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The predictive role of systemic immune-inflammation index in non-ischemic cardiomyopathy

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ABSTRACT

Aims: The systemic immune-inflammation index (SII), a useful marker of systemic inflammation, has been shown to be associated with cardiovascular diseases in previous studies. Inflammation is known to have a significant role in heart failure, but no study has evaluated the relationship between inflammatory parameters and prognosis in patients with non-ischemic cardiomyopathy (NICM). This study aimed to explore the relationship between SII and long-term mortality in patients with non-ischemic cardiomyopathy.

Methods: The study enrolled 326 consecutive patients with NICM. The median 25-month follow-up mortality results of the patients were recorded retrospectively. SII, a combined index based on the count of three parameters, was calculated as follows: neutrophil count x platelet count/lymphocyte count. Patients with a higher SII value than the median SII were accepted as having a high SII, and the remaining patients were defined as having a low SII. The survival curves of the patients with high and low SII values during the study period were analyzed using the Kaplan-Meier method.

Results: The mean age of the participants was 46.6 years. The mean SII value was 598.4 in patients without mortality and 722.7 in those with mortality. In the multivariate logistic regression analysis, SII was found to be an independent predictor of mortality. The median SII value of the patients who participated in the study was 644. Upon dividing the patients into two groups according to the median SII value, the mortality rate was determined to be 48.4% in the high SII group and 27.4% in the low SII group.

Conclusion: High SII values were observed to be associated with long-term mortality in patients with NICM. SII, which is easily accessed and simply calculated, can be used to predict mortality risk in these patients. Prospective and larger cohort studies are needed to clarify the causality of this relationship.

Keywords: Heart failure, non-ischemic cardiomyopathy, systemic immune-inflammation index

INTRODUCTION

Non-ischemic cardiomyopathy (NICM) is a myocardial disease characterized by left ventricular dilatation and contractile dysfunction in the absence of previous myocardial infarction, pathologies obstructing coronary blood flow, and valvular disease associated with systolic dysfunction.[1,2] The incidence of NICM in the general population varies between 1/2,500 and 1/250.[3] Both genetic and environmental factors are involved in the etiopathogenesis of NICM, and the end point is systolic dysfunction with dilatation.[4] The most common symptoms in patients are circulatory disorders due to heart failure (HF), arrhythmias, and thromboembolic events.[5] NICM is more common in middle-aged individuals and men, and it is among the common causes of heart transplantation, especially in Western societies.[6,7] In recent years, favorable improvements in terms of survival have been observed due to advances in diagnosis, classification, and treatment methods (pharmacological, mechanical support, and heart transplantation).[8] Nevertheless, the risk of HF, ventricular arrhythmias, and related mortality is not low in this patient group, with a 10-year survival rate lower than 60%.[4,6,9,10] Risk stratification in patients with NICM is essential in predicting poor clinical outcomes. Therefore, it is important to investigate markers that will detect poor clinical outcomes at an earlier period and implement preventive treatment.

Patients with NICM, contrary to those with ischemic cardiomyopathy, are younger and have fewer comorbidities. Therefore, age and comorbidity have less effect on poor clinical outcomes in these patients,[10] and survival is more related to the aggravation of HF and the

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associated conditions.[9,10] Previous studies have shown that several parameters, such as low left ventricular ejection fraction (LVEF) and high brain natriuretic peptide (BNP) levels are associated with a poor prognosis.[10,11] However, there is limited data showing that some systemic inflammatory parameters are also associated with poor clinical outcomes in patients with NICM. Several studies conducted with these patients have shown a relationship between the degree of myocardial disease and biochemical parameters indicating an inflammatory response, such as C-reactive protein (CRP), C3 and C4 complement, and ceruloplasmin.[12,13] In addition, high CRP values have been associated with poor survival in these patients.[14] In recent years, the systemic immune-inflammation index (SII), which is a much better and easily accessible and calculable biochemical marker of systemic inflammation, has been investigated in various cardiovascular diseases. SII can be simply derived from the counts of neutrophils, lymphocytes, and platelets. These three immune cells are collected via a hemogram, which is a basic laboratory test.[15] SII has been previously investigated as a potential marker for various diseases such as cancer. In addition to cancer, several studies have been published on cardiovascular diseases such as chronic coronary syndrome, HF, and acute coronary syndrome in terms of poor clinical outcomes.[16-19] However, there is no scientific evidence that SII is an independent risk factor for poor prognosis in patients with NICM. The aim of the current study was to investigate the relationship between SII and mortality in patients with NICM.

METHODS

Ethics

The study was carried out with the permission of the Scientific Research Evaluation and Ethics Committee of Ankara City Hospital (Date: 12.09.2023, Decision No: E1-23-4000). We obtained an informed consent form from all patients for the procedure. All procedures were undertaken in accordance with ethical rules and the principles of the Declaration of Helsinki.

Study Population

The study sample consisted of 326 consecutive patients presenting to our hospital between March 2019 and February 2022, for whom severe coronary artery disease was excluded by diagnostic procedures and a diagnosis of NICM was established. Patients with an acute infection, hematological diseases, malignancies, systemic inflammatory and autoimmune diseases, severe valvular heart disease and/or prosthetic heart valves, chronic kidney disease, chronic liver disease, restrictive and hypertrophic cardiomyopathy, or antibiotic use, as well as those who had received blood or blood product replacement within the last three months, were excluded. The median 25-month follow-up mortality results of the patients were recorded retrospectively. Since the study was planned retrospectively, written informed consent could not be obtained from the patients.

Analysis of Patients' Data and Laboratory Analysis

Demographic characteristics, laboratory parameters, and cardiovascular risk factors were obtained from the hospital data system. Venous blood samples were collected at the time of presentation to the hospital. Biochemical measurements were performed using a molecular analyzer in the hospital's biochemistry laboratory. Complete blood count parameters were measured using an autoanalyzer. At presentation, transthoracic echocardiography was performed, and LVEF was calculated with the modified Simpson's method in the apical two and four-chamber views in both end-diastole and end-systole.

Definitions

SII is a combined index based on the count of three parameters: neutrophils, platelets, and lymphocytes. SII was calculated as follows: neutrophil count x platelet count / lymphocyte count. The diagnosis of NICM was based on the absence of severe stenosis of the coronary vessels by various imaging modalities, including conventional coronary angiography, coronary computerized tomography angiography, or cardiac magnetic resonance imaging, as well as the confirmation of reduced LVEF by echocardiography. Hypertension (HT) was defined as current antihypertensive use, a systolic blood pressure of 140 mmHg, or a diastolic blood pressure of ≥90 mmHg. Patients with a fasting blood glucose value of >126 mg/dl, those with a documented diabetes mellitus (DM) diagnosis, or those using oral antidiabetics or insulin at the time of presentation were accepted as diabetic. Current tobacco users were defined as smokers. Effort-induced dyspnea was classified according to the New York Heart Association (NYHA) functional classification.

Statistical Analysis

Analyses were performed using SPSS Statistics version 24.0 for Windows (SPSS Inc, Chicago, IL). The distribution patterns were defined using the Kolmogorov-Smirnov method. Data were presented as mean and standard deviation, median and interquartile range, or percentages as appropriate. While the Student's t-test was used to compare data with a normal distribution, the Mann-Whitney U test was used to compare the data without a normal distribution. Categorical variables were compared with the chi-square test. The effects of different variables on clinical outcomes were assessed by Cox regression analysis. The

variables for which the unadjusted P value was <0.10 in the univariate Cox regression analysis were identified as potential risk markers and included in the multivariable Cox regression model. Patients with a higher SII value than the median SII were accepted as having a high SII, and the remaining patients were defined as having a low SII. The survival curves of the patients with high and low SII values during the study period were analyzed using the Kaplan-Meier method, and statistical assessment was performed using the log-rank test. A p value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 326 patients were included in the study. The patients were divided into two groups: those with and without mortality. The mean age of the patients was 46.6 years, and 188 (57.7%) were male. The median follow-up period of the patients was 25 (interquartile range: 20-38) months. Of the patients, 124 (38%) had mortality during the follow-up period. The patients' baseline demographics and clinical and laboratory parameters are shown in Table 1. A significant difference was found between the mortality and non-mortality groups in terms of gender (p=0.001). There was no significant difference in terms of age, DM, HT, or smoking between the groups. The group with mortality had a lower LVEF (24.5±12.4 vs. 22.1±11.9%; p=0.005). In addition, systolic pulmonary artery pressure (sPAP) was significantly higher in this group (40.32±15.5 vs. 45.4±12.6 mmHg; p=0.001). The NYHA functional capacity was lower in the mortality group (p<0.001). Blood urea nitrogen, BNP, and SII were significantly higher in the mortality group. The blood sodium level, neutrophil count, and lymphocyte count were significantly higher in the non-mortality group.

A stepwise multivariate COX regression analysis was performed to assess the independent predictors of mortality and revealed that SII was an independent predictor of mortality (hazard ratio: 3.566, confidence interval: 1.922-5.184; p<0.001). sPAP, NYHA functional class, blood sodium level, and BNP were other independent predictors of mortality (Table 2). The median SII value of the patients included in the study was 644, and the patients were further evaluated in high SII and low SII groups according to the median SII value. The mortality rate was 48.6% for the high SII group and 27.4% for the low SII group (p<0.001). Subsequently, the Kaplan-Meier mortality curves for the low and high SII groups revealed worse mortality for the patients with a high SII (log-rank p<0.001, Figure 1).

Table 1. Comparison of groups according to the baseline demographics and clinical and laboratory characteristics

Variables	Non-mortality group (n=202)	Mortality group (n=124)	p value
Age	46.5±11.8	46.9±9.8	0.244
Male, n (%)	111 (54.9)	77 (62.3)	0.001
Diabetes mellitus, n (%)	49 (24.3)	31 (25.0)	0.312
Hypertension, n (%)	43 (21.3)	27 (21.8)	0.285
Smoking, n (%)	25 (12.4)	15 (12.1)	0.683
LVEF (%)	24.5±12.4	22.1±11.9	0.005
sPAP (mmHg)	40.32±15.5	45.4±12.6	0.001
NYHA functional class	3 (2-4)	3 (3-4)	<0.001
Glucose (mg/dl)	101.12 ±24.54	102.43±12.56	0.874
Creatinine (mg/dl)	1.04±0.63	1.09±0.45	0.832
BUN (mg/dl)	43.23±11.12	46.23±13.11	0.003
Na (mEq/L)	141.2±8.3	135.4±6.7	0.001
K (mEq/L)	4.1±0.6	4.1±0.9	0.819
AST (U/L)	22.12±12.45	23.02±11.43	0.738
ALT (U/L)	19.14±11.62	20.85±10.55	0.629
BNP (ng/L)	869.1±342.6	1453.5±543.5	<0.001
Hemoglobin (gr/dl)	12.5±4.5	12.3±5.6	0.583
WBC count (10^9/L)	8.45 (6.45-10.23)	8.23 (6.94-9.25)	0.136
Neutrophil count (10^9/L)	5.36 (3.94-6.14)	5.24 (3.89-6.22)	0.045
Lymphocyte count (10^9/L)	1.95 (1.34-2.36)	1.67 (1.22-2.08)	0.001
Platelet count (10^9/L)	245.6 (191.2-276.4)	236.9 (188.4-268.4)	0.144
SII	598.4 (415.5-899.4)	722.7 (488.6-1033.5)	<0.001
ICD, n (%)	138 (68.3)	87 (70.1)	0.235
CRT-D, n (%)	78 (38.6)	47 (37.9)	0.433

LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; NYHA, New York Heart Association; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; BNP, brain natriuretic peptide; WBC, white blood cell; SII, systemic immune inflammation index; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy defibrillator.

Table 2. Results of univariate and multivariate logistic regression analyses for the prediction of mortality

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.007 (0.985-1.015)	0.267	-	
Male gender	2.143 (1.231-2.856)	0.002	1.879 (0.984-3.444)	0.088
LVEF	1.836 (1.114-2.563)	0.006	1.455 (0.934-2.544)	0.122
sPAP	2.345 (1.522-3.122)	<0.001	2.455 (1.655-3.655)	<0.001
NYHA functional class	2.834 (1.954-3.433)	<0.001	3.444 (2.421-4.124)	<0.001
BUN	1.243 (1.122-1.434)	0.004	1.199 (0.849-1.656)	0.188
Blood sodium	2.614 (1.399-3.256)	<0.001	2.433 (1.123-3.676)	0.001
BNP	3.623 (1.983-6.655)	<0.001	3.231 (1.844-5.624)	<0.001
SII	3.987 (2.124-5.733)	<0.001	3.566 (1.922-5.184)	<0.001

HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; NYHA, New York Heart Association, BUN, blood urea nitrogen; BNP, brain natriuretic peptide; SII, systemic immune-inflammation index.

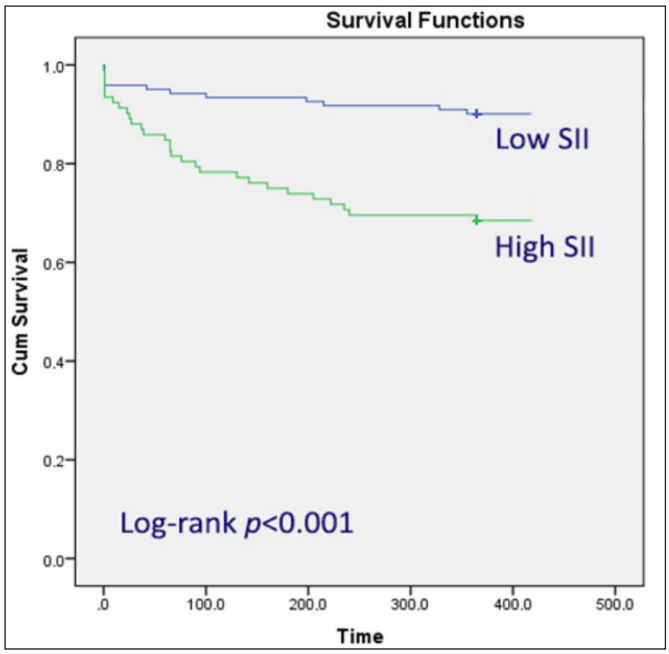

Figure 1. Kaplan-Meier survival curves (SII, systemic immune inflammation index)

DISCUSSION

The present study was designed to investigate the association between SII and long-term mortality in patients with NICM, and the results suggested that a high SII could predict mortality in this patient group regardless of other factors. We consider that our study is important because it is the first in the literature to reveal such an association and the potential of SII as a readily available marker for prognosis in NICM.

Heart failure is a chronic pathophysiological process with high mortality rate. Older age is one of the strongest determinants of mortality.[20] However, NICM patients are diagnosed at younger ages. This patient group has less comorbidities. Therefore, other predictors besides age and comorbidity should be investigated to predict mortality risk. In various studies, a relationship between heart failure and inflammatory parameters has been observed.[16,20,21] Therefore, identification of reliable inflammatory markers that reflect inflammatory burden and predict clinical outcomes is of great clinical importance. In another study, lower lymphocyte counts in patients with heart failure have a higher mortality rate.[22]

Despite advances in the treatment of patients with NICM, especially in the last decade, HF remains the most common cause of mortality.[23] Having simple markers that can be used to predict both early and late prognosis in NICM can allow clinicians to identify patients with poor prognosis and perform their treatment and follow-up more closely. BNP is one of the most powerful parameters for prognosis prediction in patients with HF.[21] Similar to the results of previous studies, our study showed a significant relationship between a high BNP value and mortality.[24] However, the difficulty of access to this parameter and its high cost limits its use in clinical practice. In addition, BNP values may be affected by differences in age, gender, body weight, and laboratory kits.[25] This has increased the importance of easily accessible and low-cost parameters in patient follow-up and led researchers to explore more possible parameters.

Recent studies have shown that HF, which is the main prognostic marker in patients with NICM, is closely related to the inflammatory response. In vitro and in vivo studies have shown that inflammation is a central pathophysiological process in the whole spectrum of HF, whether it is acquired or genetic and whether acute or chronic, and is associated with poor outcomes.[26,27] Studies have shown that cytokines such as tumor necrosis factor-alpha and interleukin-6 increase in relation to myocardial apoptosis and necrosis in these patients, and this is associated with poor clinical outcomes.[28] In another study, CRP, which is frequently used as an indicator of inflammatory response, was shown to be negatively associated with survival in patients with NICM.[14] Although these inflammatory parameters are highly predictive of the

prognostic outcomes of patients, their clinical use is limited due to their high costs and difficult access. SII, which has been associated with the prognosis of many cardiovascular diseases in recent years, is a new inflammatory biomarker that can be easily calculated based on a complete blood count analysis. In our study, high values of SII, which shows both immune and inflammatory responses, were found to be useful in predicting poor prognosis and increased long-term mortality in patients with NICM.

SII has been found to be an indicator in the prognosis prediction of some cardiovascular diseases.[16,19] This index is based on the counts of neutrophil, lymphocyte, and platelet cells, which are responsible for both inflammatory and immune-thrombotic responses in blood circulation. However, the mechanism of how this index has an adverse prognostic association with HF and other cardiovascular diseases is yet to be clarified.[16]

In the present study, the multivariate regression analysis performed showed that high SII, low blood sodium, high sPAP, lower NYHA functional capacity, and high BNP values were also independent risk factors in predicting poor prognosis in patients with NICM. These findings are consistent with previous studies.[21,24,29] A commonality among the independent risk factors in our study is that they are all typical characteristics of patients with severe HF. Given that HF is the most common cause of mortality in NICM, the detection of these risk factors in severe HF can explain the relationship observed in our study.

Limitations

This study has several limitations. The primary limitation is the absence of patient randomization and possible selection bias due to the retrospective design. Consecutive patients were included in the study to eliminate this bias. In addition, we did not have data on the causes of mortality, which would have made the study more powerful. Therefore, it was not possible to evaluate cardiovascular or non-cardiovascular mortality outcomes. Finally, the patients included in the study were not classified according to the NICM etiologies.

CONCLUSION

The results of this study showed that SII, which can be easily calculated with a hemogram routinely obtained at the time of presentation, could be used to predict long-term prognosis in patients with NICM. A high SII value was found to be an independent risk factor for long-term mortality. SII can be used as a practical biochemical marker for the prediction of poor prognosis in patients with NICM.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 12.09.2023, Decision No: E1/4000/2023).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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