S22222

By murat özmen

WORD COUNT 2097
TIME SUBMITTED 24-NOV-2024 11:46AM
PAPER ID 113123038

Abstract

Background : The systemic immune-inflammation index (SII), a novel marker derived from the combination of platelet, neutrophil, and lymphocyte counts, has been linked to unfavorable clinical outcomes in various malignancies and inflammatory conditions. This study aims to assess the association between SII and disease prognosis in patients with heart failure with reduced ejection fraction (HFrEF).

Methods: A total of 521 patients (72% male; mean age: 67.4 ± 13.5 years) diagnosed with HFrEF were retrospectively analyzed. Clinical, demographic, laboratory, and echocardiographic data were collected. SII scores were calculated for all patients, and their prognostic significance and clinical outcomes were evaluated.

Results : 521 patients were analyzed. According to current findings, all-cause mortality occurred in 86 patient during the follow-up period. The mean SII in the mortality group was higher than in the survivors and was found to be statistically significant. (878.57 vs 643.65; p=0.003, respectively) In the multivariable regression model SII was found to be an independent risk factor for mortality. (p = 0.031) The AUC of SII for mortality prediction was 0.602 (95% CI = 0.531-0.673), the cut-off value was 729, and the sensitivity and specificity were 59.3% and 59.6% (p = 0.003)

Conclusion: This study demonstrates a significant association between SII and both survival and prognosis in patients with HFrEF. Notably, the SII index was found to be an independent predictor of mortality in this patient population.

Introduction

The condition in which cardiac output cannot meet the metabolic and perfusion needs of various tissues and organs is known as heart failure with low ejection fraction (HFrEF). This condition is accompanied by clinical findings such as dyspnea, congestion, and decreased activity tolerance.[1] More than 1 million patients diagnosed with heart failure are hospitalized in the United States and Europe. This is a significant condition that increasingly threatens human health. As human life expectancy increases, the incidence of heart failure is expected to increase by more than 50 percent in the future. Early detection of high-risk patients, more aggressive treatment measures, and development of new biomarkers that can assist in the clinical management of patients are of vital importance.[3]

Abnormal immune activation and persistent inflammation are central to the pathophysiology of heart failure.[4] Repair and remodeling are fundamental processes following myocardial damage in the initiation and progression of heart failure. Immune and inflammatory cells such as neutrophils and lymphocytes play critical roles in these stages, along with inflammatory mediators such as tumor necrosis factor (TNF) and interleukin-6 (IL-6).[4] These inflammatory mediators lead to cardiomyocyte hypertrophy, apoptosis and fibrosis, which may lead to adverse cardiac remodeling and progressive left ventricular dysfunction.[5] Consequently, inflammatory markers have been associated with poor prognosis in heart failure, and anti-inflammatory therapies are being explored as potential treatment strategies.[6]

The systemic immune-inflammation index (SII) is a composite marker derived from neutrophil, lymphocyte, and platelet counts, reflecting both local immune responses and systemic inflammation.[7] Lymphocytes are primarily associated with specific immune pathways, whereas neutrophils and platelets produce cytokines associated with nonspecific immune responses. SII has a very important role in reflecting the inflammatory status compared to individual immune cells. To date, it has been confirmed that SII is associated with poor prognosis of some cardiovascular diseases (aortic stenosis, infective endocarditis, etc.), including coronary artery disease.[8-10] This study aimed to evaluate SII in patients with reduced ejection fraction heart failure (HFrEF) and to

investigate the relationship of this index with accompanying comorbidities and prognosis of the disease.

Materials and Methods

Our study was conducted in the Cardiology Clinic of Erzurum City Hospital. Data were collected retrospectively from patients who applied to our outpatient clinic between January 2021 and December 2021. Patients over the age of 18 diagnosed with HFrEF and patients whose hemogram biochemistry and transthoracic echocardiography (TTE) results could be accessed in the hospital automation system were included in the study. Patients with a history of malignancy, active infection, and chronic inflammatory diseases were excluded from the study. The patients' CVs were also obtained from the data in the hospital system. SII was calculated with the formula platelet count x neutrophil count/lymphocyte count.[10] Mortality due to cardiovascular causes was recorded after 1 year.

Laboratory analyses were performed using standardized clinical systems. Hemogram values were measured using the Sysmex XN-1000 Clinical System, while biochemical biomarkers were analyzed with the BECKMAN COULTER AV 5800 Clinical System. Troponin levels were determined using the BECKMAN COULTER DXI-600 Clinical System.

Transthoracic echocardiography was performed by placing the patients slightly on the left side and obtaining appropriate apical four-chamber images. Images in which the left ventricle was smallest and widest during systole and diastole were detected. Left ventricule (LV) end-systolic and end-diastolic volumes and EF were automatically calculated according to the modified Simpson's rule.

Data were analyzed with IBM SPSS V27. Compliance with normal distribution was examined with Kolmogorov-Smirnov and Shapiro-Wilk tests. Mann Whitney U test was used to compare data that were not normally distributed according to binary groups. The relationship between non-normally distributed quantitative variables was examined with Spearman's rho correlation coefficient. Analysis results were presented as mean ± standard deviation and median (minimum – maximum) for quantitative variables, and as frequency and percentage for categorical variables. Using SII as a diagnostic test to

predict HFrEF mortality, specificity and sensitivity values were calculated using the receiver operating characteristics (ROC) analysis. The significance level was accepted as p<0.05.

Results

A total of 521 patients were enroled the study. 72 % of the patients were male, and the average age of all patients was 67 ± 13.5. Comorbidities of the patients and mortality rates during follow-up are given in Table-1.

Laboratory and demographic characteristics of patients who did or did not develop mortality during follow-up are listed in Table-2. According to the this, a meaningful difference was observed between the groups in age, hemoglobin, platelets, lymphocyte, C-reactive protein (CRP), creatinin, albumin, uric asid, Low-Density Lipoproteine (LDL), calcium and SII.

In the univariate analysis, increase in age (Odds Ratio (OR)=1.060; p=<0.001), SII level (OR=1.000; p=0.001), creatinine (OR=1.556; p<0.001), calcium (OR=0.514; p=<0.001) and EF (OR=0.963 ; p=0.012) were determined as possible risk factors for mortality. In the multivariable regression model, in which possible risk factors were included age (OR=1.066; p<0.001) and SII (OR=1.000; p = 0.031) was found to be an independent risk factor for mortality.(-2 Log-Likelihood: 157,001 Nagelkerke R2 :0.27; p = <0.001) (Table-3)

ROC analysis was used to examine the ability of SII to discriminate mortality. The area under the curve (AUC) of SII was 0.602 (95% CI = 0.531-0.673), the cut-off value was 729, and the sensitivity and specificity were 59.3% and 59.6% (p = 0.003). The AUC values are shown in Figure-1.

In multivariable Cox regression, SII was independently associated with a increased risk of mortality.(p = 0.006) In the survey analysis, patients were divided into equal percentiles according to SII values. Data showing high mortality, especially in the group with high SII, in the survival analysis.(For percentile 5 (SII 1348-9532) HR: 2.065(1.107-9.851)) (Figure -2)

Discussion

Despite recent advances in drug therapy and mechanical device support treatments, chronic heart failure (CHF) remains one of the most common causes of hospitalization. Its incidence and prevalence are increasing[11]. In the west, CHF is the most common cause of hospitalization and death, especially in elderly patients[12]. New mechanisms for the treatment of CHF need to be investigated, thus improving survival and slowing the disease. The relationship between the development and progression of CHF and the immune system is known. There is an imbalance between pro-inflammatories and anti-inflammatories in CHF. Monocyte/HDL-C ratio played an important role in indicating multivessel disease. Many inflammatory markers such as this have been associated with cardiovascular diseases.[13]

The systemic immune-inflammation index (SII), which combines neutrophil, lymphocyte, and platelet counts into a single parameter, provides a sensitive measure of systemic inflammation. This comprehensive approach has gained significant interest among cardiologists, as studies have shown that SII is more effective than the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in assessing inflammatory status in cardiovascular diseases. [14-15] In our study, SII was significantly higher in patients who died of heart failure ($p = 0.003$).

SII, an independent predictor of cardiovascular endpoints, has recently been the subject of many studies.[16-18] In the study conducted on patients in whom fractional flow reserve (FFR) was measured, it was determined that it was hemodynamically superior to PLR and NLR in predicting SII coronary stenosis.[16] Additionally, SII was found to be an independent predictor of contrast nephropathy in patients with severe aortic stenosis who underwent aortic valve implantation.[19]

Recently identified as a new indicator of inflammation, SII is an easy, inexpensive and routine test that provides accurate and reliable information about parameters such as red blood cells, neutrophils, platelets and lymphocytes.[20] SII can be considered as a combination of NLR and PLR, so it is calculated by the formula platelet count x neutrophil count/lymphocyte count[20]. In recent studies, SII is a strong independent

predictor of major adverse events and prognosis in patients with malignancy. In our study, the SII value, which can be easily used in clinical practice, was found to be statistically significant with the mortality of heart failure patients (p = 0.003). In our study, SII was observed as an independent predictor of mortality. (p=0.04)

Atherosclerosis, a chronic inflammatory condition, has been shown in previous studies to be closely linked to inflammatory processes.[21] In recent years, it has been shown that markers such as neutrophil-lymphocyte ratio and platelet-lymphocyte ratio are indicators of inflammation and that they are related to atherosclerosis.[22,23] Similarly, in our study, platelet, neutrophil and lymphocyte values and SII values, which is an inflammation marker, were calculated and were shown to be associated with coronary artery disease by causing atherosclerosis. There are studies in the literature that associate SII with the severity and prognosis of coronary artery disease(CAD).[8,24] Our study supports existing studies. In our study, statistical significance was found between CAD and SII (P<0.001). Especially in our study, SII was found to be statistically significant in patients with hypertension, AF, diabetes, and cardıovascular dıseases (CVD).

CHF has the highest rates of hospitalization and death in the world, and this condition tends to increase with age and continues to be an increasingly costly condition in developed countries.[25] In addition to improving prognosis in diseases that cause financial burden such as CHF, new treatment research for patient risk stratification will have significant impacts. N-terminal proBNP (NT-proBNP), a widely used laboratory parameter in CHF, is good for prognosis, but it has some disadvantages in risk assessment, such as having a half-life and being affected by age and gender.[26] Therefore, the investigation of different biomarkers and the studies conducted on these biomarkers have been the focus of researchers. The results of the studies have shown that SII is an independent biomarker of short-term poor prognosis of CHF. Inflammation, which has an important place in the development of heart failure, also plays an important role in the pathophysiology of heart failure.[27] Our study supported existing studies. Increased and activated inflammation-related cytokines play an important role as a poor prognostic indicator in heart failure. Cytokines such as tumor necrosis factor α (TNF-α), Interleukin-6 (IL-6) are significantly higher in the serum of patients with heart failure and may help early diagnosis of heart failure with their various features.[28-30] Although these parameters have a good place in prognostic evaluation, their in-hospital use is limited due to their

high costs. SII is a new biomarker that is simple, fast, cheap and systematically reflects in vivo inflammatory conditions. A routine blood test for hospitalized or outpatient patients is a routine evaluation for almost all patients. SII can improve the prognosis of patients by identifying high-risk patients and planning treatment without additional costs compared to NT-proBNP, cytokines and other prognostic parameters. Finally, this study could not fully elucidate the mechanism underlying the relationship between high SII and poor prognosis of CHF patients. New studies in larger study series are needed to elucidate this mechanism.

Limitations

Despite the strengths of our study, there are some limitations to acknowledge. The study was conducted in a single-center setting and relied on data obtained through chart review. Additionally, as it was a retrospective analysis, data were missing for other inflammatory markers, limiting our ability to compare the systemic immune-inflammatory index with these markers. Another limitation is the exclusion of patients with heart failure with preserved ejection fraction, which may impact the generalizability of the findings.

Conclusion

High SII levels are strongly associated with poor short-term outcomes in patients with CHF, including increased in-hospital all-cause mortality. Given its simplicity and efficacy, SII serves as a practical prognostic tool for routine clinical use in patients with heart failure.

S22222

ORIGINALITY REPORT

25%
SIMILARITY INDEX

PRIMARY SOURCES

1	dergipark.org.tr Internet	63 words — 3%
2	www.medrxiv.org Internet	62 words — 3%
3	Faruk Aydınyılmaz, Nail Burak Özbeyaz, İlkin Guliyev, Engin Algül, Haluk Furkan Şahan, Kamuran Kalkan. "Effect of Atherogenic Index of Plasma on Pre-Percutaneous Coronary Intervention Thrombolysis in Myocardial Infarction Flow in Patients With ST Elevation Myocardial Infarction", Angiology, 2023 Crossref	38 words — 2%
4	www.frontiersin.org Internet	37 words — 2%
5	Metin Cagdas, Aziz Inan Celik, Tahir Bezgin, Nart Zafer Baytugan et al. "Predictive value of P wave parameters, indices, and a novel electrocardiographic marker for silent cerebral infarction and future cerebrovascular events", Journal of Electrocardiology, 2023 Crossref	31 words — 1%
6	www.jpedres.org Internet	31 words — 1%

7	Yiyang Tang, Xiaofang Zeng, Yilu Feng, Qin Chen, Zhenghui Liu, Hui Luo, Lihuang Zha, Zaixin Yu. "Association of Systemic Immune-Inflammation Index With Short-Term Mortality of Congestive Heart Failure: A Retrospective Cohort Study", Frontiers in Cardiovascular Medicine, 2021 Crossref	26 words — 1%
8	Seda Karakaya Çataldaş, Fatma Atkan, Ayşe Eminoğlu. "The effect of psychodrama-based intervention on therapeutic communication skills and cognitive flexibility among nursing students: A 12-month follow-up study", Nurse Education in Practice, 2024 Crossref	24 words — 1%
9	Muhammet Fatih Topuz, Nurullah Ture, Gonul Akdag, Ozlem Arik, Pinar Yildiz Gulhan. "The importance of systemic immune-inflammation index in obstructive sleep apnea syndrome", European Archives of Oto-Rhino-Laryngology, 2022 Crossref	22 words — 1%
10	acamedicine.org Internet	18 words — 1%
11	d2v96fxpocvxx.cloudfront.net Internet	17 words — 1%
12	jcancer.org Internet	14 words — 1%
13	journals.lww.com Internet	14 words — 1%
14	www.researchsquare.com Internet	14 words — 1%

15	lib.ossn.ru Internet	13 words — 1%
16	www.mdpi.com Internet	13 words — 1%
17	doaj.org Internet	12 words — 1%
18	ijcmbs.com Internet	11 words — < 1%
19	www.seruvenyayinevi.com Internet	11 words — < 1%
20	hub.tmu.edu.tw Internet	10 words — < 1%
21	journals.plos.org Internet	10 words — < 1%
22	mirt.tsnmjournals.org Internet	10 words — < 1%
23	www.pubfacts.com Internet	10 words — < 1%
24	www.science.gov Internet	9 words — < 1%
25	DILEK MENTESOGLU, NILGÜN ATAKAN. "The association between Behçet disease activity and elevated systemic immune–inflammation index: A retrospective observational study in a tertiary care hospital", The National Medical Journal of India, 2024 Crossref	8 words — < 1%

26	R Lee. "Functional and prognostic implications of left ventricular contractile reserve in patients with asymptomatic severe mitral regurgitation", Heart, 2005 Crossref	8 words — < 1%
27	Tatum, Sean Michael. "Cardiomyocyte Ceramides Drive Heart Failure and Cardiometabolic Dysfunction", The University of Utah, 2024 ProQuest	8 words — < 1%
28	www.ncbi.nlm.nih.gov Internet	6 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	OFF