THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Association Between Systemic Immune-Inflammation Index and Cardiac Resynchronization Therapy Response in Patients with Heart Failure

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an established treatment for selected patients with heart failure (HF); however, a substantial proportion of patients do not derive clinical or echocardiographic benefit. Systemic inflammation has been implicated in adverse myocardial remodeling and may influence response to CRT. This study aimed to evaluate the association between the systemic immune-inflammation index (SII) and CRT response.

Methods: This retrospective, single-center study included 110 patients with HF who underwent CRT implantation. Clinical, echocardiographic, and laboratory parameters, including SII, were assessed at baseline and at 6-month follow-up. Cardiac resynchronization therapy response was defined using combined echocardiographic and clinical criteria. Associations between inflammatory markers and CRT response were analyzed.

Results: Nonresponders demonstrated significantly higher baseline SII levels compared with responders. During follow-up, SII values increased significantly in nonresponders, whereas no significant change was observed in responders. Baseline C-reactive protein (CRP) levels were similar between groups. Chronic ischemic heart disease and elevated baseline SII were independently associated with CRT nonresponse. The discriminatory ability of baseline SII for CRT nonresponse was moderate.

Conclusion: Elevated SII was associated with an increased likelihood of CRT nonresponse and persistent inflammatory activity during follow-up. These findings suggest that SII reflects an unfavorable inflammatory and biological milieu related to impaired CRT response, rather than a direct causal mechanism. Systemic immune-inflammation index may serve as a complementary biomarker for risk stratification in patients undergoing CRT.

Keywords: Cardiac resynchronization therapy, heart failure, inflammation, nonresponder, systemic immune-inflammation index

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Received: November 25, 2025
Accepted: February 4, 2026
Available Online Date: April 2, 2026

Cite this article as: Şipal A, Önder ŞE, Bozyel S, et al. Association between systemic immune-inflammation index and cardiac resynchronization therapy response in patients with heart failure. *Anatol J Cardiol.* 2026;XX(X):X-X.

DOI: 10.14744/AnatolJCardiol.2026.5742

INTRODUCTION

Heart failure (HF) is a progressive clinical syndrome characterized by impaired cardiac function and substantial morbidity and mortality. Despite advances in pharmacological therapy, many patients remain symptomatic. Cardiac resynchronization therapy (CRT) improves symptoms, ventricular function, and survival in appropriately selected patients[1]; however, approximately 30% of patients fail to demonstrate meaningful benefit despite meeting guideline-based indications.[2]

The variability in CRT response has prompted extensive investigation into clinical, electrocardiographic, imaging, and laboratory predictors.[3-8] In recent years, systemic inflammation has emerged as an important contributor to HF progression and adverse remodeling. Elevated inflammatory markers, including C-reactive protein, interleukins, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio, have been associated with poor cardiovascular outcomes.[9-14]

The systemic immune-inflammation index (SII), derived from neutrophil, lymphocyte, and platelet counts, integrates inflammatory, immune, and prothrombotic

pathways. Although SII has been evaluated in several cardiovascular conditions, its association with CRT response has not been adequately explored. Therefore, this study aimed to investigate the relationship between SII and CRT response, with particular emphasis on distinguishing association from causation.

METHODS

Patients

The study population consisted of 110 HF patients who underwent CRT implantation in the center between January 2019 and January 2024, in accordance with the current guideline recommendations. The study included 112 HF patients who met the following criteria:

- Persistent symptoms despite optimal medical therapy [New York Heart Association (NYHA) class II-IV].
- Severe left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] ≤ 35%).
- Presence of left bundle branch block (LBBB) on a 12-lead electrocardiogram (ECG) with prolonged QRS duration (≥130 milliseconds) in sinus rhythm.
- Successful implantation of the left ventricular lead in recommended coronary sinus side branches.
- Achieved over 90% biventricular pacing during follow-up.

Patients were excluded from the study if they had the following:

- Mechanical heart valves.
- A history of myocardial infarction or coronary artery bypass grafting within the last 6 months.
- Malignancies, chronic inflammatory diseases, or autoimmune diseases.
- Hematological diseases, moderate-to-severe renal, or liver dysfunction.

HIGHLIGHTS

- Elevated baseline systemic immune-inflammation index (SII) levels were associated with nonresponse to cardiac resynchronization therapy (CRT).
- During follow-up, SII values increased significantly in nonresponders, whereas responders demonstrated relative inflammatory stability rather than a significant reduction in SII.
- High baseline SII levels were independently associated with a significantly increased likelihood of being a CRT nonresponder and with poorer clinical and echocardiographic outcomes.
- Persistent elevation of inflammatory biomarkers—including SII, C-reactive protein, B-type natriuretic peptide (BNP), and troponin—in nonresponders suggests that ongoing systemic inflammation may limit CRT efficacy.
- These findings indicate that SII may serve as a complementary, easily accessible biomarker for patient characterization and risk stratification before CRT implantation.

- Non-LBBB morphology on ECG.
- Patients with pacemaker to CRT upgrades.

Additionally, patients with a life expectancy of less than 12 months or a follow-up period shorter than 6 months were not included. This study is a retrospective analysis of prospectively collected data, and institutional ethics approval was obtained in accordance with the principles of the Helsinki Declaration.

Blood Samples

Venous blood samples were collected before the procedure and at the sixth-month follow-up. Laboratory parameters such as hemoglobin, creatinine, leukocytes, platelets, neutrophils, lymphocytes, C-reactive protein (CRP), and low-density lipoprotein (LDL) levels were recorded. Based on these results, the SII was calculated using the formula: SII = Platelet count × Neutrophil count / Lymphocyte count.

Clinical Evaluation

All patients underwent a clinical evaluation, including NYHA classification, QRS duration, and comorbidity assessment. This was performed by an independent physician blinded to other data. QRS duration was measured on surface ECG, taking the widest QRS complex from leads II, V1, and V6. Patients were evaluated for age, sex, history of coronary artery disease, diabetes, hyperlipidemia, hypertension, and other comorbidities.

Patients with a history of coronary artery disease and/or prior myocardial infarction were classified as ischemic. Those without a history of myocardial infarction or revascularization and with no more than 50% atherosclerotic lesions in 2 or more epicardial vessels, the left main coronary artery, or the proximal left anterior descending artery were classified as non-ischemic.

Echocardiography

Standard echocardiographic imaging was performed both before CRT implantation and at the sixth-month follow-up. Echocardiographic imaging was conducted in a resting state with the patient in the left lateral decubitus position, using the equipment available in the clinic (Vivid 7 Ultrasound System; GE, Horten, Norway). Measurements were made according to the recommendations of the American Society of Echocardiography. The LVEF was calculated using the modified Simpson method.

Device Implantation and Optimization Protocol

All patients received a CRT device with a defibrillator (CRT-D). The CRT-D implantation was performed transvenously via the left subclavian route. Before the placement of the left ventricular (LV) lead, routine coronary sinus venography was performed. The LV lead was preferably positioned in the lateral or posterolateral branches of the coronary sinus. The right atrial lead was implanted in the atrial appendage, and the right ventricular lead was positioned in the apex region. Atrioventricular (AV) and interventricular interval optimization was performed by an experienced cardiologist using Doppler echocardiography, with transmitral flow and velocity-time integral measurements used to achieve the shortest possible QRS duration and maximize ventricular synchrony.

To evaluate the potential impact of LV lead positioning on CRT response, pacing sites (posterior, posterolateral, and lateral coronary sinus branches) between responders and nonresponders were compared, with lead positioning determined using fluoroscopic guidance during implantation. To further assess its influence on CRT outcomes, a secondary analysis was conducted at the 6-month follow-up, evaluating the relationship between lead position and key echocardiographic and clinical parameters, including LVEF improvement, NYHA class reduction, and hospitalization rates.

Definition of Cardiac Resynchronization Therapy Response

Left ventricular reverse remodeling was assessed quantitatively based on the improvement in LVEF following CRT, with an increase of ≥5% at the 6-month follow-up considered indicative of a positive echocardiographic response. Clinical response was defined as an improvement of at least 1 NYHA functional class level without any HF-related hospitalizations during the follow-up period. Patients meeting both echocardiographic and clinical response criteria were classified as responders, while those who did not fulfill these criteria were classified as nonresponders.

Statistical Analysis

The statistical analyses were conducted using IBM SPSS Statistics v26 software. The normality of the variables was assessed using the Kolmogorov–Smirnov test. The chi-squared test and Fisher's exact test were utilized to compare categorical variables. Fisher's exact test was applied when more than 20% of the cells had expected frequencies less than 5, while the chi-squared test was used when this condition was not met. *P*-values were two-tailed. For continuous variables, the Mann–Whitney *U*-test was conducted to compare the medians (median: 25th-75th percentiles) of 2 independent groups, and the Student's *t*-test was performed to compare the means (mean ± SD) of 2 independent groups. A *P*-value below .05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of variables in predicting CRT response. The area under the curve (AUC) was used as a measure of predictive power, with a *P*-value below .05 indicating statistical significance. Confidence intervals for the AUC were calculated to determine the reliability of the estimates. Cox regression analysis was employed to identify independent predictors of CRT response. Hazard ratios with 95% CIs were calculated to estimate the strength and direction of associations between predictors and outcomes. Variables with *P*-values below .05 in the univariate analysis were included in the multivariate Cox regression model. Statistical significance was defined as a *P*-value below .05.

Ethical Approval

This study was approved by an independent Institutional Ethics Committee (Approval Date: November 13, 2025; Decision Number: 2025-128) and conducted in accordance with the principles of the Declaration of Helsinki. Because this research involved a retrospective analysis of previously recorded clinical data, the requirement for informed consent was waived by the ethics committee.

RESULTS

A total of 110 patients who met the inclusion criteria and experienced no complications were included in the study. Of these, 35.5% (n = 39) were female, and 64.5% (n = 71) were male. Among the participants, 43.6% (n = 48) had chronic ischemic heart disease, 21.1% (n = 23) had diabetes, and 30.9% (n = 34) had hypertension. Pacing was performed in the posterior branch in 72.7% (n = 80), the posterolateral branch in 20.9% (n = 23), and the lateral branch in 6.4% (n = 7). Symptomatically, 45.5% (n = 50) of the patients were classified as NYHA Class II, and 54.5% (n = 60) as Class III prior to the procedure. Echocardiographic evaluations conducted before the procedure showed mild mitral regurgitation in 62.7% (n = 69), moderate mitral regurgitation in 29.1% (n = 32), and severe mitral regurgitation in 8.2% (n = 9).

Patients were divided into 2 groups based on their response to CRT: responders (n = 81) and nonresponders (n = 29). There were no significant differences between the groups in terms of age ($P = .927$) or gender distribution ($P = .930$). Similarly, no significant differences were observed in the prevalence of diabetes ($P = .126$) or hypertension ($P = .627$) between groups. However, chronic ischemic heart disease was significantly more prevalent in the nonresponder group (65.5%) compared to the responder group (35.8%) ($P = .006$).

Baseline LVEF was similar between groups, with median values of 28% (nterquartile range [IQR]: 25-32) in responders and 28% (IQR: 25-31) in nonresponders ($P = .762$). The nonresponder group had significantly higher baseline platelet counts ($P < .001$), SII ($P = .007$), and troponin levels ($P = .020$). Other hematological and biochemical parameters, baseline QRS duration, and mitral regurgitation severity showed no significant differences between groups (Table 1).

The distribution of LV lead placement sites was comparable between CRT responders and nonresponders. Posterior, posterolateral, and lateral pacing sites showed no significant differences between groups ($P = .991$) (Table 1). Given the lack of statistical significance, LV lead positioning did not appear to influence CRT response in this study.

Analysis of changes in SII between baseline and follow-up showed a statistically significant increase in SII values in the nonresponder group ($Z = -2.865$, $P = .004$), indicating elevated systemic inflammation in nonresponders over time. In contrast, in the responder group, no significant difference was found in SII values between baseline and follow-up ($Z = -0.951$, $P = .342$).

At the 6-month follow-up, significant differences were observed between the groups in hematological, biochemical, and echocardiographic parameters (Table 2). The nonresponder group had significantly higher neutrophil counts ($P = .037$) and platelet counts ($P < .001$), while no significant difference was observed in lymphocyte levels ($P = .242$). Inflammatory and biochemical markers, including SII ($P < .001$), CRP ($P < .001$), BNP ($P < .001$), and troponin ($P < .001$), were significantly higher in nonresponders. Left ventricular ejection fraction was significantly lower in the nonresponder group ($P = .004$), whereas mitral regurgitation severity did

Table 1. Baseline Characteristics of Responders and Nonresponders

	Total n = 110	CRT Responder n = 81	CRT Nonresponder n = 29	*P*
Age (years)	70 (63-76)	70 (62-77)	70 (66-75)	.927
Gender (F/M) %	39/71 (34.8/63.4)	29/52 (35.8/64.2)	10/19 (34.5/65.5)	
Chronic ischemic heart disease, n (%)	48 (42.9)	29 (35.8)	19 (65.5)	.006
Diabetes, n (%)	23 (20.5)	14 (17.3)	9 (31)	.126
Hypertension, n (%)	34 (30.4)	24 (29.6)	10 (34.5)	.627
Pacing site, n (%)				
Posterolateral	80 (71.4)	59 (72.8)	21 (72.4)	.991
Lateral	23 (20.5)	17 (21.0)	6 (20.7)	
Posterior	7 (6.3)	5 (6.2)	2 (6.9)	
Glomerular filtration rate, median (IQR)	62.00 (54.75-69.00)	62.00 (56.00-69.00)	65.00 (52.5-69.00)	.881
Basal neutrophil, median (IQR)	4.60 (3.68-6.00)	4.60 (3.60-6.05)	4.60 (3.70-5.65)	.984
Basal platelet, median (IQR)	239 000 (186 750-272 500)	222 000 (177 500-258 000)	272 000 (255 000-298 000)	<.001
Basal lymphocyte, median (IQR)	1.90 (1.55-2.20)	1.90 (1.60-2.25)	1.70 (1.50-2.15)	.237
Basal SII, median (IQR)	581.57 (407.78-806.66)	551.28 (363.71-749.34)	714.00 (507.05-1066.02)	.007
Basal CRP, median (IQR)	2.40 (1.58-3.13)	2.50 (1.45-3.20)	2.40 (1.65-3.00)	.701
Basal BNP, median (IQR)	904.50 (573.25-1367.00)	950.00 (628.50-1529.50)	756.00 (480.00-1159.50)	.173
Basal troponin, median (IQR)	0.010 (0.010-0.020)	0.010 (0.010-0.020)	0.010 (0.010-0.010)	.020
Basal QRS, median (IQR)	163 (158-168)	162 (158-167)	163 (159-169)	.333
Basal mitral regurgitation, n (%)				
No regurgitation	0 (0)	0 (0)	0 (0)	.943
Mild regurgitation	69 (61.6)	51 (63.0)	18 (62.1)	
Moderate regurgitation	32 (28.6)	23 (28.4)	9 (31.0)	
Severe regurgitation	9 (8)	7 (8.6)	2 (6.9)	
Basal Ejection fraction, median (IQR)	28 (25-32)	28 (25-31)	28 (25-32)	.762
Basal NYHA, n (%)				.900
II	50 (45.5)	37 (45.7)	13 (44.8)	
III	60 (54.5)	44 (54.3)	16 (55.2)	
ACEI/ARB, n (%)	110 (100)	81 (100)	29 (100)	1.000
Beta bloker, n (%)	110 (100)	81 (100)	29 (100)	1.000
SGLT-2 inh., n (%)	87 (79.09)	65 (80.2)	22 (75.9)	.720

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CRT, cardiac resynchronization therapy; e-GFR, estimated glomerular filtration rate; F, female; IQR, interquartile range; M, male; MRA, mineralocorticoid receptor antagonist; SGLT-2 inh., sodium-glucose cotransporter-2 inhibitor, SII, systemic immune-inflammation index.

not differ significantly ($P = .062$). The QRS duration was significantly longer in nonresponders ($P < .001$).

Regarding clinical outcomes, hospitalization rates were significantly higher in the nonresponder group ($P = .001$). Although the incidence of implantable cardioverter-defibrillator (ICD) shocks was higher in nonresponders, the difference was not statistically significant ($P > .05$).

Logistic regression analysis identified chronic ischemic heart disease and high baseline SII levels as significant predictors of CRT nonresponse. The model achieved an overall accuracy of 74.5%, correctly classifying 44.8% of nonresponders and 85.2% of responders. Chronic ischemic heart disease was associated with a higher likelihood of nonresponse ($P = .007$), with affected patients being 3.5 times more likely to be nonresponders (odds ratio [Exp(B)] = 3.524, 95% CI: 1.405-8.836). High baseline SII levels were also significantly associated with CRT nonresponse ($P = .020$), with an approximately 3-fold increased likelihood of nonresponse (odds ratio [Exp(B)] = 3.030, 95% CI: 1.187-7.736). Gender was not a significant predictor of CRT response ($P = .828$), with an odds ratio of 1.112 (95% CI: 0.427-2.901).

The AUC for the ROC analysis of the baseline SII index was 0.669 (Figure 1), with a standard error of 0.059 and a *P*-value of .007. The 95% CI for the AUC ranged from 0.553 to 0.784, demonstrating moderate predictive power.

At 6 months, no significant association was observed between LV lead positioning and clinical or echocardiographic response to CRT. Patients with posterior, posterolateral, and lateral lead placements exhibited similar rates of LVEF improvement and NYHA class reduction (Table 2). These findings suggest that LV lead position alone was not a determinant of CRT response in this cohort.

Baseline characteristics were comparable between responders and nonresponders with respect to age, sex, and major comorbidities, except for a higher prevalence of chronic

Table 2. Six-Month Follow-Up Values of Both Groups

	Total n = 110	CRT Responder n = 81	CRT Nonresponder n = 29	*P*
Control neutrophil, median (IQR)	5.40 (4.10-6.33)	5.10 (4.10-6.20)	5.90 (4.50-7.40)	**.037**
Control platelet, median (IQR)	214.000 (183.000-266.000)	202 000 (160 000-256 000)	266 000 (232 500-300 500)	**<.001**
Control lymphocyte, median (IQR)	1.90 (1.38-2.20)	1.90 (1.40-2.30)	1.80 (1.25-2.10)	.242
Control SII, median (IQR)	633.96 (453.37- 945.54)	579.57 (370.50-798.06)	924.59 (704.84-1155.19)	**<.001**
Control CRP, median (IQR)	2.10 (1.30-2.53)	1.60 (1.20-2.10)	3.10 (2.30-3.70)	**<.001**
Control BNP, median (IQR)	599.00 (263.00-947.00)	365.00 (217.00-745.00)	947.00 (722.00-1634.50)	**<.001**
Control troponin, median (IQR)	0.020 (0.010-0.040)	0.010 (0.010-0.025)	0.060 (0.030-0.125)	**<.001**
Pacing QRS, median (IQR)	128 (124-134)	126 (122-131)	135 (132-140)	**<.001**
Control mitral regurgitation, n (%)				
No regurgitation	3 (2.7)	3 (3.7)	0 (0)	.062
Mild regurgitation	83 (74.1)	64 (79.0)	19 (65.5)	
Moderate regurgitation	22 (19.6)	14 (17.3)	8 (27.6)	
Severe regurgitation	2 (1.8)	0 (0)	2 (6.9)	
Control EF, median (IQR)	31 (28-35)	32 (29-36)	29 (26-32)	**.004**
Hospitalization, n (%)	5 (4.5)	0 (0)	5 (17.2)	**.001**
ICD shock, n (%)	2 (1.8)	0 (0)	2 (6.9)	.068

CRT, cardiac resynchronization therapy; IQR, interquartile range.

ischemic heart disease among nonresponders. Baseline SII levels were significantly higher in nonresponders, whereas baseline CRP levels did not differ between groups.

During follow-up, SII values increased significantly in the nonresponder group, indicating persistent or worsening systemic inflammation. In contrast, no significant difference was observed between baseline and follow-up SII values in the responder group, suggesting relative inflammatory stability.

QRS duration at follow-up was longer in nonresponders. Given the standardized implantation and optimization protocol, this finding was interpreted as reflecting differences in electrical remodeling and myocardial substrate rather than unequal CRT optimization.

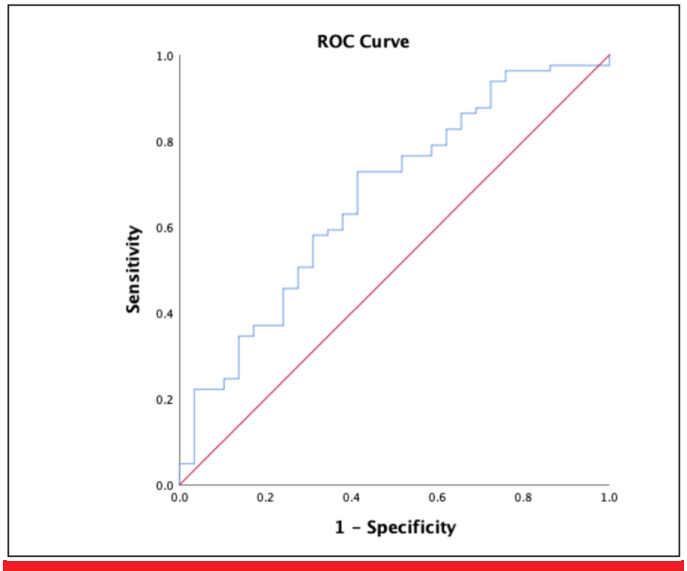

Figure 1 Receiver operating characteristic curve for the predictive performance of the systemic immune-inflammation index in identifying nonresponders to cardiac resynchronization therapy.

In the nonresponder group, 5 patients (17%) experienced HF-related hospitalization during the follow-up period. Importantly, all baseline blood samples were obtained during clinically stable conditions and at least 4 weeks after the last episode of hospitalization or acute decompensation. Patients with blood sampling performed during acute decompensated HF were not included in the analysis.

DISCUSSION

The principal finding of this study is that elevated SII is associated with CRT nonresponse and with persistent systemic inflammation during follow-up. Importantly, these findings should be interpreted as associative rather than causal. At baseline, higher SII levels in nonresponders ($P = .007$) indicate that pre-existing systemic inflammation is associated with a reduced likelihood of CRT success, reinforcing the hypothesis that inflammatory burden may impair ventricular remodeling and response to resynchronization therapy. Over time, nonresponders exhibited a further increase in SII levels ($P < .001$), whereas responders maintained relatively stable values, suggesting that persistent inflammation may contribute to the lack of functional and structural improvement despite CRT implantation. These findings suggest that SII not only serves as a pre-procedural risk stratification tool but also reflects ongoing inflammatory processes that may impair CRT efficacy, making it a valuable biomarker for patient selection and long-term monitoring.

Cardiac resynchronization therapy is an effective treatment modality for patients with HF and prolonged QRS duration, aimed at improving symptoms, enhancing quality of life, and reducing mortality risk.[15] Given the progressive nature of HF, the potential of CRT to improve cardiac function has

established it as a pivotal therapeutic option.[16] However, identifying patients who will respond favorably to CRT remains a clinical challenge, underscoring the need for novel biomarkers to predict therapeutic response. Differences in follow-up QRS duration likely reflect heterogeneous myocardial substrate and electrical remodeling rather than disparities in CRT optimization. Inflammation-related myocardial fibrosis and microvascular dysfunction may contribute to impaired resynchronization and limited QRS narrowing.

Systemic immune-inflammation index has emerged in recent years as a valuable biomarker that reflects a combination of inflammatory and thrombotic processes in various clinical contexts. Calculated using neutrophil, platelet, and lymphocyte counts, SII serves as a comprehensive measure of inflammatory burden and immune response.[17]

In this study, the aim was to investigate the role of the SII as a prognostic marker in HF patients undergoing CRT. Given the potential impact of systemic inflammation on CRT outcomes, previous research has explored its influence on patient response rates and clinical prognoses. Stavrakis et al[17] previously reported that elevated inflammatory markers negatively impact response rates and are associated with worse clinical outcomes in CRT patients. Similarly, high SII values have been shown to reflect increased inflammatory burden and thrombotic activity, which may limit the effectiveness of CRT.[18] In alignment with these findings, these results demonstrated that responders exhibited a notable reduction in inflammation, suggesting that alleviating inflammatory processes may have a beneficial impact on myocardial remodeling. These observations reinforce the potential role of SII as a predictive biomarker and emphasize the importance of addressing inflammation to optimize outcomes in CRT recipients.

In the present study, responders did not demonstrate a significant change in SII values between baseline and follow-up, indicating relative inflammatory stability over time. In contrast, nonresponders exhibited a significant increase in SII levels, reflecting persistent or worsening systemic inflammation. This divergence suggests that the absence of inflammatory progression, rather than a reduction in inflammatory burden, may characterize patients who respond favorably to CRT. Within this context, previous studies have suggested that favorable ventricular remodeling after CRT may be accompanied by attenuation of systemic inflammatory activity, particularly in selected patient populations. Karaüzüm et al[19] demonstrated that a reduction in inflammation following CRT is associated with improved LVEF levels. This suggests that CRT not only provides mechanical hemodynamic benefits but also supports myocardial recovery by reducing inflammation. This effect was particularly pronounced in patients with low baseline SII values.[20]

The NYHA classification is a standard tool for assessing the severity of HF symptoms. In this study, higher baseline SII values were associated with more severe NYHA classes (III-IV), and the responder group exhibited improvements in NYHA classification alongside reductions in SII following CRT. Specifically, patients in NYHA III-IV who experienced symptomatic improvement after CRT demonstrated significant decreases in SII, underscoring the role of inflammation in CRT success. Cleland et al[15] previously reported that CRT supports symptomatic improvement, particularly in patients with NYHA III-IV classification. Given that SII reflects both inflammatory and thrombotic processes, it may serve as a more comprehensive predictor of NYHA class and CRT response.

Mitral regurgitation (MR) is a common complication in HF patients and has the potential to improve through the hemodynamic benefits of CRT. In this study, higher baseline SII values were associated with more severe MR, and significant improvement in MR severity was observed in the responder group alongside reductions in SII following CRT. Di Biase et al[21] reported similar findings, demonstrating significant MR improvement in patients who exhibited reduced inflammatory markers post-CRT. This suggests that CRT mitigates the burden on mitral valve dysfunction by modulating inflammation, thereby supporting MR improvement.

The relationship between baseline and 6-month SII values and QRS durations provides valuable insights into the electrical effects of CRT. Elevated pre-CRT SII values were generally associated with prolonged QRS durations, and patients with higher baseline SII values showed limited QRS shortening following CRT. In contrast, the responder group exhibited significant QRS shortening, accompanied by reductions in SII. The potential pathophysiological mechanisms underlying these findings, as noted in previous studies, include the role of heightened inflammation in promoting myocardial fibrosis, which impairs ventricular synchronization and prolongs QRS duration.[22] Additionally, increased platelet levels may contribute to microcirculatory dysfunction, adversely affecting electrical conduction, which further explains these observations.[23] These findings highlight the influence of inflammation on electrical synchronization and underscore the importance of SII as a marker in understanding CRT outcomes.

To comprehensively evaluate inflammation's impact on CRT response, this study assessed hematological and biochemical markers such as CRP, neutrophils, platelets, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). Elevated levels of these parameters in nonresponders indicate persistent inflammation and associated thrombotic activity, potentially impairing ventricular remodeling and limiting CRT efficacy. Conversely, responders demonstrated significantly lower and decreasing levels of these inflammatory markers post-CRT, highlighting the role of inflammation control in enhancing CRT's mechanical and clinical benefits.

Previous investigations have shown that long-term CRT can enhance intrinsic ventricular activation, with responders exhibiting marked reductions in native QRS duration

and improvements in dyssynchrony indices such as interventricular mechanical delay (IVMD) and opposing wall delay (OWD).[24] This pattern of intrinsic electromechanical recovery underscores the importance of myocardial substrate in determining CRT efficacy. Consistent with this framework, these findings suggest that elevated SII levels may hinder the heart's ability to achieve such intrinsic improvements, potentially contributing to the variability in remodeling and clinical response observed among CRT recipients.

These findings underscore the critical role of inflammation and related biological processes in determining CRT response. Elevated SII, along with increased levels of CRP, NLR, and PLR in nonresponders, emphasizes the predictive value of these markers. Incorporating SII and related inflammatory biomarkers into pre-implantation assessments may help identify optimal CRT candidates, facilitating more targeted management strategies and potentially improving patient outcomes. Although baseline CRP levels were similar between responders and nonresponders, SII demonstrated significant baseline differences and dynamic changes over time. This discrepancy likely reflects fundamental differences between these biomarkers. Cardiac resynchronization therapy represents a single acute-phase reactant influenced by transient inflammatory stimuli, whereas SII integrates neutrophil activation, lymphocyte suppression, and platelet-related prothrombotic activity. Consequently, SII may better capture chronic, low-grade inflammatory and immune dysregulation that characterizes advanced HF.

These findings provide valuable insights into the impact of inflammation on CRT outcomes and emphasize the need for further research. Future large-scale studies could explore innovative approaches to managing inflammation in this patient population, potentially enhancing CRT success rates and refining therapeutic strategies.

Study Limitations

Our study has several limitations. First, being a retrospective and single-center study limits the generalizability of the findings. Second, not all inflammation-related biomarkers were analyzed, and the potential effects of other inflammatory markers could not be evaluated. Third, the study considered only the increase in LVEF as an echocardiographic response to CRT, due to the absence of other important parameters. Additionally, the relatively short follow-up period may be insufficient to assess long-term outcomes.

Despite these limitations, this study suggests that the use of the SII may be valuable in predicting the response to CRT therapy and provides a meaningful contribution to the literature.

CONCLUSION

Elevated SII is associated with CRT nonresponse and persistent inflammatory activity during follow-up. Systemic immune-inflammation index appears to reflect underlying inflammatory and immune dysregulation linked to impaired CRT benefit rather than exerting a causal effect. Incorporation of SII into pre-implant evaluation may aid in patient characterization and risk stratification.

Data Availability: The data supporting this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: This study was approved by the Kocaeli City Hospital Scientific Research Ethics Committee (Approval Date: 13 November 2025; Protocol Number: 2025-128).

Informed Consent: As this is a retrospective study, the requirement for informed consent was waived by the ethics committee.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.Ş., T.A.; Design – A.Ş., T.A.; Supervision – T.A., M.Ç.; Resources – O.M.Ç., M.A.; Materials – Ş.E.Ö., S.B., S.N.D., T.E.G.; Data Collection and/or Processing – A.Ş., T.A., M.Ç.; Analysis and/or Interpretation – A.Ş., Ş.E.Ö.; Literature Search – A.Ş., Ş.E.Ö.; Writing – A.Ş.; Critical Review – T.A., M.Ç.

Declaration of Interests: The authors have no conflicts of interest to declare.

AI-Assisted Technologies Statement: No generative artificial intelligence (AI)-assisted technologies were used in the writing, editing, data analysis, or figure creation of this manuscript.

Funding: No specific grant was received from any funding agency in the public, commercial, or not-for-profit sectors.

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