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# THE ROLE OF THE SYSTEMIC IMMUNE-INFLAMMATION INDEX IN PREDICTING RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY

## KARDİYAK RESENKRONİZASYON TEDAVİSİNE YANITIN ÖNGÖRÜLMESİNDE SİSTEMİK BAĞIŞIKLIK-İNFLAMATUVAR İNDEKSİNİN ROLÜ

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Abstract

Aim: Cardiac resynchronization therapy (CRT) is a reliable treatment modality in patients with systolic dysfunction. However, not every patient appears to benefit from CRT. The systemic immune inflammation index (SII) is closely linked to the poor prognosis of various cardiovascular disorders. However, there is no study investigating whether SII has predictive value in determining response to CRT in dilated cardiomyopathy patients. Therefore, we intend to investigate the association between SII and response to CRT.

Methods: A total of 220 patients (mean age 61.2±10.8 years; 120 men) implanted with CRT were involved in this study. Echocardiographic and laboratory measurements were evaluated prior to CRT. Response to CRT was determined as a≥ 15% decrease in left ventricular end-systolic volume at one-year follow-up.

Results: Patients grouped as CRT responders and non-responders. Of these, 143 (64.6%) were considered to be CRT responders, while the remaining 77 (33.4%) were non-responders. Female sex (OR: 3.823, CI: 1.568-9.324 p=0.003), QRS duration (OR: 1.224, CI: 1.158-1.335 p<0.001), and SII (OR: 0.996 CI: 0.995-0.997 p<0.001) were shown to be independent predictors of CRT response in multivariate analysis. A cut-off value of SII >825 estimated no response to CRT with 80% sensitivity and 75% specificity.

Conclusions: SII was associated with unresponsiveness to CRT. Therefore, it may be used to determine optimal patient selection for CRT implantation in routine clinical practice.

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

Öz

Amaç: Kardiyak resenkronizasyon tedavisi (KRT), sistolik disfonksiyonu olan hastalarda güvenilir bir tedavi yöntemidir. Ancak, KRT'nin faydası belli hasta grupları ile sınırlıdır. Sistemik immün inflamatuvar indeks (SII), çeşitli kardiyovasküler bozuklukların kötü prognozu ile ilişkilidir. Bununla birlikte, dilate kardiyomiyopati hastalarında SII'nin KRT'ye yanıtı belirlemede prediktif değeri olup olmadığını araştıran bir çalışma bulunmamaktadır. Bu nedenle, bu çalışmada SII ile KRT'ye yanıt arasındaki ilişkiyi araştırmak amaçlandı.

Yöntemler: Bu çalışmaya KRT implante edilen toplam 220 hasta (ortalama yaş 61,2±10,8 yıl; 120 erkek) dahil edildi. KRT öncesi ekokardiyografi ve laboratuvar ölçümleri değerlendirildi. KRT'ye yanıt, bir yıllık takipte sol ventrikül sistol sonu hacminde ≥ %15 azalma olarak belirlendi.

Bulgular: Hastalar, KRT'ye yanıt verenler ve yanıt vermeyenler olarak gruplandırıldı. Bunlardan 143'ü (%64,6) KRT'ye yanıt veren olarak kabul edilirken, kalan 77'si (%33,4) yanıt vermeyendi. Kadın cinsiyet (OR: 3.823, CI: 1.568-9.324 p=0.003), QRS süresi (OR: 1.224, CI: 1.158-1.335 p<0.001) ve SII (OR: 0.996 CI: 0.995-0.997 p<0.001) çok değişkenli analizde KRT yanıtının bağımsız öngörücüleri olarak bulundu. SII >825'lik bir sınır değeri, %80 duyarlılık ve %75 özgüllük ile KRT'ye yanıt olmadığını öngördürmüştür.

Sonuç: Bu çalışmada SII'nin KRT'ye yanıtsızlığı öngördüğü gösterilmiştir. Bu nedenle SII rutin klinik uygulamada KRT implantasyonu için optimal hasta seçimini belirlemede kullanılabilir.

Anahtar Kelimeler: Kardiyak resenkronizasyon tedavisi, sistemik immün-inflamatuvar indeks, kalp yetmezliği

## Introduction

Myocardial dysfunction is a progressive and complicated clinical disorder associated with ventricular remodeling and changes in intracardiac pressure. Cardiac resynchronization therapy (CRT) is an effective interventional treatment method in dilated cardiomyopathy patients with wide QRS duration[1]. CRT increases patients' symptom-free days and duration of exercise, and reduces hospital admissions and mortality for heart failure[1]. However, not all patients benefit equally from CRT[2].

Previous studies have reported that female gender, non-ischemic cardiomyopathy, left bundle branch block (LBBB), longer QRS duration, and sinus rhythm is associated with a positive response to CRT[3]. However, limited data are still available to determine which patients will benefit from CRT. Overall, one-third of patients are unresponsive to CRT[2,4].

Several inflammatory mediators and immune system cells [lymphocytes (L), neutrophils (N), platelets (P), etc.] play a significant role in pathogenesis of myocardial dysfunction[5]. However, the pathophysiological basis of the interaction among leukocyte subsets, inflammatory markers, and heart failure is complex[6]. Although there have been some studies using inflammatory biomarkers or immune system cells to determine the patient's response to CRT, none have been able to evaluate previously identified pathophysiological mechanisms as a whole in the similar patient group[7,8,9,10]. Therefore, there is still a need to identify different predictors that reveal different aspects of cardiomyopathy.

The systemic immune-inflammation index (SII) is a new inflammatory biomarker that incorporates lymphocyte (L), neutrophil (N), and platelet (P) counts[11]. So far, it has been affirmed that SII is closely linked to the poor prognosis of various cardiovascular disorders, such as myocardial infarction, infective endocarditis, aortic valve disease, and heart failure, and showed good application prospects[12,13,14,15]. However, there are no studies investigating whether SII has predictive value in determining response to CRT.

In light of this, our study sought to elucidate the role of SII as a potential predictor of response to CRT in heart failure patients.

## Materials and Methods

- *Study population*

This retrospective study involved 220 consecutive patients with systolic dysfunction (mean age: 61.2±10.8 years; male: 120), who were implanted with CRT at a tertiary hospital between March 2014, and April 2021. Ethical approval was taken from the Kosuyolu Training and Research Hospital local Ethics Committee, and the principles of the Declaration of Helsinki had carried out (Document No.2022/10/606). Written and oral informed permission was taken from each patient. Patients with (1) symptomatic chronic congestive dilated cardiomyopathy despite optimal medical therapy [New York Heart Association (NYHA) functional class II, III or ambulatory class IV)], (2) left ventricular ejection fraction (LVEF) ≤ 35% and wide QRS duration ( > 130 ms) were included in the study. QRS duration was evaluated from all possible leads in the 12-lead electrocardiogram (ECG) recorded 1 month prior to CRT implantation and the longest QRS duration was analyzed.

Patients with atrial fibrillation (AF), bundle branch blocks other than LBBB, decompensated heart failure, history of coronary artery revascularization within six months, acute or chronic all inflammatory or infectious diseases, hematologic diseases, malignancies, renal or hepatic diseases, left ventricular lead placed in branches other than the lateral or postero-lateral branches of the coronary sinus were excluded from the study. Moreover, patients without close follow-up (follow-up interval of fewer than 12 months) and detailed clinical information were also not included in the study.

Figure 1 shows patient selection and exclusion criteria.

The study participants were categorized into two groups based on their response to CRT. A ≥ 15% reduction in left ventricular end-systolic volume (LVESV) (compared to baseline) at 12 months follow-up was classified as CRT responders[16].

Baseline clinical and demographic characteristics were recorded for each patient, including age, gender, hypertension (HT), diabetes mellitus (DM), heart failure etiology, and other comorbidities. Patients with significant coronary artery disease and/or a previous history of the acute coronary syndrome were classified as ischemic. Patients without a history of the acute coronary syndrome and ≥50% evidence of coronary atherosclerotic lesions were classified as non-ischemic.

We have followed up the patients for 1 year after CRT implantation and clinical examinations, routine laboratory tests, and echocardiographic measurements (at baseline and 12 months after CRT implantation) were performed. Heart failure functional assessment was assessed during routine clinical examinations with the NYHA classification.

All patients received the maximum tolerated doses [beta blockers, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and diuretics] before and after CRT implantation.

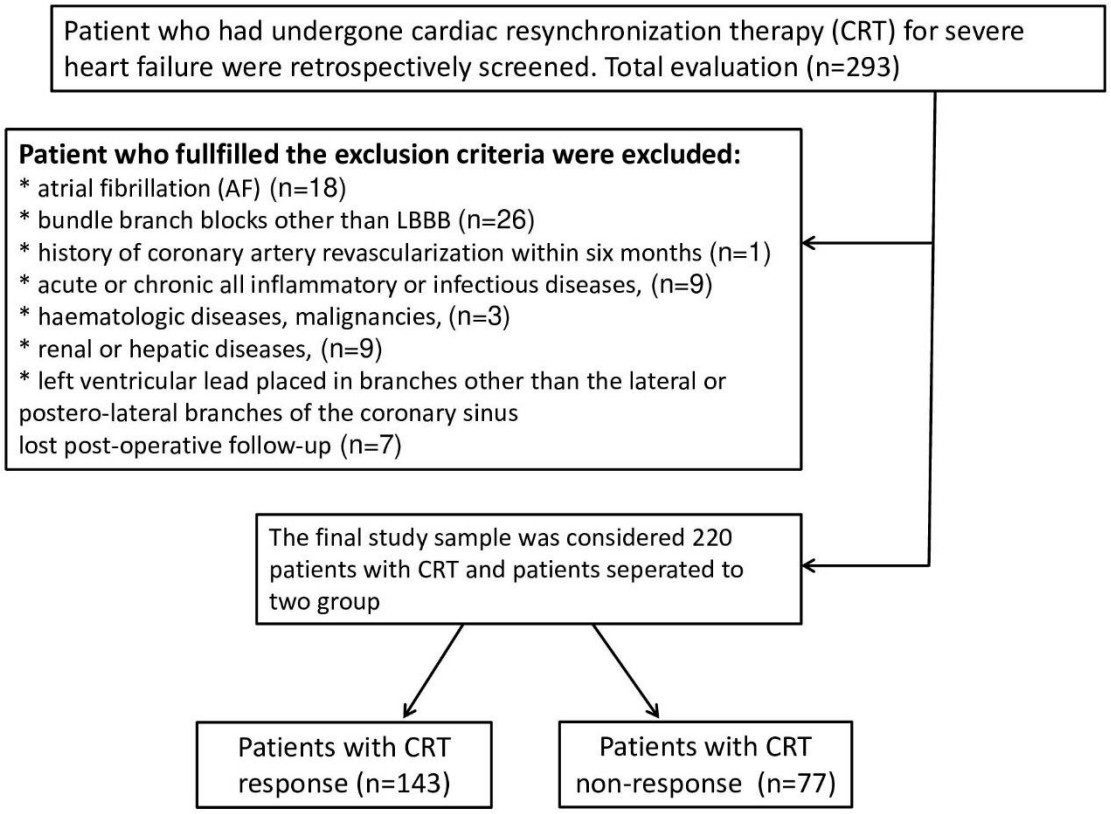


**Figure 1.** Patient inclusion and exclusion flow chart

- *Echocardiography*

Transthoracic echocardiography (TTE) (VIVID 7) was performed in all patients both before and 12 months after the CRT procedure. After CRT implantation, all echocardiographic measurements were evaluated while the CRT was in active pacing mode. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were measured from standard view. Teicholz formula was used to calculate left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV). To calculate the LVEF the modified biplane Simpson method was used[17].

- *Blood samples*

Laboratory parameters were measure prior to CRT implantation as part of the routine clinical evaluation. Complete blood count (CBC), including neutrophils (N (, lymphocytes (L) and platelets (P), was analyzed without delay. The analyzer automatically calculated the absolute numbers of white blood cell (WBC) subgroups (neutrophils N, lymphocytes L, etc.). All other laboratory parameters were measured using commercially available kits. The SII was calculated as neutrophil-to-lymphocyte ratio (N/L) X total platelet count (P) [SII= (N/L ratio) X P][11].

- *CRT device implantation*

CRT devices were implanted transvenously, targeting the lateral or posterolateral coronary sinus branch for left ventricular lead position in the vast majority of patients[1]. Epicardial lead was placed in the posterolateral region by a minimally invasive method by the cardiothoracic surgeon in 16 cases where transvenous lead could not be placed due to procedural difficulties.
The CRT device mode was set to DDD or DDDR mode to maximize biventricular pacing with 100 ms atrioventricular sensing delay and 130 ms paced delay, optimized according to our clinic's standard protocols. During follow-up, lead positions and pacing mode were analyzed at regular intervals. Biventricular stimulation rate was over 90% in all patients (96.2% ± 1.8%).

- *Statistical analysis*

SPSS version 21 (SPSS, Inc., Chicago, Illinois) was used to carry out statistical evaluation. After determining the CRT response group by the given formula initially, patients were divided into two groups as response (+) and non-response (-). Continuous and normally distributed variables were compared through the two-tailed Student t-test which were presented as mean values, and non-normally distributed continuous variables were tested by Mann Whitney u test which were presented as interquartile ranges.
In addition, a percentage scheme was used to present categorical variables which were analyzed by a chi-square test. The second categorization was made before and after the CRT implantation group. Related parameters were compared by paired sample t-test between these groups. The unadjusted $p<0.1$ value was considered to be clinically significant. At the last stage, parameters that were clinically associated with CRT response were included in univariate and multivariate regression analyses respectively. In addition, the predictive value of SII was estimated by the areas under the receiver operating characteristic (ROC) curve analysis.

## Results

A total of 220 patients (mean age 61.2±10.8 years, 120 men) with LBBB and heart failure underwent successful CRT implantation. Drug treatment included ACEI or ARB in 92%, beta-blockers in 95%, MRA in 85%, diuretics in 88%. All medications were continued after CRT implantation. The medication was similar in both groups.

Patients were categorized into two groups based on response to CRT. Of these, 143 (64.6%) were considered to be CRT responders, while the remaining 77 (33.4%) were non-responders. Baseline clinical, hematological, electrocardiographic and echocardiographic parameters are displayed in Table 1.

Age, HT, DM, alcohol consumption and smoking were similar between responders and non-responders. There was also no significant difference in biventricular stimulation rate between the two groups (96.4% vs. 94.6%, respectively (p=0.530).

Mean NYHA functional class before CRT implantation in responders and non-responders were 2.79±0.5 and 2.69±0.6, respectively (p=0.083). Also, preprocedural LVEF, LVEDD, and LVEDV were similar in both groups. However, pre-procedure LVESD, and LVESV were significantly lower in patients who responded to CRT. Responders to CRT were more often female, had non-ischemic cardiomyopathy, and had a wider QRS duration on the 12-lead ECG (Table 1).

**Table 1.** Baseline demographic, echocardiographic and hematological parameters of responder and non-responder patients

| Variables | All (n=220) | CRT response (n=143) | CRT non-response (n=77) | p |
|---|---|---|---|---|
| Female (n,%) | 100 (45.5) | 80 (55.9) | 20 (26) | 0.002* |
| Age (years) | 61.2±10.8 | 60.7±11.2 | 62.2±10 | 0.335 |
| HT (n,%) | 98 (44.5) | 64 (44.8) | 34 (44.2) | 0.523 |
| DM (n,%) | 52 (23.6) | 34 (23.8) | 18 (23.4) | 0.543 |
| Alcohol (n,%) | 33 (15.0) | 21 (14.6) | 12 (15.5) | 0.243 |
| Smoking (n,%) | 78 (35.4) | 51 (35.6) | 27 (35.0) | 0.546 |
| Ischemic (n,%) | 54 (24.5) | 24 (16.8) | 30 (39) | <0.001* |
| Nonischemic (n,%) | 166 (75.5) | 119 (83.2) | 47 (61) | <0.001* |
| LVEF (%) | 26±5.2 | 26.9±4.9 | 26.2±5.8 | 0.310 |
| LVEDD (mm) | 6.9±0.7 | 6.9±0.7 | 7±0.9 | 0.573 |
| LVESD (mm) | 5.9±0.7 | 5.8±0.7 | 6.1±0.8 | 0.003* |
| LVEDV (ml) | 256±64 | 253±58 | 260±74 | 0.433 |
| LVESV (ml) | 181±52 | 173±48 | 196±57 | 0.002* |
| NLR | 2.9 (2.2-3.9) | 2.5 (1.9-3.3) | 3.7 (3-4.7) | <0.001* |
| PLR | 121 (94-169) | 107 (91-136) | 194 (150-258) | <0.001* |
| SII | 617 (443-958) | 481 (391-706) | 1007 (866-1060) | <0.001* |
| CRP (mg/L) | 3 (1-3.6) | 3.1 (0.9-3.8) | 1.9 (1.2-3.1) | 0.511 |
| WBC ($x10^9$/L) | 8.1±1.6 | 8.2±1.6 | 8±1.7 | 0.336 |
| QRS duration (ms) | 151±9.1 | 155.5±8.6 | 144.9±5.3 | <0.001* |
| NYHA class (mean) | 2.75±0.5 | 2.79±0.5 | 2.69±0.6 | 0.083 |

CRT: cardiac resynchronization therapy, DM: diabetes mellitus, HT: hypertension, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume, LVESD: left ventricular end-systolic diameter, LVESV: left ventricular end systolic volume, NLR: neutrophil/lymphocyte ratio, NYHA: New York Heart Association, PLR: platelet/lymphocyte ratio, SII: systemic immune inflammation index. Numerical variables were presented as median with range or mean ±SD, and categorical variables as number and percentages. *P<0.05

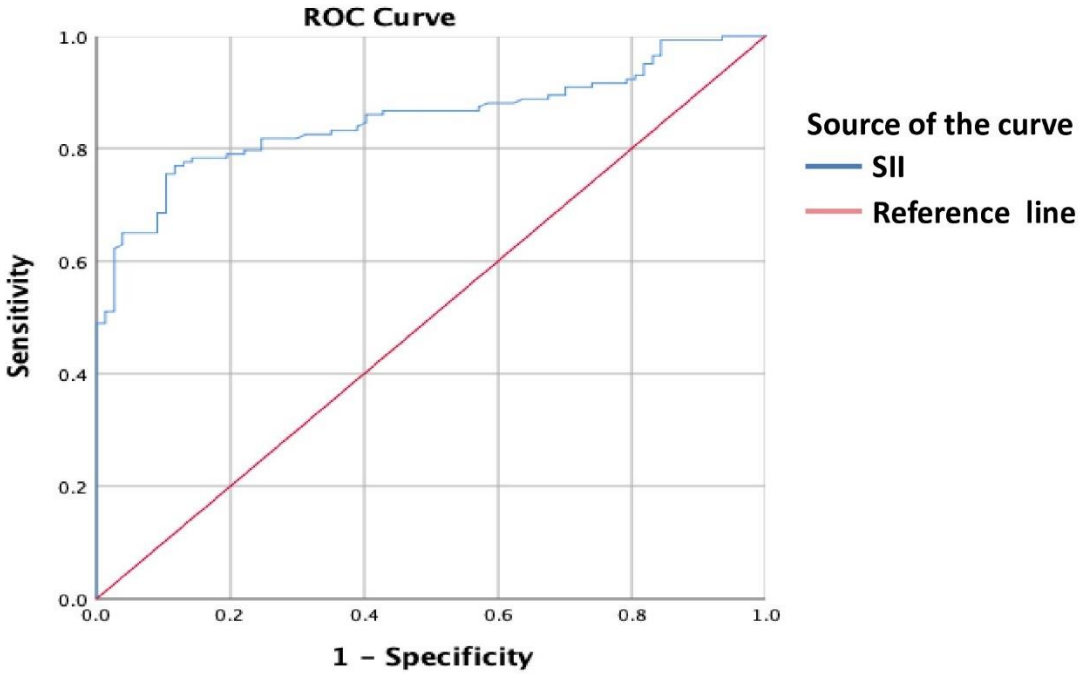


**Figure 2:** Receiver operating characteristic curve analysis of SII for prediction of response to CRT

**Table 2.** Comparison of baseline and 1 year of echocardiographic parameters in responder and non-responder patients

| Variables | CRT response | | p | CRT non-response | | p |
|---|---|---|---|---|---|---|
| | Baseline | 1 year | | Baseline | 1 year | |
| LVEF (%) | 26.9±4.9 | 38.4±7.5 | <0.001* | 26.2±5.8 | 21±5.2 | <0.001* |
| LVEDD(mm) | 6.9±0.7 | 6.2±0.5 | <0.001* | 6.9±0.3 | 7±0.5 | <0.001* |
| LVESD(mm) | 5.8±0.7 | 4.9±0.7 | <0.001* | 5.8±0.3 | 5.9±0.2 | <0.001* |
| LVEDV(ml) | 253±58 | 195±38 | <0.001* | 248.6±27.3 | 259.6±44 | <0.001* |
| LVESV(ml) | 173±48 | 121±41 | <0.001* | 172.3±20.4 | 175.6±14 | <0.001* |

LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume, LVESD: left ventricular end-systolic diameter, LVESV: left ventricular end systolic volume.
Numerical variables were presented as mean ±SD., *P<0.05

**Table 3.** Independent predictors of CRT response in multivariate analysis

| Variables | Univariable OR (95% CI) | p | Multivariable OR (95% CI) | p |
|---|---|---|---|---|
| Age | 0.988 (0.962-1.014) | 0.353 | | |
| Female | 2.473 (1.338-4.570) | 0.004* | 3.823 (1.568-9.324) | 0.003* |
| Nonischemic | 3.165 (1.679-5.967) | <0.001* | 1.741 (0.787-3.859) | 0.171 |
| Pre-QRS | 1.207 (1.146-1.271) | <0.001* | 1.224 (1.158-1.335) | <0.001* |
| Pre-LVEF | 1.028 (0.975-1.083) | 0.309 | | |
| Pre-LVESD | 0.569 (0.389-0.832) | 0.004* | 5.124(0.065-10.642) | 0.330 |
| Pre-LVESV | 0.992 (0.986-0.997) | 0.003* | 0.958 (0.884-1.037) | 0.288 |
| Pre-SII | 0.996 (0.995-0.997) | <0.001* | 0.996 (0.995-0.997) | <0.001* |
| Pre-NLR | 0.431 (0.323-0.574) | <0.001* | 1.493 (0.862-2.586) | 0.152 |
| Pre-PLR | 0.977 (0.970-0.984) | <0.001* | 0.995 (0.980-1.009) | 0.455 |

LVEF: left ventricular ejection fraction, LVESD: left ventricular end-systolic diameter, LVESV: left ventricular end systolic volume, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, Pre: pre- procedural, SII: systemic immune inflammation index. *P<0.05

Before CRT implantation, median neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and SII were significantly higher in the CRT non-responder group than in the responder group. However, WBC and CRP levels were similar in both groups before CRT implantation (Table 1).

Echocardiographic parameters before and 12 months after CRT implantation are presented in Table 2. At 1 year after CRT implantation, LVEF had significantly improved from 26.9±4.9% to 38.4±7.5% in responders. Also, LVEDD, LVESD, LVEDV, LVESV had significantly decreased in responders. However, no significant improvement in left ventricular size, volume, and function was detected in those who did not respond to CRT (Table 2).

We performed regression analysis to determine predictors associated with CRT response. Female sex (OR: 3.823, CI: 1.568-9.324 p=0.003), QRS duration (OR: 1.224, CI: 1.158-1.335 p<0.001), and SII (OR: 0.996 CI: 0.995-0.997 p<0.001) were found to be independent predictors of CRT response in multivariate analysis. (Figure 2)

The ROC curve analysis was performed to identify the relationship between SII and response to CRT. A cut-off value of SII in predicting non-response to CRT was 825 with 80% sensitivity and 75% specificity (area under the curve (AUC): 0.853 (95% confidence interval (CI): 0.803–0.902, p< 0.001).

## Discussion

In the present study, we evaluated several aspects, including clinical, biochemical, echocardiographic, and electrocardiographic determinants of CRT responsiveness at 1 year following CRT implantation. The main finding of this study is that high level of SII was associated with non-response to CRT. In addition, female gender and longer QRS duration were revealed to be significant determinants of response to CRT.

Several prognostic parameters have already been introduced to predict the CRT response in patients undergoing CRT implantation for heart failure. These parameters are primarily based on demographic and clinical parameters including age, gender, heart failure etiology, LBBB morphology

and QRS duration[3]. Additionally, serum levels of inflammatory markers, lymphocyte count, NLR, and PLR are key prognostic inflammatory parameters that support the predictive value of these indices[7,8,9,10]. However, no data exist on the association between SII and CRT response, which was evaluated in patients with dilated cardiomiyopathy in this study. And the results confirmed that high level of SII could be an independent predictor for CRT unresponsiveness. A cut-off value of SII >825 predicted inconclusive CRT response with 80% sensitivity and 75% specificity. As we know, the relationship between SII and response to CRT was firstly evaluated by the current study. Recently, Tang et al. investigated the potential predictive value of SII in 4606 patients with decompansated heart failure to assess poor prognosis, which showed that the SII value was divided into three parts as <1144.28, ≥1144.28, <2730.11 and ≥2730.11, and the third tertile of the SII group was significantly associated with short term mortalities, as well as the high risk of major adverse cardiac events (MACEs) occurence[15]. Also, Hayiroglu et al. investigated the effect of SII on long-term mortality and true ICD shock during 10 years follow-up in patients with ICD. They found that, in patients with an SII ≥1119, mortality and appropriate ICD shock rates were significantly higher at long-term follow-up[18].

The SII may be considered a modified but reliable version of NLR and PLR[11,19]. In a study by Agacdiken et al. NLR was significantly higher in the CRT non-responder group, and a higher baseline NLR was associated with CRT unresponsiveness[7]. Similarly, Balcı et al. showed that higher PLR and NLR values were related with inconclusive CRT response[8]. However, in our study, although NLR and PLR were elevated in the CRT non-responder group and were associated with CRT non-responsiveness in univariate analysis, multivariate analysis eliminated their significance. Indeed, our study highlighted the independent efficacy of SII for CRT non-responsiveness independent of NLR and PLR. As the combined effect of NLR and PLR was assessed at SII, it may have better predicted CRT non-response independent of other variables.

In the same line with previous large randomised clinical trials, female gender and longer QRS duration were revealed to be independent predictors of CRT response. Unlike other major studies, the non-ischemic etiology was not associated with CRT response in multivariate analysis. This consequnces may arise from that the majority of the patients in the current study had non-ischemic etiology and therefore the effect of ischemic etiology was not adequately evaluated.

## Conclusion

SII, an inexpensive and readily available test calculated from a complete blood count, was found to be associated with unresponsiveness to CRT. Therefore, it may be used to determine optimal patient selection for CRT implantation in routine clinical practice.

- *Limitations*

The current study has a few limitations. First of all, as well as being retrospective study, it was also a single-center experience. Secondly, the follow-up period after CRT implantation was relatively short. It would be important to identify additional changes in left ventricular volume and function after a longer follow-up period. Finally, well established inflammatory markers were not evaluated and compared with SII as they are expensive and not readily available in daily practice.

**Author contributions**

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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Authors declared no financial support.

**Ethical approval**

Ethical approval was taken from the Kosuyolu Training and Research Hospital local Ethics Committee, and the principles of the Declaration of Helsinki had carried out (Document No.2022/10/606).

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