.62)	113 (55.94)	35.53	<.001	42 (8.33)	43 (18.14)	12.998	<.001
Tumor, n (%)	77 (4.08)	43 (4.99)	3.234	.072	14 (2.67)	6 (2.97)	0.05	.823	19 (3.86)	13 (5.49)	1.004	.316
AR, n (%)	617 (32.70)	634 (73.64)	29.009	<.001	254 (48.38)	140 (69.30)	10.473	.001	186 (37.80)	145 (61.18)	12.89	<.001
WBC × 10 ⁹ /L	8.46 ± 1.35	10.33 ± 1.82	7.661	.006	8.02 ± 1.77	9.19 ± 1.98	12.46	.02	8.04 ± 1.77	10.00 ± 1.02	9.55	.002
Creatinine, μmol/L	417.62 (337.24-539.64)	396.80 (323.44-511.80)	2.968	.085	371.63 (229.22-716.65)	270.32 (187.23-556.03)	3.009	.083	439.55 (282.13-664.83)	538.07 (392.91-751.09)	1.01	.315
Uric acid, μmol/L	487.53 ± 295.66	485.10 ± 297.59	0.303	.582	560.24 ± 297.31	531.21 ± 257.05	0.352	.553	469.24 ± 226.79	503.31 ± 296.51	0	.999
Triglycerides, mmol/L	1.86 ± 2.71	1.70 ± 2.37	4.965	.026	1.55 ± 1.08	1.32 ± 0.68	6.503	.011	1.81 ± 2.26	1.56 ± 0.89	7.746	.006
Total cholesterol, mmol/L	3.66 ± 1.10	3.69 ± 1.17	1.534	.216	3.64 ± 1.09	3.60 ± 1.01	0.389	.533	3.60 ± 0.96	3.70 ± 1.33	12.204	.001
HDL-cholesterol, mmol/L	0.97 ± 0.33	0.95 ± 0.34	4.779	.029	0.93 ± 0.29	0.89 ± 0.29	0.344	.558	0.99 ± 0.29	0.94 ± 0.33	1.89	.17
LDL-cholesterol, mmol/L	2.35 ± 0.90	2.39 ± 0.95	1.113	.291	2.37 ± 0.87	2.40 ± 0.81	1.285	.257	2.29 ± 0.85	2.37 ± 1.12	8.567	.004
NT-proBNP, ng/L	4883.08 (1686.66-6809.57)	7444.54 (4199.86-9322.76)	40.422	<.001	5670.33 (1945.53-6746.06)	8070.59 (4169.05-8969.57)	8.882	.003	4605.81 (1654.72-5749.57)	7712.14 (4726.20-8821.06)	10.531	.001

Note: The data are articulated as median with interquartile range for continuous variables and count with percentage for categorical variables. SII: Systemic Immune-Inflammation Index; CAD: Coronary Artery Disease; HTN: Hypertension; VHD: Valvular Heart Disease; DM: Diabetes Mellitus; CMP: Cardiomyopathy; AR: Atrial fibrillation; WBC: White Blood Cell; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide. Categorical variables were analyzed using chi-square tests, and continuous variables were analyzed with T-tests for comparisons between two groups. The Mann-Whitney U test was utilized for NT-proBNP levels due to its non-normal distribution. All p-values presented are two-tailed, with statistical significance defined as $P < .05$. This table delineates the prevalence of CAD, HTN, VHD, DM, CMP, AR, age, WBC count, and triglyceride levels among patients stratified by SII levels above and below the median value of 916.68.

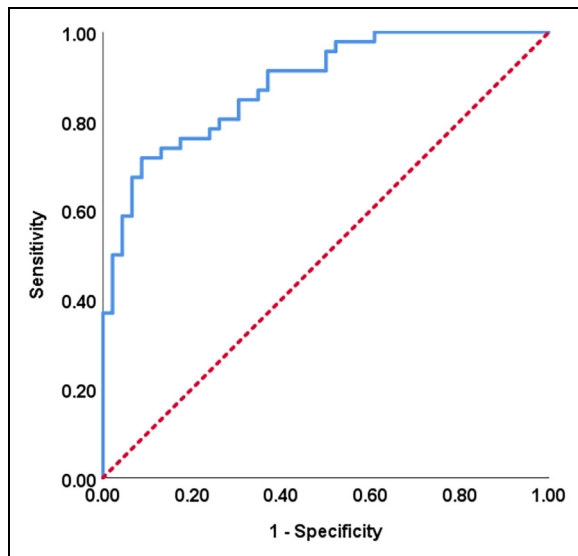


Figure 2. ROC analysis of the SII for forecasting ACM. The ROC curve in Figure 2 illustrates the discriminative ability of SII levels in stratifying patients according to their risk of ACM. The AUC for patients in the high SII category, set at a threshold of 916.68, is calculated to be 0.88, with a 95% confidence interval ranging from 0.82 to 0.95 ($P < .001$). This result signifies a robust predictive capability to distinguish patients who encountered ACM from those who did not. The ROC curve's placement above the non-discrimination threshold (the dashed line) highlights the diagnostic efficacy of SII in this scenario. The AUC value, in conjunction with the highly significant P -value, implies a strong association between higher SII levels and an elevated risk of mortality.

experiencing ACM relative to those in the low SII category (hazard ratio [HR] = 1.43, 95% confidence interval [CI]: 1.271-1.627, $P < .001$). Similarly, in the subgroup of patients with HFrEF, the high SII group demonstrated a 36.2% increased risk of ACM compared to the low SII group (HR = 1.362, 95% CI: 1.023-1.813, $P < .001$). In the HFmrEF subgroup, the high SII group had a 62.9% increased risk of ACM relative to the low SII group (HR = 1.629, 95% CI: 1.208-2.196, $P < .001$). Furthermore, in the HFpEF subgroup, the high SII group showed a 60.2% increased risk of ACM compared to the low SII group (HR = 1.602, 95% CI: 1.288-1.992, $P < .001$). Even after accounting for factors such as age, NT-proBNP, and white blood cell count, these findings remained consistent, with all P -values being less than .05 (Table 4).

Discussion

Inflammatory processes have long been recognized as integral to the pathogenesis and progression of CHF. The SII, which amalgamates the NEU, PLT, and Lym, has garnered increasing attention as a potential biomarker in

cardiovascular medicine. In this study, we embarked on a detailed exploration of the relationship between SII levels and the clinical outcomes of CHF patients, with a particular emphasis on stratifying patients based on EF.

Our research findings demonstrated a robust and consistent association between SII and ACM across all EF subgroups. This significant correlation was not only statistically validated but also held firm even after accounting for a comprehensive array of confounding variables. Notably, in the cohort with elevated SII levels, there was a substantial 43.8% increase in the risk of ACM, as evidenced by a HR of 1.43 and a 95% CI spanning from 1.271 to 1.627, with a highly significant P -value of less than .001. This observation was uniformly applicable to patients with HFrEF, HFmrEF, and HFpEF. Such results are in harmony with previous research that has firmly established the role of inflammatory biomarkers as crucial determinants of adverse cardiovascular events.²⁰⁻²²

The stratification of patients by EF unveiled distinct and clinically relevant patterns in the relationship between SII and clinical outcomes. In HFrEF patients, elevated SII levels were closely linked to a heightened ACM risk. This finding implies that in this subgroup, more aggressive anti-inflammatory interventions may potentially be warranted to mitigate the elevated risk. Conversely, in HFpEF patients, the significant relationship between SII and outcomes indicates that SII can serve as a valuable tool for identifying high-risk individuals within this subset who would benefit from closer monitoring and targeted therapies. Overall, the combination of SII assessment and EF stratification represents a novel and powerful approach that can significantly enhance risk stratification and clinical decision-making in the management of CHF.

Recent studies have expanded the scope of SII's potential applications beyond the realm of CHF. For instance, a study by Liu et al²³ unearthed a significant association between SII and depressive symptoms, particularly in individuals without pre-existing cardiovascular disease. This discovery suggests that SII may possess the capacity to not only predict cardiovascular outcomes but also to identify patients at risk of developing psychological comorbidities. This dual role highlights SII's potential as a comprehensive biomarker that can provide insights into both the physical and mental health aspects of patients. Additionally, research by Keting Liu et al²⁴ demonstrated that SII and the neutrophil-to-lymphocyte ratio (NLR) are potent predictors of disease severity in large artery atherosclerosis (LAA) stroke patients. This finding resonates with our own results, further emphasizing the role of SII as an independent risk factor for a diverse range of cardiovascular diseases and its ability to accurately predict disease severity. Collectively, these studies serve to underline the broad applicability and significance of SII in different cardiovascular contexts, thereby further validating its importance as a prognostic biomarker.

Table 3. Comparative Analysis of ACM and Readmission Rates in Relation to SII Across CHF Categories.

Variable	Tatol(n = 2748)				HFReEF(n = 727)				HFmrEF(n = 729)				HFpEF(n = 1292)			
	SII < 916.68 (n = 1887)	SII ≥ 916.68 (n = 861)	F/χ ² /H value	P-value	SII < 916.68 (n = 525)	SII ≥ 916.68 (n = 202)	F/χ ² /H value	P-value	SII < 916.68 (n = 492)	SII ≥ 916.68 (n = 237)	F/χ ² /H value	P-value	SII < 916.68 (n = 870)	SII ≥ 916.68 (n = 422)	F/χ ² /H value	P-value
ACM, n(%)	683(36.20)	422(49.01)	56.913	<.001	210(40.00)	103(50.99)	7.186	.007	157(31.91)	127(53.59)	31.602	<.001	316(36.32)	192(45.50)	10.028	.002
Readmission, n(%)	551(29.20)	182(21.14)	19.312	<.001	138(26.29)	41(20.30)	2.398	.022	151(30.69)	46(19.41)	6.768	.009	262(30.11)	95(22.51)	9.274	.002

Note: The data are displayed as counts with percentages. ACM: All-cause mortality; HFReEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; SII: Systemic Immune-Inflammation Index. Statistical significance was ascribed to p-values less than 0.05. This table examines the frequency of all-cause mortality and readmission rates in relation to SII levels, distinguishing between low and high SII groups within the general cohort and across various CHF subtypes. The low SII cohort is delineated by SII values beneath the median value of 916.68, whereas the high SII cohort comprises individuals at or above this threshold.*

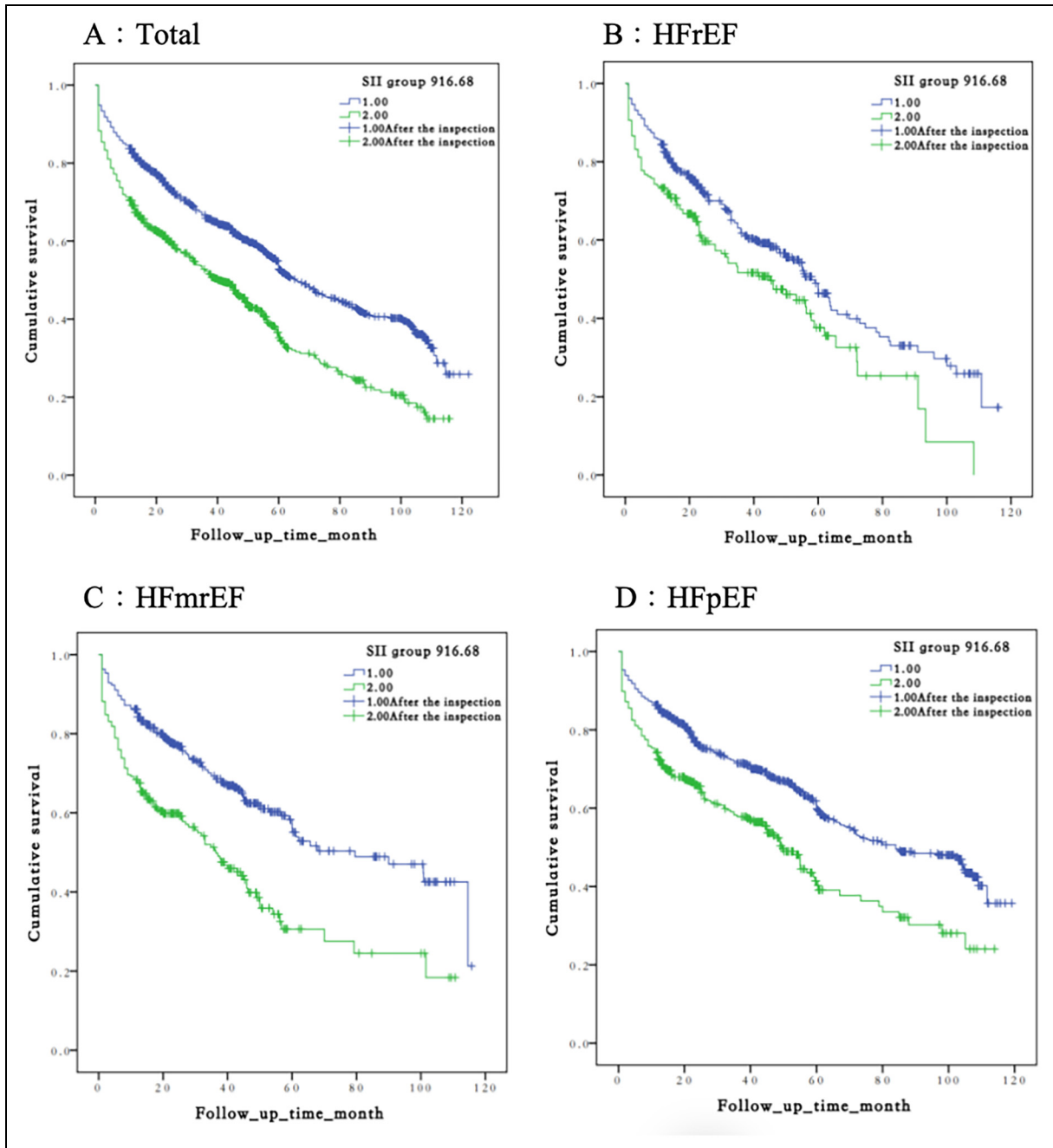


Figure 3. Kaplan-Meier estimates of cumulative survival in relation to SII categories across CHF categories. Figure 3A illustrates the cumulative survival probabilities for the cohort stratified by low SII levels (<916.68) against high SII levels across the entire study population. Panels 3B, 3C, and 3D delineate the survival probabilities for the subgroups of HFrEF, HFmrEF, and HFpEF, respectively. Across all categories, the low SII group consistently exhibits significantly superior survival rates when compared to the high SII group ($P < .001$).

Our study makes a novel and valuable contribution to the field by focusing on the hitherto under-explored relationship between SII and mortality rates among CHF patients, specifically differentiated by EF categories. The application of the ROC curve to determine the most effective SII threshold for predicting ACM represents another key strength of our study. This methodological approach

not only refines the risk stratification process but also introduces a more accurate and data-driven methodology for clinical decision-making.¹⁷

The predictive utility of SII in CHF patients can potentially be attributed to its ability to reflect the systemic inflammatory milieu and immune system activity. Inflammatory mediators and immune cells are known to

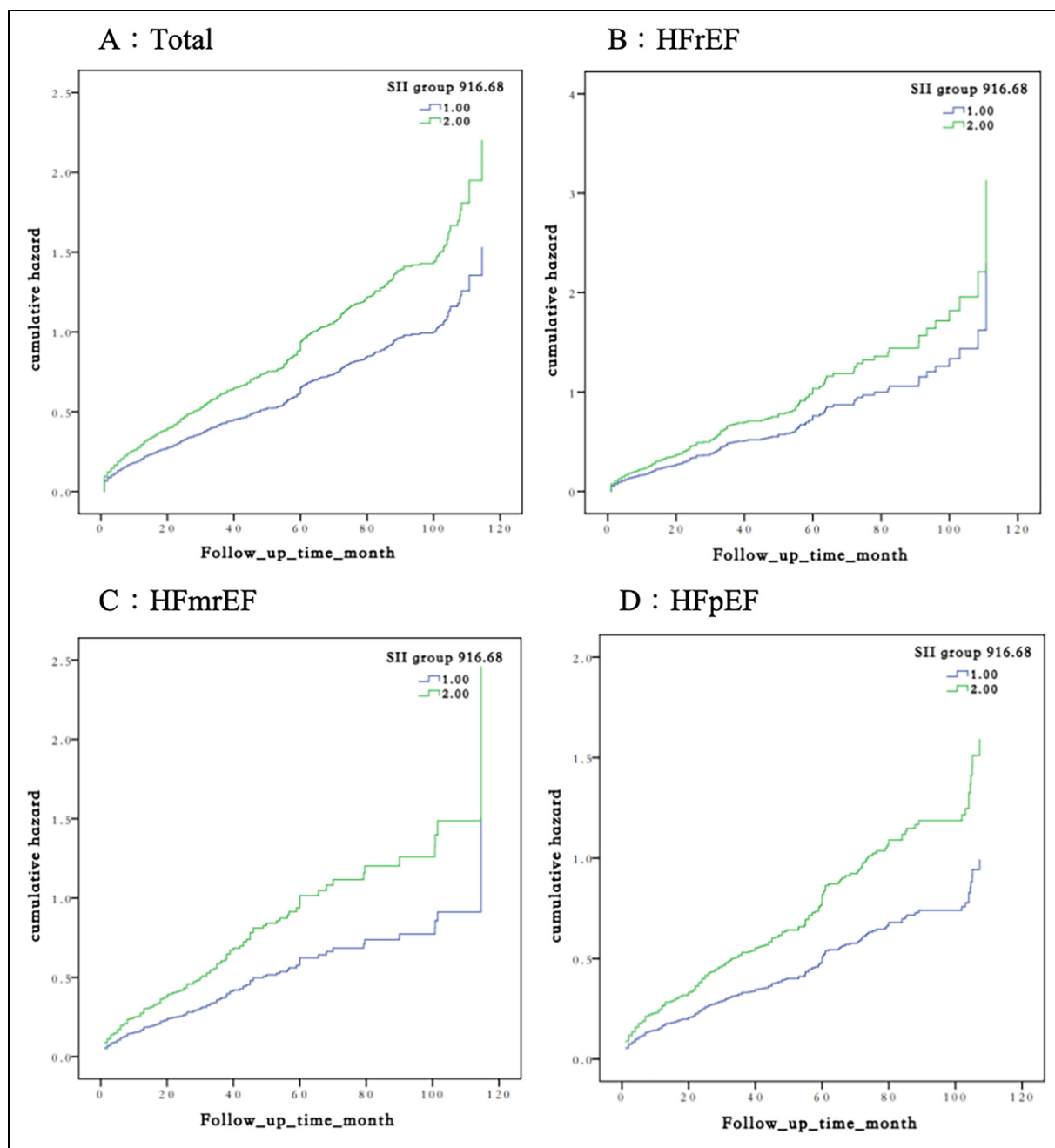


Figure 4. Kaplan-Meier curves of cumulative hazard for all-cause mortality in relation to SII categories across CHF categories. Figure 4A displays the cumulative hazard for all-cause mortality for the cohort categorized by low SII levels (<916.68) in contrast to high SII levels across the entire study population. Panels 4B, 4C, and 4D depict the cumulative hazard for the subgroups of HFrEF, HFmrEF, and HFpEF, respectively. In all subgroups analyzed, the low SII group presents markedly reduced cumulative hazard rates ($P < .001$).

play a central and decisive role in the pathophysiology of CHF.⁵ They actively participate in processes such as myocardial injury, fibrosis, and adverse cardiac remodeling,^{4,25–27} As an integrated marker of inflammation, SII has the potential to encapsulate the intricate and dynamic interplay between the immune response and the cardiovascular system. This unique characteristic allows SII to offer

a more comprehensive prognostic insight compared to conventional risk factors, which often focus on only a single aspect of the disease process.

An interesting and somewhat unexpected finding in our investigation was the observed inverse correlation between SII and triglyceride levels in CHF patients. Specifically, patients within the low SII category exhibited elevated

Table 4. Multivariable Analysis of SII and ACM Risk in Heart Failure Subgroups.

Variables	Tatol(n = 2748))						HF+EF(n = 727)						HFmrEF(n = 729)						HFpEF(n = 1292)					
	B	SE	Wald	P	HR	95% CI	B	SE	Wald	P	HR	95% CI	B	SE	Wald	P	HR	95% CI	B	SE	Wald	P	HR	95% CI
SII	.363	.063	33.315	<.001	1.438	1.271 1.627	.309	.146	4.482	<.001	1.362	1.023 1.813	.488	.152	10.251	<.001	1.629	1.208 2.196	.471	.111	17.970	<.001	1.602	1.288 1.992
Age	.029	.002	141.800	<.001	1.030	1.025 1.035	.016	.006	7.377	.007	1.016	1.004 1.027	.035	.006	31.842	<.001	1.036	1.023 1.049	.038	.004	72.489	<.001	1.039	1.030 1.048
NT-proBNP	.000	.000	202.385	<.001	2.007	1.302 2.977	.000	.000	31.751	<.001	1.31	1.12 1.54	.000	.000	20.682	<.001	2.158	1.271 3.665	.000	.000	49.746	<.001	1.63	1.22 2.18
CAD	-.199	.065	9.529	.002	.819	.722 .930	-.094	.185	.258	.611	.910	.634 1.307	-.077	.172	.200	.655	.926	.661 1.297	-.413	.110	14.098	<.001	.662	.533 .821
VHD	.059	.078	.566	.452	1.061	.910 1.237	.153	.182	.707	.401	1.165	.816 1.664	-.286	.207	1.903	.168	.751	.501 1.128	.111	.137	.657	.418	1.118	.854 1.463
CMP	-.248	.108	5.339	.021	.780	.632 .963	-.437	.195	5.041	.025	.646	.441 .946	-.231	.306	.570	.450	.794	.436 1.446	-.266	.311	.729	.393	.767	.416 1.411
WBC	.011	.003	12.016	<.001	1.011	1.005 1.017	.027	.007	16.391	<.001	1.027	1.014 1.040	.025	.012	4.553	.033	1.025	1.002 1.049	.003	.005	.352	.023	1.003	.993 1.013
AR	.073	.062	1.409	.235	1.076	.953 1.215	-.075	.137	.299	.585	.928	.709 1.214	-.074	.154	.230	.631	.929	.687 1.256	-.032	.114	.081	.775	.968	.775 1.209

Note: Table 4. Adjusted for confounding variables, this table presents the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality (ACM) associated with high versus low SII levels in the overall heart failure population and across subgroups defined by ejection fraction categories: heart failure with reduced ejection fraction (HF+EF), heart failure with mid-range ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF). SII: Systemic Immune-Inflammation Index; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; WBC: White Blood Cell. All P-values are from the Wald test and are two-tailed, with statistical significance set at $P < .05$. The adjusted model includes age, NT-proBNP, and WBC, among other relevant covariates.

triglyceride levels in contrast to those in the higher SII categories. This finding contradicts the typical association of systemic inflammation with increased triglyceride levels.²⁸ One possible explanation for this counterintuitive observation could be related to the complex metabolic shifts that occur in CHF patients. It is conceivable that a low SII in this context may signify a distinct metabolic condition or a unique inflammatory signature that warrants further in-depth research.

Furthermore, our research indicated that the levels of SII did not show significant variance between patients with and without comorbid tumor-related conditions. This result implies that within the context of CHF, there is no direct and obvious correlation between SII levels and tumor-related illnesses. This is particularly noteworthy given the well-established connections between inflammation and cancer.²⁹ It is possible that the inflammatory environment observed in CHF patients may not be the primary or decisive factor influencing tumor development or progression. Alternatively, other factors may exert a more dominant influence on this patient cohort. This observation also highlights the heterogeneity of CHF patients and the complex, multifaceted nature of tumor genesis. It underscores the need for a more sophisticated and comprehensive understanding of the intricate interactions between inflammation, heart failure, and cancer.³⁰

Beyond its prognostic value, SII holds promise as a pivotal factor in tailoring treatment approaches for CHF patients. The continuous monitoring of SII levels could facilitate the early identification of patients who are at an increased risk of adverse outcomes. Such patients may potentially benefit from more intensive medical intervention or more frequent monitoring regimens. There is an urgent need for future research to investigate whether interventions designed to modulate the immune-inflammatory response, such as the use of anti-inflammatory agents or immunotherapies, could potentially improve the clinical outcomes for CHF patients with elevated SII levels.

However, it is important to acknowledge the limitations of our study. Firstly, the retrospective design of the study inherently introduces the potential for selection bias and restricts our ability to establish a definitive causal relationship between SII levels and the prognosis of CHF. Prospective research endeavors are therefore essential to confirm and strengthen the link between SII and CHF outcomes. Secondly, our study cohort was relatively homogeneous, primarily consisting of patients from a single medical institution in China. This may limit the generalizability of our findings to other populations and ethnic groups. Thirdly, despite our efforts to adjust for several confounding variables, there remains the possibility of other unmeasured factors that could have influenced the results. Fourthly, the determination of the optimal SII cutoff value for forecasting adverse outcomes was based on the ROC curve within our study. However, it is important

to note that this cutoff value may vary depending on the characteristics of the study population and the specific clinical context. Despite these limitations, the robustness of our findings is reinforced by the consistent association between elevated SII levels and an increased risk of ACM across a diverse range of CHF subpopulations.^{31,32}

In conclusion, while our study has provided valuable insights into the role of SII in CHF, further research is needed to overcome the identified limitations and to fully elucidate the potential of SII as a clinical tool for risk stratification and treatment guidance in CHF patients.

Conclusions

The comprehensive analysis presented in this study has yielded significant and reliable insights into the prognostic significance of the SII within the context of CHF. The data clearly and convincingly demonstrate a strong and consistent correlation between elevated SII values and an increased risk of ACM, regardless of the subgroup stratifications based on EF. This correlation remained highly significant even after meticulously accounting for a multitude of confounding variables, thereby firmly establishing the independent and predictive utility of SII in prognosticating outcomes in CHF.

Although the retrospective nature of this study presents certain inherent limitations, including the potential for selection bias and the inability to definitively establish causal relationships, the results were rigorously validated using stringent statistical methodologies. Specifically, multivariable analysis and the Wald test were employed to confirm the reliability of SII as a prognostic marker across various CHF subpopulations. These statistical tests provided strong evidence supporting the robustness of our findings and the validity of SII as a valuable tool in CHF prognosis.

It is crucial to recognize and consider the limitations of our study. The patient demographic was largely confined to a single geographic region, and the data was retrospectively collected. These factors may potentially limit the generalizability of our findings to broader populations. Therefore, future research efforts should focus on incorporating more heterogeneous populations and larger sample sizes to corroborate and expand upon our initial observations. This will help to ensure that the findings are applicable across different settings and patient groups.

Our findings strongly advocate for the incorporation of SII into clinical decision-making processes as a valuable risk stratification tool for CHF patients. Future research endeavors should prioritize validating these findings through prospective studies and investigating the potential of SII-guided interventions to enhance patient outcomes. Additionally, further research is needed to elucidate the underlying mechanistic links between SII and CHF prognosis. Understanding these mechanisms may reveal novel

therapeutic targets, thereby potentially revolutionizing the management of this complex and debilitating condition.

In summary, despite the acknowledged limitations of the study, the robustness of the findings and the potential clinical implications of SII as a prognostic biomarker in CHF are substantial. Continued research in this area is of utmost importance to translate these findings into improved clinical practices and, ultimately, to achieve better outcomes for patients with CHF.

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Author Contributions

Each author of this manuscript has significantly contributed to the research reported, encompassing various aspects such as the conception of the study, its design, the execution, data acquisition, analysis, and interpretation. All authors have been involved in drafting, revising, or critically reviewing the article and have granted their final approval for the version to be published. They concur with the selection of the journal for submission and are committed to being accountable for all facets of the work. All listed authors have made a significant, direct, and intellectual contribution to the research and have given their approval for its publication.

Data Availability

The datasets that were utilized or analyzed during the course of this research are accessible to interested parties upon reasonable request by contacting the principal investigator.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study protocol was conducted in full compliance with the Declaration of Helsinki and received ethical approval from the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (approval number 202207-019). Given the retrospective design of the study, the Ethics Committee waived

the requirement for informed consent from participants. All methods were performed in accordance with the relevant guidelines and regulations.

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