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Effect of Systemic Inflammatory Response Index (SIRI) and Systemic Immuno-Inflammation Index (SII) on mortality in heart failure patients

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ABSTRACT

Introduction: Heart failure (HF) is a structural and functional disease that affects millions of people worldwide. The role of inflammation has been demonstrated in many diseases. However, the impact of the Systemic Inflammatory Response Index (SIRI) and the Systemic Immuno-Inflammation Index (SII) on mortality in HF patients has not been adequately investigated. Therefore, in this study, we aimed to demonstrate the effect of SIRI and SII on mortality in patients diagnosed with HF.

Methods: Our research is a retrospective, single-centre study comprising patients who were diagnosed with HF and presented at the emergency department. We focused on those diagnosed with decompensated HF between January and November 2022. The study recorded the demographic information and hemogram parameters of the patients. The patients' in-hospital mortality status was recorded and the effect of these parameters on mortality was assessed.

Results: We recruited 122 eligible patients for our research study. Patients with mortality exhibited significantly higher median SIRI levels compared to those without mortality (6.07 (1.99-12.23) vs 2.46, p=0.038), and the group with mortality had significantly higher median SII levels compared to the other group (6625.05 (4704.73-7539.51) vs. 982.48 (180.69-1929.45); p<0.001). ROC curves were generated to assess the efficacy of WBC, SIRI, SII, and CRP parameters in discriminating mortality, and it was confirmed that WBC, SIRI, and SII were all statistically significant predictors of mortality. SIRI and SII demonstrated superior diagnostic ability compared with WBC and CRP , as evidenced by their respective AUC values of 0.929 and 0.671, sensitivities of 91.7% and 50%, and specificities of 91% and 94%.

Conclusions: SIRI and SII can be used as mortality indicators in heart failure patients.

Keywords: heart failure, systemic immuno-inflammation index, systemic inflammatory response index

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INTRODUCTION

Heart failure (HF) is a common structural and functional disease that affects millions of people worldwide [1]. Patients frequently visit the emergency department with complaints of dyspnoea, fatigue, and oedema, making it a significant cause of both morbidity and mortality [2]. The incidence, prevalence, and hospitalization rates of heart failure tend to increase with age, placing a significant economic burden on healthcare systems [3]. HF is increasingly important and understanding the associated factors is vital. Investigating markers associated with mortality in these patients may help identify those at high risk [4].

Studies have shown a consensus regarding the effect of the sympathetic nervous system and the renin angiotensin aldosterone system on the pathogenesis of HF and the endogenous mechanisms and the progression of HF as a result of overexpression of neurohormones. It has been revealed that, in addition to neurohormones, cytokines also play an important role. Over the last decade, the role of inflammation in the pathogenesis of HF has been increasingly recognized as an important therapeutic target. Atherosclerosis development involves a crucial process, i.e, inflammation, which is an established factor in cardiovascular diseases and atherosclerosis. The impact of inflammation on a systemic proinflammatory state induced by comorbidities as a source of microvascular endothelial cell inflammation that triggers cardiac remodeling and dysfunction has been highlighted [5,6]. Inflammation has links to many ailments, like gastrointestinal disorders, malignancies, primarily cardiovascular diseases, and more [7]. Inflammation markers such as the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and C-reactive protein (CRP) have been recognised for their involvement in HF. Current research suggests

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the systemic immune-inflammation index (SII) and the Systemic Inflammatory Response Index (SIRI), derived from basic haematological parameters, may also play a crucial role in inflammation in various diseases, including malignancies, gastrointestinal disorders and sepsis [8-11]. Although there are very few studies on the subject in the literature, one study suggests that SIRI may be a promising new inflammatory biomarker for prediction [12]. A study on SII showed that in critically ill patients with CHF, a high SII level could effectively predict high rates of 30- and 90-day mortality and hospital deaths, as well as the risk of developing major cardiovascular adverse events [13].

Patients with higher SIRI values had a longer hospital or intensive care stay. Our study aims to investigate the impact of SIRI and SII on the mortality of diagnosed HF patients.

METHODS

Our research is a retrospective study conducted at a single centre, which included patients with HF who presented to the emergency department. The study consisted of patients aged 18 and above, who were diagnosed with decompensated HF between January and November 2022. In our study most were admitted with a principal diagnosis of HF and underwent transthoracic echocardiography. We included patients with HF who were considered New York Heart Association (NYHA) functional class III or IV, as well as patients with a brain natriuretic peptide (BNP) level of ≥500 pg/mL. Exclusion criteria included those with chronic kidney, liver and malignancy diseases other than HF, pregnant women, patients under 18 years of age, a history of hematological disease, serious infection, cancer or recent use of corticosteroids within 3 months before admission. Additionally, patients who were hospitalized outside our hospital and those who showed symptoms of infection affecting the lungs were also excluded from the study.

Demographic data and routine haemogram parameters, such as white blood cell (WBC), neutrophil, platelet, lymphocyte, and monocyte counts, were recorded for the patients, along with routine biochemical parameters. The CRP (mg/L) was measured in a serum Vacusera 5 ml mini 0.2 K3 EDTA tubes (Vacusera, ˙Izmir, Turkey), samples were immediately analyzed with Beckman Coulter AU680 (Beckman Coulter, CassinaDe' Pecchi, Italy). Haemogram was measured in a serum Vacusera 2 ml mini 0.2 K3 EDTA tubes (Vacusera, ˙Izmir, Turkey) and samples were processed by the Sysmex XN-series automated hematology analyzer (Sysmex Co., Kobe, Japan) within 1 hour from collection.

While a detailed medical history and physical examination were taken during hospital admission, blood samples were also collected for laboratory examinations within the first hour of admission to the emergency department. From the haemogram values, the patients' SII and SIRI values were calculated. As is known from the literature, SIRI was calculated using the formula (neutrophil count x monocyte count)/lymphocyte count, while SII was calculated using (platelet count x neutrophil count)/lymphocyte count. The patients' in-hospital mortality status was recorded and the effect of these parameters in-hospital mortality was assessed. The patients were divided into 2 groups, and those in group 1 were the surviving HF patients; those in group 2 are HF patients who died.

Statistical analysis

Data analysis was conducted using SPSS 25.0 in this study. Kolmogorov-Smirnov test was used when testing normality. Continuous variables were compared using mean ± standard deviation or mean (interquartile range (IQR)), and categorical variables were presented as frequency and percentage (%). Categorical data were analysed using Pearson's chi-squared test or Fisher's exact test based on their applicability. To compare parameters that could affect in-hospital mortality, we used Student's t-test for variables with a normal distribution and the Mann-Whitney U test for those without a normal distribution. Regression analysis was conducted to identify factors impacting in-hospital mortality. Optimal values for indicating in-hospital mortality were determined via receiver operating characteristic (ROC) analysis. A test with an AUC value greater than others has a better diagnostic value. We set a statistically significant p-value at $P < 0.05$.

RESULTS

The study included a total of 122 patients who met the inclusion criteria. Of these, 110 patients (91.2%) belonged to Group 1, and the mortality group comprised 12 patients (9.8%). Both groups predominantly comprised male individuals, and there were no notable differences in hospitalization durations or comorbidities. However, WBC count (12.91±4.45 vs. 9.97±3.4; p=0.004), neutrophil count (11.3±3.75 vs. 7.38±3.39; p=0.022), and CRP level (22.3 [10.02-58.95] vs 10.95 [4.8-37.25]; p<0.001) were substantially higher in the mortality group as compared to that of non-mortal participants. Furthermore, the mortality group displayed a significantly higher median of SII levels compared to the other group (6625.05 [4704.73-7539.51] vs. 982.48 [180.69-1929.45]; p<0.001, Figure 1). The median SIRI levels exhibited a statistically

Table 1. Demographics and laboratory findings in patients with heart failure

Demographics/ laboratory findings	Group 1 (n=110)	Group 2 (n=12)	P value
Age (years) ± SD	75.54 ± 7.4	77.16 ± 7.39	0.717
Gender (Male), n (%)	65 (59.1%)	7 (58.3%)	0.960
Length of stay (day), median	3	3	0.807
Atrial Fibrillation, n (%)	18 (16.3%)	0 (0%)	**0.031**
Hypertension, n (%)	42 (38.1%)	8 (66.6%)	0.059
Hyperlipidemia, n (%)	58 (52.7%)	7 (58.3%)	0.711
Coronary Artery Disease, n (%)	55 (50.0%)	6 (50.0%)	1.000
WBC count (×10³/mm³), mean ± SD	9.97 ± 3.40	12.91 ± 4.45	0.004
Neutrophils (×10³/mm³), mean ± SD	7.38 ± 3.39	11.30 ± 3.75	0.022
Lymphocytes (×10³/mm³), mean ± SD	1.73 ± 1.03	1.00 ± 0.62	0.726
Platelets (×10³/mm³), mean ± SD	237.0 ± 82,6	397.2 ± 70.2	0.259
CRP (mg/dL), median (IQR)	10.95 (4.80-37.25)	22.30 (10.02-58.95)	< 0.001
NLR, median (IQR)	3.82 (2.19-7.86)	13.87 (8.12-18.94)	< 0.001
SII, median (IQR)	982.4 (180.7-1929.4)	6625.0 (4704.7-7539.5)	**< 0.001**
SIRI, median (IQR)	2.46 (1.26-4.27)	6.07 (1.99-12.23)	**0.038**

Abbreviations: CRP- C-reactive protein; IQR- interquartile range; NLR- neutrophil to lymphocyte ratio; SD- standard deviation; SII- systemic immuno-inflammation index; SIRI- systemic inflammatory response index; WBC: white blood cell.

Table 2. Predictors of in-hospital mortality in patients with heart failure

Variable	OR	95% CI	P value
Gender	2.476	0.524-15.520	0.281
Age	1.094	0.981-1.228	0.105
SII	0.919	0.830-0.991	0.040
SIRI	1.001	1.000-1.004	0.006

Multivariable logistic regression analysis was applied. Abbreviations: CI- confidence interval, OR- odds ratio, SII- systemic immuno-inflammation index, SIRI- systemic inflammatory response index.

significant increase in patients who suffered mortality than in those who did not (6.07 [1.99-12.23] vs. 2.46 [1.26-4.27], p=0.038, Figure 1). Table 1 exhibits a comparison between the demographic data and laboratory values of the groups.

Gender (OR 2.476, 95% CI 0.524-15.52, p=0.281), SII (OR 0.919, 95% CI 0.830-0.991, p=0.004), and SIRI (OR 1.001, 95% CI 1.000-1.004, p=0.006) regression analysis was performed and among these, SIRI and SII demonstrated the ability to predict mortality (as shown in Table 2). ROC curves were generated to assess the efficacy of WBC, SIRI, SII, and CRP parameters in discriminating mortality, and it was confirmed that WBC, SIRI, and SII were all statistically significant predictors of mortality (as depicted in Figure 2). SII and SIRI demonstrated superior diagnostic ability, as evidenced by their AUC values of 0.929 and 0.671, sensitivities of 91.7% and 50.0%, and specificities of 91.0% and 94.0%, respectively (Table 3, p<0.001, Figure 2).

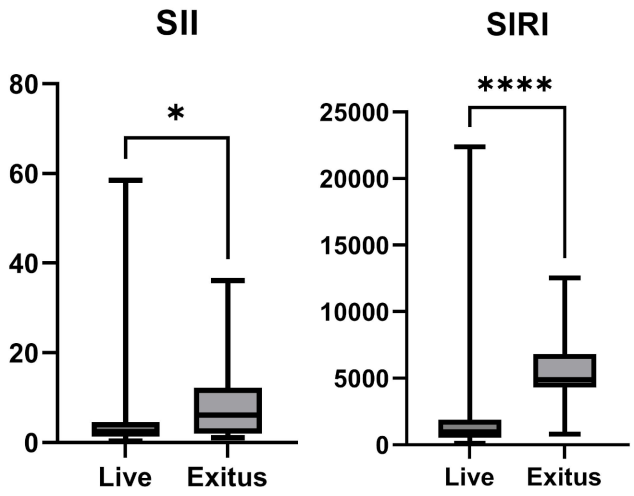

Fig. 1. Box plot analyses of SII (systemic immuno-inflammation index) and SIRI (systemic inflammatory response index) for heart failure patient groups

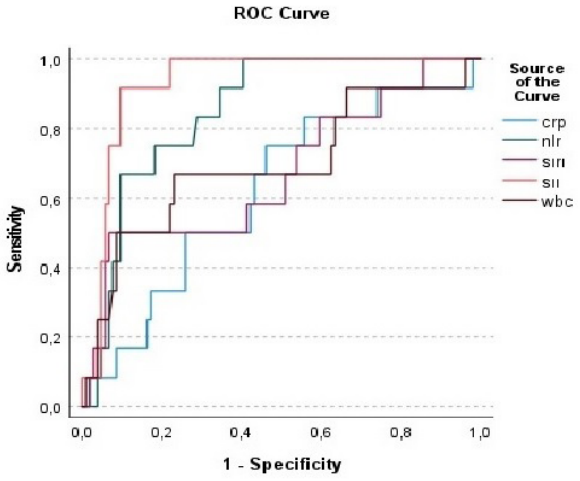

Fig. 2. Receiver operating characteristic curves of parameters to predict mortality in heart failure

DISCUSSION

This study examined the relationship between two new inflammatory markers, SII and SIRI, and in-hospital mor-

Table 3: The receiver operating characteristic curves for in-hospital mortality in heart failure patients

	Cut-off	AUC	Sensitivity (%)	Specificity (%)	P value
WBC (×10³/mm³)	11.80	0.694	66.7	77.0	0.036
SII	3986.19	0.929	91.7	91.0	< 0.001
SIRI	9.12	0.671	50.0	94.0	< 0.001
CRP (mg/dL)	13.35	0.620	75.0	54.0	0.049

Abbreviations: AUC- area under the ROC curve; CRP- C-reactive protein; SII- systemic immuno-inflammation index; SIRI- systemic inflammatory response index; WBC- white blood cell.

tality in patients with HF. The results of our investigation indicate that SIRI possesses high sensitivity and specificity and can be used as an indicator of in-hospital mortality. Moreover, SII also displayed high specificity.

Although limited research has explored the correlation between SII and SIRI with HF in recent years, existing studies suggest that inflammation has a prognostic impact in diseases that progress with inflammation, such as acute cholecystitis, cancer, diabetes, and chronic kidney failure [12-15]. Additionally, systemic inflammation, which is known to cause late-stage HF and myocardial damage, plays a significant role in the onset and advancement of HF [16].

Myocardial inflammation persists in individuals with both ischemic and non-ischemic HF, and engages diverse inflammatory cells (neutrophils, monocytes, macrophages, and lymphocytes) and cytokines (such as IL-6, TNF, etc.) [16]. Consequently, SIRI may provide a better reflection of the long-term inflammatory status of HF. Neutrophils fulfil a crucial role in coordinating the inflammatory response of the immune system and host defense [17]. Circulating monocytes infiltrate the heart soon after myocardial injury, contributing to repair processes and inflammation. This pathophysiological condition indirectly influences left ventricular remodelling [12]. Lymphopenia has been demonstrated as an independent prognostic indicator of HF mortality [18]. Notwithstanding, these factors alone may not be adequate as markers of inflammation.

SIRI and SII are affordable and extensive markers for inflammation. They can be used to identify inflammation with ease. A research study on elderly patients with HF revealed that higher SIRI values are an independent factor linked with mortality within 90 days. Furthermore, an association was found between elevated SIRI and increased duration of hospital stay and intensive care unit admission [19]. In a recent cohort study consisting of 85,154 participants, researchers examined the correlation between the novel inflammation markers SIRI and SII and mortality rates for cardiovascular diseases over a decade. The study found that both indices were linked to a higher risk of stroke and all-cause mortality [20]. Furthermore, an elevated SII score resulted in a relative increase in neutrophil and platelet counts and a reduction in lymphocyte count, potentially associated with an inflammatory response [21].

However, in patients with HF, neutrophils may become activated and release considerable quantities of proinflammatory cytokines and oxidative stress substances, which can contribute to the advancement of cardiovascular disease and the emergence of HF [21]. Prior research carried out using different methodologies and for different target populations has demonstrated a correlation between SII and cardiovascular diseases and metabolic syndrome [22]. Recently, Peng and colleagues investigated the prognostic role of SII in older patients who underwent percutaneous coronary intervention for acute myocardial infarction (AMI). They concluded that SII might serve as a potential prognostic biomarker for AMI patients [23]. Likewise, another study examined the ability of SII to predict long-term clinical outcomes in patients with coronary artery disease (CAD). In this study, 5,602 patients with coronary artery disease who received percutaneous coronary intervention were monitored for major adverse cardiac events (MACE). The findings indicated that patients displaying a high systemic immune-inflammation index (SII) (≥694.3 cut-off value) experienced an increased risk of suffering from cardiac death, non-fatal myocardial infarction, non-fatal stroke, MACE, and total major events [24]. SIRI and SII were significantly associated with the risk of mortality in HF patients, and SIRI has been shown to provide better prognostic discrimination than C-reactive protein. Compared with patients in the lowest quartile of SIRI in this study, patients in the highest quartile exhibited a 134% higher risk of in-hospital mortality (adjusted odds ratio, 2.34; 95% confidence interval [CI], 1.16-4.72) and a 45% higher risk of long-term mortality (adjusted hazard ratio, 1.45; 95% CI, 1.25-1.67) [25]. A recent study found that SIRI may be a promising new inflammatory biomarker for predicting all-cause mortality in elderly patients with HF, and patients with higher SIRI values had longer hospital or intensive care unit stays. Moreover, this study also confirmed a statistically significant positive correlation between SIRI and the inflammatory marker CRP, highlighting the importance of systemic inflammation as a determinant of outcome in HF patients [26] Ma et al. found that SIRI may be a new, promising inflammatory marker for the prognosis of HF patients undergoing percutaneous coronary intervention [26].

Although HF is typically viewed as the final stage of diverse cardiovascular diseases, it is crucial to take note

of the potential disparities in pathological mechanisms [27]. There is a lack of research regarding the correlation of HF and SII in the literature. Recently, a comprehensive study with 48,154 participants found a positive correlation between HF and SII levels. The study discovered that SII < 1104.78 was significantly linked to a lower risk of HF incidence at a cut-off value of 1104.78, which supports the hypothesis that SII can reduce the risk of HF [28]. Additionally, Yuan et al. conducted a study on HF patients to assess the predictive value of SII for mortality. Mortality risk was monitored at 30, 60, 180, and 365 days after admission to intensive care in 9,174 patients. The study found that mortality risk was different for HF patients at various levels of SII and time points [29].

Our study has some limitations. The first of these is that it was designed retrospectively and single-centered. Since the study date covers the period during and after the COVID-19 pandemic, we are aware that the number of patients followed decreased compared to previous years and does not adequately demonstrate the importance of the study. We acknowledge that inflammation parameters such as SIRI and SII are parameters that may require dynamic monitoring and that we have important limitations such as the time of admission and the monitoring of inflammation parameters during hospitalization. Multicenter, prospective studies are needed to show that these parameters are effective markers of mortality.

CONCLUSIONS

Based on the results of our study, it can be concluded that SIRI and SII are easily applicable markers that can be used as indicators of in-hospital mortality in HF patients. These findings suggest that SIRI and SII have the potential to be valuable and easily implementable biomarkers for predicting in-hospital mortality in HF patients.

ABREVIATIONS

AMI- acute myocardial infarction

BNP- brain natriuretic peptide

CAD- coronary artery disease

CRP- C-Reactive protein

HF- Heart Failure

MACE- major adverse cardiac events

NYHA- New York Heart Association

ROC- receiver operating characteristic

SII- systemic immuno-inflammation index

SIRI- systemic inflammatory response index

WBC: White Blood Cell

AUTHORS' CONTRIBUTION

CB – conceptualization, methodology, writing the original draft and reviewing it for important intellectual content

FS – data acquisition, analysis, and interpretation; writing the original draft

OZ – data acquisition, analysis, and interpretation, writing the original draft

GY – data acquisition, analysis, and interpretation; writing the original draft

YFY – conceptualization, methodology, writing the original draft and reviewing it for important intellectual content

All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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