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Orgınal Article

The Prognostic Role of the Systemic Inflammatory Index (SII) in Heart Failure Patients

Kalp Yetmezliği Hastalarında Sistemik İnflamatuvar İndeksin (SII) Prognostik Rolü

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Abstract

Background: The prevalence of heart failure (HF) is increasing worldwide with new treatment methods (percutaneous, medical) that improve survival in heart diseases. Inflammation plays a central role in the development of HF, and many inflammatory markers have been studied to determine HF survival. In this study, we aimed to investigate the relationship between Systemic Immune-Inflammation Index and survival in patients with HF.

Material Method: A total of 672 HF were included in this retrospective and observational study. The primary end-point of the study was all-cause mortality. The median follow-up duration of the study patients was 21 (8-42) months.

Results : 672 patients were analyzed, and all-cause mortality developed in 278 of these patient groups during the follow-up period. The number of all-cause mortality was 113 (34%) in the low SII group, and the number of all-cause mortality was 165 (49%) in the high SII group.

Conclusion: This is the first and only study in the literature showing the relationship between the SII index and survival in patients with HF. In addition, the main finding of our study is that the SII index is an independent predictor of mortality in patients with HF.

Keywords: Systemic immune-inflammation index, heart failure, inflammatory markers

ÖZ

Amaç: Kalp hastalıklarında sağkalımı artıran yeni tedavi yöntemleri (perkütan, medikal) ile kalp yetersizliği (KY) prevalansı dünya çapında artmaktadır. Enflamasyon, KY gelişiminde merkezi bir rol oynar ve KY sağkalımını belirlemek için birçok inflamatuar belirteç incelenmiştir. Bu çalışmada KY hastalarında Sistemik İmmün-İnflamasyon İndeksi (SII) ile sağkalım arasındaki ilişkiyi araştırmayı amaçladık.

Materyal ve Metod: Bu retrospektif ve gözlemsel çalışmaya toplam 672 KY dahil edildi. Çalışmanın primer sonlanım noktası, tüm nedenlere bağlı ölümlerdi. Çalışmaya alınan hastaların median takip süresi 21 (8-42) aydı.

Bulgular:672 hasta analiz edildi ve bu hasta gruplarının 278' inde takip süresince tüm nedenlere bağlı ölüm gelişti. Düşük SII grubunda tüm nedenlere bağlı ölüm sayısı 113 (%34), yüksek SII grubunda tüm nedenlere bağlı ölüm sayısı 165 (%49) idi.

Sonuç: Literatürde KY' li hastalarda SII indeksi ile sağkalım arasındaki ilişkiyi gösteren ilk ve tek çalışmadır. Ayrıca çalışmamızın ana bulgusu, SII indeksinin KY hastalarında mortalitenin bağımsız bir göstergesi olduğudur.

Anahtar Kelimeler: Sistemik immün-inflamasyon indeksi, kalp yetmezliği, inflamatuar belirteçler

Highlights

- SII may have prognostic significance in the follow-up of HF patients.

INTRODUCTION

The prevalence of heart failure (HF) is increasing worldwide with new treatment methods (percutaneous, medical) that increase survival in heart diseases(1-3). Despite the development of new medical and mechanical treatments, 5-year mortality due to HF exceeds that of many cancers by 42-60%(4-6). Inflammation plays a central role in HF development, and many inflammatory markers have been studied to determine HF survival(7-11). Inflammation-related biomarkers have gained a particular interest in the cardiovascular era(7, 12-15).

The Systemic Immune-Inflammation Index (SII) consists of a combination of 3 inflammatory parameters (neutrophils, lymphocytes, and platelets) and can be calculated based on a complete blood count (CBC)(16). In addition, the SII is a strong prognostic indicator of adverse outcomes in various types of cancer(17, 18). In addition, SII was demonstrated to predict mortality in infective endocarditis and coronary artery disease(19, 20). In recent years, it has been shown that SII is associated with mortality in coronary artery disease, valve disease and myocardial infarction(20-23).

In this study, we aimed to identify the relationship between SII and survival in patients with HF.

Materials and Methods

Study Design and Systemic Immune-Inflammation Index (SII)

A total of 672 HF were included in this retrospective and observational study. SII was determined as absolute platelet count × absolute neutrophile count/lymphocyte count(20). The SII value of all patients was calculated, and the median value was calculated. The patient group with more than the median value constituted the high SII group, while the group with less than the median value formed the low SII group. The primary end-point of the study was all-cause mortality. The median follow-up duration of the study patients was 21 (8-42) months. The patients were split into two groups during the follow-up period: those with all-cause mortality and those without The patients were split into two groups during the follow-up period: those with all-cause mortality and those without all-cause mortality. Cumulative survival rates were determined by the Kaplan-Meier analysis and compared between the two groups using the log-rank test. The clinical and laboratory characteristics linked to heart failure mortality were analyzed using the Cox proportional hazard model.

Statistics analysis

All analyses were carried out using IBM SPSS Statistics for Macintosh, Version 26.0 (IBM Corp., Armonk, New York, USA). During the follow-up period, patients were divided into two groups as those who developed all-cause mortality and those who did not. Kolmogorov–Smirnov test was used to determine the distribution of numerical variables. The Student's t-test was implemented to the continuous variables, which conforms to the normal distribution, and the results were presented as mean and standard deviation. Conversely, the Mann-Whitney-U test was performed for the non-normal distributed variables. According to the results of this test, the median and interquartile range values were given. The Chi-squared test was applied for categorical variables, and data presented as numbers and percentages. Cumulative survival rates were determined by the Kaplan-Meier analysis and compared between the two groups using the log-rank test. Kaplan-Meier analysis was performed for the two groups according to the median SII value. Comparisons between groups were made according to the Log-rank test. Cox proportional hazard model was applied to clinical and laboratory features which are thought to be related to mortality for heart failure. The significance level of the results obtained was interpreted with the P value at the 95% confidence interval. A P value of < 0.05 was considered statistically significant.

Results

After the application of exclusion criteria, finally, 672 patients were analyzed, and all-cause mortality developed in 278 of these patient groups during the follow-up period (Table 1). The median SII value of the patients was calculated as 666 x 10^3. Mortality rates in the two groups constructed based on this value were compared. The number of all-cause mortality was 113 (34%) in the low SII group, and the number of all-cause mortality was 165 (49%) in the high SII group (Figure 1). Median survival time in the whole study population was 59 (42-77, 95% CI) months**,** whereas median survival time in the low and high SII groups was 85 months (54-117, 95% CI), 42 months (29-55, 95% CI) respectively (P<.001) (Figure 2). The male gender was statistically significantly higher in the mortality group (288 (53%) vs. 254 (91%)) . In addition, while left ventricular ejection fraction (20 (18-26) vs. 20 (15-22)) was found to be lower in the mortality group, systolic pulmonary artery pressure was 42 (35-54) vs. 48 (40-58)) and functional capacity class was higher in the mortality group (P<.001 in all

parameters). Urea nitrogen, NT-proBNP, and SII were significantly higher in the mortality group (P<.001 in all parameters). Time-dependent Cox regression analysis revealed that a high SII (≥666x10^3) level was found to be an independent predictor of mortality (Table 2).

Table 1. Baseline characteristics of study populations

Variables (n=672)	**All-Cause Mortality**		
	Without event (n= 394)	**With event (n= 278)**	**P value**
Demographic and clinical features			
Age (years)	49 (39-54)	50 (41-57)	.014
Gender (male)	288 (53%)	254 (91%)	<.001
Diabetes mellitus (n=600)	92 (27%)	71 (27%)	.815
Hypertension (n=651)	56 (15%)	36 (13%)	.535
Atrial fibrillation (n=657)	129 (34%)	80 (29%)	.355
Implantable cardiac defibrillator (n=670)	306 (78%)	196 (70%)	.026
Etiology (ischemic) (n=661)	141 (37%)	97 (35%)	.611
Left ventricular ejection fraction (%)	20 (18-26)	20 (15-22)	<.001
Systolic pulmonary artery pressure (mmHg)	42 (35-54)	48 (40-58)	<.001
NYHA (New York Heart Association) functional capacity class			<.001
Class I	63 (16%)	18 (6%)	
Class II	157 (40%)	65 (23%)	
Class III	140 (36%)	110 (40%)	
Class IV	34 (8%)	85 (31%)	
Laboratory findings			
Glucose (mg/dl)	102 (90-123)	99 (88-116)	.027
Urea nitrogen (mg/dl)	40 (31-51)	48 (37-66)	<.001
Creatinin (mg/dl)	1.06 (0.87-1.25)	1.03 (0.86-1.16)	.066
Aspartate transaminase (SGOT) (U/L)	23 (18-30)	27 (20-35)	<.001
Alanine transaminase (SGPT) (U/L)	21 (16-32)	25 (16-41)	.009
Total bilirubin (mg/dl)	0.92 (0.59-1.54)	1.59 (0.92-2.40)	<.001
NT-proBNP (pg/mL) (n= 387)	903 (284-2467)	1605 (722-4090)	<.001
Hemoglobin (g/dL)	13.9±1.9	13.1±1.9	<.001
Hematocrit (%)	43.1±5.5	40.9 ± 5.5	<.001
White cell count (10^3/mm^3)	8.20 (6.88-9.40)	7.82(6.69-9.25)	.111
Neutrophil count (10^3/mm^3)	5.17 (4.01-6.30)	5.20 (4.37-6.40)	.138
Lymphocyte count (10^3/mm^3)	1.90 (1.44-2.40)	1.60 (1.26-2.10)	<.001
Platelet count (10^3/mm^3)	229 (190-280)	220 (180-272)	.111
Systemic immune-inflammation index (x10^3)	607 (420-919)	732 (499-1068)	<.001

Table 2. Time dependent Cox-regression analysis for all-cause mortality

Variables	**All-cause mortality**		
	Hazard ratio	**95% CI**	**P value**
Age	1.02	1.01-1.03	.002
Gender	1.39	0.85-2.29	.414
Left ventricular ejection fraction, %	0.95	0.92-0.97	<.001
Ischemic cardiomyopathy	0.88	0.67-1.16	.362
Diabetes mellitus	0.81	0.61-1.08	.156
Hypertension	1.01	0.69-1.47	.972
Implantable cardiac defibrillator	0.73	0.55-0.97	.028
Aspartat transaminase	1.01	1.00-1.01	<.001
High SII (≥666x10^3)	1.51	1.19-1.92	.001

SII= Systemic immun-inflammtion index

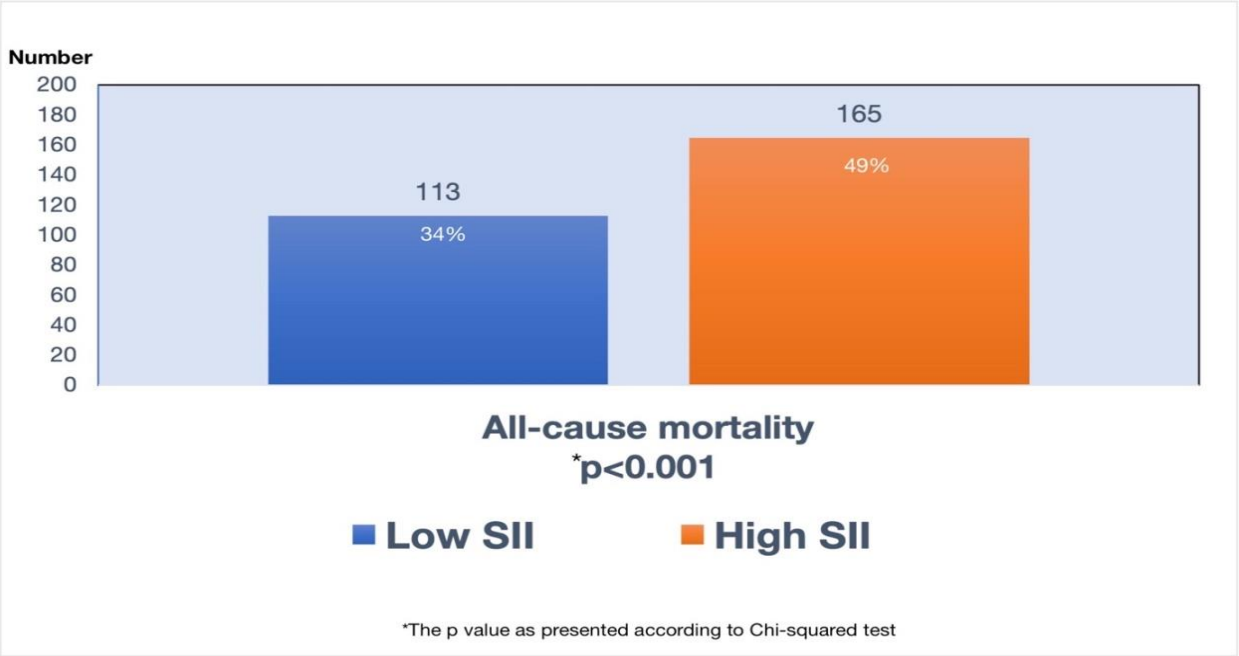

Figure 1. Number of all-cause mortality in both groups.

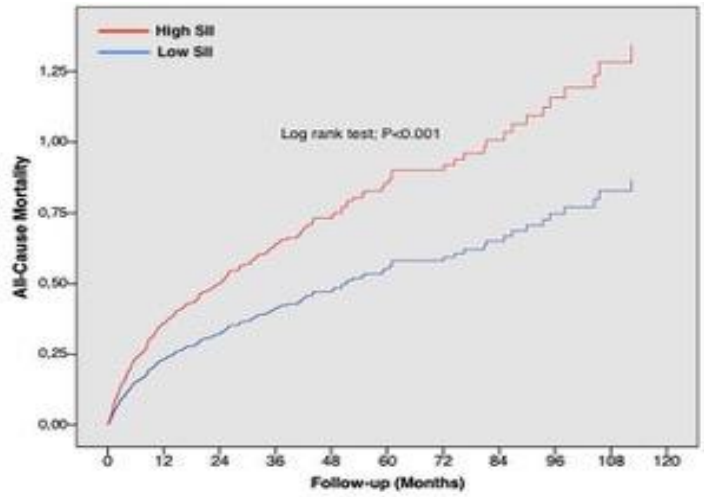

Figure 2. Kaplan meier survival analysis

Discussion

As far as we are concerned, this is the first and only study that has assessed the relationship between the SII index and survival in HF patients. In addition, the main finding of our study is that the SII index is an independent predictor of mortality in patients with HF.

HF is the final common path of all heart diseases, rising in incidence and prevalence, and to a pandemic (24). Despite the many advances in the current pharmacotherapy and mechanical device therapy strategies, HF remains one of the most common causes of hospitalization. It is the most important cause of hospitalization and death in elderly patients in Western countries (12). Therefore, it seems necessary to investigate new pathophysiological mechanisms for possible new opportunities in the treatment of HF, thereby improving survival and slowing disease progression. The immune system's role in the development and course of HF has been determined. In HF, there is an imbalance between several proinflammatory and anti-inflammatory markers. In the past decade, many inflammatory markers have been associated with cardiovascular disease. Toprak et al. showed that the monocyte/HDL-C ratio could predict multivessel disease in patients with the acute coronary

syndrome (25). Interleukin-33 levels are elevated in HF patients, according to research by Segiet et al.(12). Similar to this, Traxler et al. shown that sST2 (soluble suppression of tumorigenicity 2), HSP27, and hs- CRP may be used to predict cardiovascular mortality and HF hospitalization(26). Kuster et al. emphasized that sST2 and growth differentiation factor-15 (GDF-15) may help evaluate the prognosis in patients with HF (27).
The immunothrombosis model provides evidence of balanced interactions between the immune and coagulation systems(28). The SII, an inflammation marker that has emerged in recent years, was developed to simultaneously assess patients' inflammatory and immunothrombotic status based on platelet count and neutrophil-to-lymphocyte ratio (NLR) The SII was initially thought to be a prognostic indicator for various malignancies(17, 29). Thanks to the combination of three inflammatory parameters (neutrophile, lymphocyte, and platelet) in a single index, SII can be considered a sensitive parameter in predicting inflammatory conditions in the patient. This has attracted the attention of cardiologists, and several studies have shown that it is superior to NLR and platelet-to-lymphocyte ratio (PLR) alone in determining the inflammatory state of cardiovascular diseases(30-36). The SII index has been the subject of numerous recent studies since it has proven to be an independent predictor of numerous unfavorable cardiovascular outcomes(20-22, 37). Erdogan et al.'s study on fractional flow reserve (FFR) in patients with chronic coronary syndrome revealed that the SII was superior to the NLR and PLR in predicting hemodynamically severe coronary stenosis(20). The authors of this study found in a recent study that in patients undergoing transcatheter aortic valve implantation for severe aortic stenosis, SII is an independent predictor of postprocedural contrast nephropathy(16). Similarly, the findings of this study demonstrated that SII is an independent predictor of survival in HF patients.

Limitations

Apart from the mentioned strengths of our study, it had some limitations because it was a single-center and recorded by file scanning. In addition, due to the retrospective study, missing data on other inflammatory markers could not be reached, which prevented us from comparing SII with other inflammatory markers. Another limitation of our study is that patients with heart failure with preserved ejection fraction were not included in the study.

Conclusion

To the best of our knowledge, this is the first and only study to evaluate the relationship between SII and survival in patients with heart failure. A high SII level is an independent predictor of mortality in patients with HF. The complete blood count is a readily accessible, inexpensive, routine examination that provides correct and reproducible information.

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