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Original Article

A lower systemic immune-inflammation index level is associated with response to cardiac resynchronization theraphy

Düşük sistemik immun-inflamasyon indeksi kardiyak resenkronizasyon tedavisine yanıt ile ilişkilidir

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Abstract

Aim: The systemic immune-inflammation index (SII), a novel inflammation-based biomarker combining platelet, neutrophil and lymphocyte counts, has been shown to be associated with worse clinical outcomes in several malignancies. However, the relationship between SII and response to cardiac resynchronization theraphy (CRT) has not been evaluated yet. The aim of this study was to investigate the association between SII and response to CRT in patients with heart failure (HF).

Material and Methods: A total of 88 patients (54.5% male; mean age 58.9±12.9 years) who underwent CRT device implantation were included in the study. Baseline clinical, demographic, laboratory and echocardiographic data of patients' were recorded. An echocardiographic CRT response was defined as a decrease in left ventricular end-systolic volume of ≥15% and/or absolute increase of 5% in left ventricular ejection fraction (LVEF) at 6-month follow-up after CRT implantation.

Results: Among included patients, a total of 51 (57.9%) patients were defined as "responders" after 6 months of CRT implantation. Lymphocyte count, LVEF and QRS width were significantly higher in responders compared to those responders. In addition, baseline creatinine and SII levels were significantly lower in responders than nonresponders. Multivariate logistic regression analysis showed that a SII of ≤973.3, LVEF and QRS width were independent predictors for response to CRT in the study population.

Conclusion: SII may be used as a novel, simple and reliable inflammatory biomarker in the prediction of response to CRT in patients with HF.

Keywords: inflammation; neutrophil; cardiac resynchronization therapy.

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Öz

Amaç: Trombosit, nötrofil ve lenfosit sayılarının kominasyonundan oluşan yeni bir inflamasyon belirteci olan sistemik immun-inflamsyon indeksinin (Sİİ) çeşitli malignitelerde kötü klinik sonlanımlarla ilişkili olduğu gösterilmiştir. Bununla birlikte, Sİİ ve kardiyak resenkronizasyon tedavisine (KRT) cevap arasındaki ilişki henüz çalışılmamıştır. Bu çalışmanın amacı, kalp yetersizliği (KY) hastalarında KRT tedavisine cevap ve Sİİ arasındaki ilişkiyi araştırmaktı.

Gereç ve Yöntemler: KRT cihaz implantasyonu yapılan toplam 88 hasta (%54,5 erkek; ortalama yaş 58,9±12,9 yıl) çalışmaya dahil edilmiştir. Hastaların temel klinik, demografik, laboratuar ve ekokardiyografik özellikleri kaydedildi. Ekokardiyografik KRT cevabı; implantasyondan 6 ay sonrasında sol ventrikül sistol sonu volümünde %15 ve üzerinde azalma ve/veya sol ventrikül ejeksiyon fraksiyonunda (SVEF) %5 ve üzerinde artış olması olarak tanımlanmıştır.

Bulgular: Çalışmaya alınan hastalardan 51 tanesi (%57,9) KRT'ye "cevap vermiş" olarak tanımlandı. Lenfosit sayısı, SVEF ve QRS genişliği KRT ye cevap veren hastalarda vermeyenlere göre anlamlı olarak daha fazlaydı. Ayrıca, bazal kreatinin ve Sİİ düzeyleri cevap veren hastalarda vermeyenlere göre anlamlı olarak daha düşüktü. Çok değişkenli lojistik regresyon analizinde; çalışma populasyonunda Sİİ'nin 973,3 ve altında olması, SVEF ve QRS genişliği KRT'ye cevabın bağımsız öngördürücüleri olarak saptandı.

Sonuç: KY hastalarında KRT tedavisine cevabın tahmininde Sİİ yeni, basit ve güvenilir bir inflamasyon belirteci olarak kullanılabilir.

Anahtar kelimeler: inflamasyon; nötrofil; kardiyak resenkronizasyon tedavisi.

Introduction

Cardiac resynchronization therapy (CRT) has emerged as an important alternative in treating chronic systolic heart failure (HF) patients with prolonged QRS complex duration [1]. Previous studies have shown that CRT induces reverse left ventricular (LV) remodeling in appropriately selected patients, improves symptoms and reduces morbidity and mortality [2,3]. Unfortunately, almost a third of patients do not respond favourably to CRT [4]. Several characteristics are associated with improved response, and thus survival following CRT implantation [5]. Optimization of patient selection for CRT will enable identification of nonresponders, who might benefit from other treatment strategies.

It has been shown that there is a relationship between the response to CRT and many hematologic inflammation-based parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and red cell distribution width (RDW) [6-8]. On the other hand, a novel parameter, combining neutrophil, lymphocyte and platelet counts, systemic immune-inflammation index (SII), as a promising inflammatory biomarker, has been described in recent years [9]. It has been reported that SII is associated with worse clinical outcomes in several malignancies [9-12]. However, the relationship between SII and response to CRT has not yet been investigated. In this study the relationship between SII and response to CRT in patiens with HF was studied.

Material and Methods

Study population

Subjects consisted of 101 consecutive patients undergoing CRT, between March 2016 and December 2018, at our cardiology department who were retrospectively enrolled into the study. Patients were included according to following criteria: (1) chronic HF with reduced LVEF (≤35%) and (2) prolonged QRS interval (≥120 msn). The exclusion criteria were: chronic hepatobiliary disease (n=1); known history of a hematologic disease (n=2); chronic inflammatory or autoimmune disease (n=4); malignancy (n=2); chronic medical therapy with steroid or nonsteroidal anti-inflammatory drugs (n=4). Thus, 13 patients were excluded and the study cohort included a total of 88 patients.

Data collected included demographic information and medical history such as age, gender, body mass index (BMI), hypertension, and diabetes mellitus. Patients' functional capacity status were evaluated according to the New York Heart Association (NYHA) classification [13]. The rhythm and QRS width of patients' were determined on admission 12-lead electrocardiography (ECG). Medical treatment including beta-blockers, angiotensin converting enzyme inhibitors (ACEi),

angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA) were computed as positive if the patients had these medications on admission.

Fasting venous blood samples were taken during hospitalization within 24-48 hours prior to CRT device implantation. Counts of platelets, lymphocytes, neutrophils and other hematological parameters were analyzed using an automated blood cell counter within 30 minutes after blood sampling. Biochemical analysis including blood urea nitrogen (BUN), creatinine, uric acid, and albumin levels were also measured using standard laboratory techniques. These laboratory results were collected from all patients and all of these data were obtained from the hospital database. SII was calculated using the formula: platelet count x neutrophil count/lymphocyte count. The NLR was calculated as the neutrophil count divided by the lymphocyte count.

The study protocol was approved by local institutional investigation committees.

Cardiac resynchronization theraphy device implantation

All pacemaker implantations were performed by left infraclavicular approach. Right atrial and right ventricular leads were implanted using a transvenous approach. LV leads were inserted by a transvenous approach through the coronary sinus into a cardiac vein of the free wall. A biventricular pacemaker (InSync III, Medtronic Inc, Minneapolis, Minnesota) or biventricular cardioverter-defibrillator (InSync III, Medtronic Inc, Minneapolis, Minnesota) was used for CRT implantation. The atrioventricular interval was optimized using Doppler echocardiography within 24-48 hours after implantation.

Echocardiography

Patients were imaged in the left lateral decubitis position with a commercially avaliable system (VIVID 7, General Electric-Vingmed, Horten, Norway). Images were obtained with a 2.5-MHz broadband transducer at a depth of 16 cm in the parasternal and apical views (standart long-axis, two- and four- chamber images). Standart two-dimensional and color Doppler data triggered to the QRS complex were recorded in cine-loop format. LV volumes were calculated using the Teicholz method, and LVEF was calculated from the conventional apical two- and four-chamber images using biplane Simpson's technique [14]. An echocardiographic CRT response was defined as a decrease in left ventricular end-systolic volume (LVESV) of ≥15% and/or absolute increase of 5% in LVEF at 6-month visit after implantation [15].

Transthoracic echocardiography was performed 1 week before pacemaker implantation and repeated 6 months later. All echocardiographic measurements after CRT implantation were performed with the device in active pacing mode.

Statistical Analysis

Continuous variables are presented as mean±standard deviation and caterogical variables as numbers, percentages or proportions. The normality of distribution of the continuous variables were determined using the Kolmogorov-Smirnov test. Between-group comparisons were performed using the chi-square test for caterogical variables, independent-samples t test for continuous variables with normal distributions and the Mann-Whitney U test for continuous variables with abnormal distributions. Multivariate logistic regression analyses were used to determine the independently associated predictors of response to CRT. Receiver operating characteristics (ROC) curve analysis was performed to identfy the optimal cut-off point value of SII for predicting response to CRT and the sensivitiy and specifity at that point was obtained. All analyses were two-sided and considered significant at a P-value <0.05. All statistical anlayses were performed using SPSS 20.0 software (IBM Inc., Chicago, Illinois, USA).

Results

The study population consisted of 88 patients. Response to CRT was observed at 51 patients (57.9%) at 6-months follow-up. All patients were taken conventional HF therapy during follow-up after CRT device implantation. Baseline clinical and demographic characteristics of responders and nonresponders are summarized in Table 1. The mean age of responders was slightly higher than those nonresponders, but it was not statistically significant (60.3±11.9 vs 56.8±14.1, p=0.322). There was no statistically difference between the responders and nonresponders in terms of gender, BMI, and etiology of HF. No significant differences in the frequency of hypertension and diabetes mellitus were observed between the groups. The NYHA functional capacity of the patients' were similar between the two groups. Although baseline LVEF (25.9±6.5 vs 21.4±5.7, p=0.002) were significant higher in responders than those nonresponders, other echocardiographic parameters including left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV) and right ventricular ejection fraction (RVEF) were similar between the two groups. Additionally, there was no statistically difference in terms of basal ECG rhythm and previous medical treatment between the responders and nonresponders. The QRS width was markedly higher in responders than those nonresponders (136.3±10.4 vs 127.8±10.5, p<0.001).

Table 1. Baseline clinical characteristics of the study patients in responders and nonresponders.

Variables	Responders (n = 51)	Non-responders (n = 37)	P-value
Age (years)	60.3±11.9	56.8±14.1	.322
Male, n (%)	25 (49.0%)	23 (62.2%)	.222
Body mass index, kg/m2	28.3±5.5	27.9±5.6	.451
Non-ischemic etiology, n (%)	34 (66.7%)	19 (51.4%)	.147
Hypertension, n (%)	35 (68.6%)	22 (59.5%)	.374
Diabetes mellitus, n (%)	14 (27.5%)	7 (18.9%)	.354
Echocardiographic features			
LVEDD, mm	68.4±7.9	69.8±10.4	.565
LVEDV, ml	234.9±75.6	249.4±88.6	.300
LVEF, %	25.9±6.5	21.4±5.7	.002
RVEF, %	51.9±18.2	56.8±7.2	.692
NYHA functional capacity, n (%)			.301
Class 1	1 (2.0%)	2 (5.4%)	
Class 2	4 (7.8%)	6 (16.2%)	
Class 3	41 (80.4%)	25 (67.6%)	
Class 4	5 (9.8%)	6 (16.2%)	
Rhythm, n (%)			.511
Sinus	44 (86.3%)	30 (81.1%)	
Atrial fibrillation	7 (13.7%)	7 (18.9%)	
QRS width, msn	136.3±10.4	127.8±10.5	<0.001
Prior medical theraphy, n (%)			
ACEi or ARB	47 (92.2%)	34 (91.9%)	.964
Beta-blocker	48 (94.1%)	35 (94.6%)	.924
MRA	44 (86.3%)	32 (86.5%)	.972

ACEi = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; LVEDD = Left ventricular end-diastolic diameter; LVEDV = Left ventricular end-diastolic volume; LVEF = Left ventricular ejection fraction; MRA = Mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RVEF = Right ventricular ejection fraction.

Pre-implantation laboratory results of responders and nonresponders are shown in Table 2. Baseline creatinine was significant higher in responders than those nonresponders (0.99±0.34 vs 1.11±0.29, p=.023). No significant differences in hemoglobin, BUN, albumin and uric acid levels were observed between the groups. There was no statistically difference in terms of RDW and platelet count between the responders and nonresponders. However, the lymphocyte count were significantly higher in responders compared to those nonresponders (2.01±0.62 vs 1.72±0.61, p=0.025). Consequently the SII was markedly higher in nonresponders than responders (631.3±386.7 vs 951.2±550.2, p=.004).

Table 2. Laboratory results of the study patients in responders and nonresponders before cardiac resynchronization therapy device implantation.

Variables	Responders (n = 51)	Nonresponders (n = 37)	P-value
Basal creatinine, mg/dL	0.99±0.34	1.11±0.29	.023
BUN, mg/dL	21.9±8.8	24.9±12.6	.342
Hemoglobin, g/dL	12.8±1.9	12.0±1.6	.107
Uricacid, mg/dL	7.06±2.4	6.56±3.05	.194
Albumin, g/dL	4.09±0.42	3.94±0.45	.248
RDW,(%)	15.7±1.59	15.8±1.37	.530
Lymphocyte count, (/mm3)	2.01±0.62	1.72±0.61	.025
Platelet count, (x109/L)	234±71	237±84	.946
SII, (x109/L)	631.3±386.7	951.2±550.2	.004

BUN = Blood ürea nitrogen; RDW = Red cell distribution width; SII = Systemic immune-inflammation index.

Multivariate logistic regression analysis model of predictors for response to CRT in the study patients are shown in Table 3. In the multivariate analysis; LVEF (p=0.040, odds ratio [OR] 1.122, 95% CI 1.005-1.251), QRS width (p=0.002, [OR] 1.105, 95% CI 1.038-1.185), and SII ≤973.3 (p=0.036, [OR] 5.542, 95% CI 1.112-24.699) were found to be independent predictors of response to CRT (Table 3). The optimal cut-off point of SII for prediction of response to CRT was found to be 973.3 (x109) in the ROC curve analysis (AUC:0.679, 95% CI 0.571-0.774, p=0.002). This cut-off value of SII ≤973.3 (x109) predicted response to CRT with a sensivity of 88.2% and specifity of 45.9% (Figure 1).

Table 3. Multivariate logistic regression analysis model of potential predictors for the response to cardiac resynchronization therapy.

Variable	Odds ratio (95% CI)	P-value
LVEF	1.122 (1.005-1.251)	.040
QRS width	1.105 (1.038-1.185)	.002
Basal creatinine	1.565 (0.189-12.926)	.678
SII ≤973.3	5.242 (1.112-24.699)	.036
Lymphocyte count	3.202 (0.918-11.167)	.068

LVEF = Left ventricular ejection fraction; SII = Systemic immun-inflammatory index.

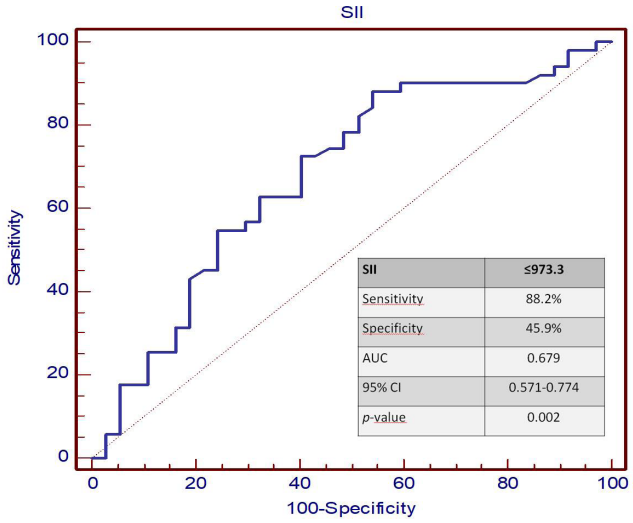

Figure 1. The reciever-operating characterisric (ROC) analysis for the systemic immune-inflammation index (SII) in prediction of response to cardiac resynchronization theraphy.

Discussion

To the best of our knowledge, this is the first study that has identified an association between the SII and response to CRT in patients with HF. In the present study we observed that SII measured within 24-48 hours prior to CRT implantation may have a role in predicting response to CRT. The SII was identified as a strong independent predictor of response to CRT, with an optimal cut-off value of ≤973.3. We also demonstrated an association between the response to CRT and other parameters which included LVEF and QRS width.

Cardiac resynchronization theraphy is considered an important treatment option of HF patients with prolonged QRS who are receiving optimal medical theraphy. However, prediction of response to CRT remains problematic and an important proportion of patients do not respond to CRT, although they are selected according to current patient selection criteria by international guidelines [16,17]. Additional echocardiographic, electrocardiographic, and blood markers have been investigated in several studies to identfy patients most likely to respond to CRT [18-21].

Full blood count is a readily avaliable, cheap and routine examination that provides accurate and reproducible information about erythrocyte, neutrophil, platelet and lymphocyte counts, RDW and parameters such NLR and PLR. On the other hand, SII has recently been described as a novel inflammatory biomarker [9]. It is calculated by the formula platelet count x neutrophil count /lymphocyte count and may be considered a combination NLR and PLR [9]. Many recent studies have demonstrated that SII is a strong independent predictor of major adverse events and prognosis in patients with several malignancies [9-12]. Patients with higher SII have increased recurrence rates, reduced survival and worse treatment response than patients with lower SII [9-12]. It is considered that a high SII level reflects an increased inflammatory condition. Thus, it has been shown that there was a correlation between the SII and other inflammatory markers, such as C-reactive protein (CRP), albumin, PLR and NLR [22,23]. It has been demonstrated that NLR and PLR are associated with response to CRT in patients with HF [6,7]. We first reported that a relationship between the NLR and response to CRT in our previous study [6]. In that study, we showed that a lower NLR was associated with good response to CRT [6]. Additionally, we also demonstrated that CRP levels were significantly reduced in responder patients in contrast to nonresponder patients [6]. Kerekanic et al. investigated the impact of CRT on serum levels of high sensitivity CRP (hs-CRP) in patients with chronic HF [24]. They demonstrated that hs-CRP levels reduced in responders after CRT implantation, but not in nonresponders [24]. Therefore, they suggested that hs-CRP could be widely used inflammatory biomarker for monitoring of CRT response [24]. In a study conducted by Balci et al., the role of baseline inflammatory markers in prediction of response to CRT was evaluated [7]. In their study, nonresponders to CRT had a higher NLR and PLR and lower lymphocyte count [7]. This result may reflect the deleterious effects of baseline inflammatory condition in patients with HF undergoing CRT [7]. In light of these data, it is well known that an increased inflammation is asscoiated with poor response to CRT. Patients who had a higher SII also had increased NLR, PLR and hs-CRP levels and these patients showed worse clinical outcomes in the follow-up [21,22]. In this context, it is not surprising that HF patients who have a higher SII levels also have poor response to CRT.

This is the first study to report the relationship between the SII and response to CRT in patients wit HF. Of note, a value of SII of ≤973.3 was an independent predictor of response to CRT in these patients. SII may be a useful, novel biomarker in prediction of response to CRT in addition to older inflammatory biomarkers such as hs-CRP, NLR and PLR.

Study Limitations

This study has some limitations. First, this retrospective study was conducted in a single-center with a small sample size. Second, the relationship SII and clinical outcomes were not evaluated. A prospective randomized multi-center study with a larger study population might increase the significance of the presented results.

Conclusion

SII, a novel inflammation-based biomarker combining platelet, neutrophil and lymphocyte counts, has been reported to be associated with clinical outcomes in several malignancies in many studies [9-12]. This is the first study to report a lower SII is associated with response to CRT in patients with HF. Pre-implantation SII, a readily avaliable and cheap biomarker, may help identfy patients who response to CRT.

Declaration of conflict of interest

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