Exp Biomed Res 2022; 5(4): 377-391
Doi: 10.30714/j-ebr.2022.157

Experimental Biomedical Research **Original article**

Systemic immune-inflammation index: A novel marker for predicting response to cardiac resynchronization therapy in patients with heart failure

Berat Uguz[1], Dursun Topal[1], Tufan Gunay[1], Selvi Oztas[1], Ismet Zengin[1], Selma Kenar Tiryakioglu[1], Alper Karakus[2]

[1]Department of Cardiology, Bursa City Hospital, Bursa, Türkiye
[2]Department of Cardiology, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Türkiye

ABSTRACT

Aim: To investigate the utility of systemic immune-inflammation index (SII) in predicting response to cardiac resynchronization therapy (CRT) among patients with heart failure (HF).
Method: A total of 78 patients with HF who underwent CRT device implantation were included in this 6-month follow up study. Data on laboratory findings including complete blood count, blood biochemistry and SII as well as the transthoracic echocardiography findings were recorded at baseline prior to CRT device implantation and 6 months after CRT.
Results: The criteria for response to CRT including improvements in New York Heart Association (NYHA), left ventricular end-systolic volume (LVESV) (decreased by ≥15%) and ejection fraction (EF) (increased by≥10%) were met by 73.1%, 65.4% and 69.2% of patients, respectively. In patients with decreased vs. increased SII values during 6-month therapy, the likelihood of meeting LVESV (84.3 vs. 15.7%, $p<0.001$), EF (81.5 vs. 18.5%, $p<0.001$) and NYHA (77.2 vs. 22.8%, $p<0.001$) response criteria for successful CRT were significantly higher. Multivariate analysis revealed that decrease in SII (OR 0.982, 95% CI: 0.970 to 0.995, $p=0.006$) and TAPSE (OR 0.602, 95% CI. 0.396 to 0.916, $p=0.018$) during treatment as the only significant determinants of presence of response to CRT in heart failure (HF) patients.
Conclusions: Our findings seem to indicate the favorable utility of SII, as a non-invasive readily available marker, in predicting response to CRT and thus enabling a beneficial reverse remodeling process via timely implementation of advanced treatments in HF patients.

Key words: Heart failure, cardiac resynchronization therapy, response to treatment, systemic immune-inflammation index, NYHA class, echocardiography.

Dr. Berat Uguz, Department of Cardiology, Bursa City Hospital, Bursa, Türkiye
E-mail: beratuguz33@hotmail.com
Received: 2022-04-03 / Revisisons: 2022-06-19
Accepted: 2022-07-05/ Published: 2022-09-15

Introduction

Cardiac resynchronization therapy (CRT) is an extensively validated and effective treatment option for patients with symptomatic heart failure (HF) who had New York Heart Association (NYHA) class II to IV, reduced (≤35%) left ventricular ejection fraction (LVEF), prolonged QRS (> 150 ms) and ventricular mechanical dyssynchrony manifesting as left bundle branch block, despite the optimal medical therapy [1-5].

The CRT, an atrial-synchronized biventricular pacing, has become an accepted treatment modality in HF patients due to its association with significant improvements in clinical symptoms by enabling reverse LV remodeling as well as the reduced mortality and long-term morbidity [3,6-8]. However, a considerable portion of HF patients (~30%), despite being selected for CRT based on criteria recommended by international guidelines, do not respond to CRT [2-5,9,10].

The predicting the response to CRT implantation is therefore considered of great value to prevent the incidence of nonresponse through adequate selection of the correct patients for CRT as a pivotal step in improving the overall efficacy of CRT treatment [2,4,11-13]. However, while clinical symptoms, ventricular remodeling indices on echocardiography, and cardiovascular events have been associated with non-responders, there is no uniform consensus or definition of CRT response criteria [11]. In addition, amongst the several echocardiographic, electrocardiographic and blood markers have been investigated to date, none is considered a definite marker with adequate sensitivity and strong predictive value to identify the patients most likely to respond to CRT [2,4,11,13-15].

Inflammatory factors, on the basis of their association with development of adverse cardiac remodeling and progressive left ventricular dysfunction, are suggested to be potential biomarkers for poor prognosis of HF [16,17]. Systemic immune-inflammation index (SII), a composite inflammatory indicator of neutrophil, platelet, and lymphocyte levels, is considered to reflect the inflammation status better than the absolute count of single immune cells, and to be an excellent indicator of local immune response and systemic inflammation [17-19]. Recently, SII has emerged as a prognostic factor for a variety of cardiovascular diseases including coronary artery disease (CAD) and aortic stenosis and infective endocarditis [20,21] as well as HF [2,17,22], while its association with treatment response and long-term outcomes has also been suggested in HF patients with intracardiac defibrillators (ICDs) or CRT [2,22]. Therefore, this study aimed to investigate the utility of SII in predicting response to CRT in HF patients via analysis of baseline and in-treatment SII values in relation to CRT response criteria defined by echocardiographic indices plus NYHA class.

Materials and methods

Study population

A total of 78 patients (mean±SD age: 64.4±10.2 years, 73.1% were males) with HF who underwent CRT device implantation were included in this 6-month follow-up study. Patients with known hepatobiliary disease, hematologic disease, chronic inflammatory disease, autoimmune disease, malignancy and those under treatment with steroid or NSAIDs were excluded from the study.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” and approved by the institutional ethics committee (Date of Approval: 15/12/2021, Reference No: 2021-23/7)

Study parameters

Data on patient demographics (age, gender), smoking status, body mass index (BMI, kg/m^2), co-morbid diseases, and concomitant medications were recorded at baseline. Data on laboratory findings including complete blood count (CBC), blood biochemistry, inflammation and immune-based prognostic markers (erythrocyte sedimentation rate [ESR], CRP,

DDimer), cardiovascular risk markers (B-type natriuretic peptide [BNP], troponin) and systemic immune inflammation index as well as the cardiac imaging (electrocardiography [ECG]) and transthoracic echocardiography) findings were recorded at baseline prior to CRT device implantation and 6 months after CRT.

Response to CRT was defined as ≥15% decrease in left ventricular end-systolic volume (LVESV) and/or ≥10% increase in ejection fraction (EF) along with an improvement in NYHA by at least 1 class at the 6th month of CRT compared to pre-treatment values. SII and CRT-response parameters (LVESV, EF and NYHA scores) before and 6 months after CRT, as well as the percent change from baseline SII values with respect to CRT-response parameters and echocardiography findings were evaluated. The determinants of response to CRT were also assessed via univariate and multivariate analyses.

Cardiologic imaging assessments

Transthoracic echocardiography was performed before CRT and 6 months after CRT in all patients by the same cardiologist. Echocardiographic evaluation was performed using a GE Vivid S5 Ultrasound Machine (GE Vingmead, Horten, Norway) with 2-4 MHz phased-array transducer, under ECG monitoring. Two-dimensional and M-mode recordings of subjects were obtained from parasternal long axis view in the left lateral decubitus position. Tissue Doppler echocardiography (TDE) were obtained from the apical four-chamber view in the supine position.

Left and right ventricle diameters were measured and left ventricular ejection fraction (EF) was calculated. Tissue Doppler images of the right ventricle were also assessed for peak systolic velocity (S), right ventricular end-diastolic (RVED) area, right ventricular end-systolic (RVES) area and RV fractional area change (FAC) calculated using the formula: (end-diastolic area – end-systolic area)/end-diastolic area × 100. The tricuspid annular plane systolic excursion (TAPSE) was obtained from the apical four-chamber view with the M mode. Tissue Doppler images of the left ventricle were assessed for peak systolic velocity (S), peak early diastolic velocity (E') and peak late diastolic velocity (A'), the trans-mitral early diastolic rapid filling (E-wave) and atrial contraction late filling (A-wave) velocities to calculate E/A ratio.

Statistical analysis

Statistical analysis was made using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). Chi-square test was used for analysis of categorical variables, while Mann-Whitney U test was used to compare two independent non-normally distributed variables. Paired samples t-test or Wilcoxon test were used for repeated measurement analysis depending on distrusting pattern of continuous variables. Spearman correlation test was performed to test relationships in ordinal or quantitative variable with non-normal distribution. Variables having p value <0.05 in univariate analysis were analyzed further in a multivariate regression model to identify significant determinants of response to CRT. Data were expressed as "mean ± standard deviation (SD), median (min-max), 95% confidence interval (CI) and percent (%) where appropriate. p<0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

The mean patient age was 64.4 (SD 10.2) years and males composed 73.1% of the study population. Hypertension (79.5%) was the leading comorbidity (Table 1).

Table 1. Demographic and clinical characteristics

Age (year)	Mean ± SD	64.4±10.2
	median (min-max)	65.5(36-85)
Gender, n (%)		
Male		57(73.1)
Female		21(26.9)
Body mass index (kg/m^2), mean±SD		25.1±2
Active smoking, n (%)		19(24.4)
Comorbidities, n (%)		
Hypertension		62(79.5)
Diabetes mellitus		32(41.0)
Coronary artery disease		52(66.7)
Chronic renal failure		5(6.4)
Concomitant medications, n (%)		
ASA		44
ß-blocker		77
ACE inhibitor		75
Spironolactone		70
Thiazide diuretic		12
Furosemide diuretic		69
Cordarone		21
Sacubitril		6
Baseline ECG findings, n (%)		
Sinus rhythm		74(94.9)
Atrial fibrillation		4(5.1)
ORS, mean (SD)		139.1±5.1

Laboratory findings and cardiac imaging

Data on CBC, blood biochemistry and echocardiography findings before and 6 months after CRT are provided in Table 2 and Table 3.

SII and CRT-response parameters (LVESV, EF and NYHA scores)

When compared to baseline values, 6-month CRT was associated with significantly increased EF (median(min-max) 21(15-35) vs. 35(15-55), $p<0.001$) and significantly decreased LVESV (184(78-291) vs. 142.5(56-265), $p<0.001$) along with significantly improved NYHA scores (3(2-4) vs. 2(1-3), $p<0.001$) and NHYA category (class III: from 85.9 to 29.5%) in HF patients. No significant difference was noted between pre-treatment vs. post-treatment SII values during 6-month CRT, while a decrease from baseline values were noted in 61.5% of patients and an increase from baseline was evident in 38.5% (Table 4).

The criteria for response to CRT including improvements in NYHA, LVESV (decreased by ≥15%) and EF (increased by≥10%) were met by 73.1%, 65.4% and 69.2% of patients, respectively (Table 4).

SII values with respect to CRT-response parameters (LVESV, EF and NYHA scores)

Median (min-max) SII values measured at baseline were significantly higher in patients with vs. without LVESV response (677.7(11.9-1661.3) vs. 497.5(72.4-1275.0), $p=0.016$), while no significant difference was noted in baseline SII values with respect to EF and NHYA response. SII values after 6-month CRT were significantly lower in patients with vs. without LVESV response (546.9(3.9-1220.7) vs. 764.7(111.9-2403.4), $p=0.017$), EF response (550.1(3.9-1220.7) vs. 789.6(111.9-2403.4), $p=0.018$) and NHYA improvement (553.3(3.93-1220.7) vs. 621.3(232.0-2403.4), $p=0.020$) (Table 5).

Percent change from baseline SII significantly differed with respect to fulfillment of CRT response criteria including a decrease rather than an increase in SII values during 6-month therapy among patients with vs. without improvements in NYHA (median -18.6 vs. 29.2, $p<0.001$),

LVESV (median -20.8 vs. 36.7, p<0.001) and EF (median -20.0 vs. 33.0, p<0.001) (Table 5).

In patients with decreased vs. increased SII values during 6-month CRT, the likelihood of meeting LVESV (84.3 vs. 15.7%, p<0.001), EF (81.5 vs. 18.5%, p<0.001) and NYHA (77.2 vs. 22.8%, p<0.001) response criteria for CRT-response was also significantly higher (Table 5). Baseline QRS values were also significantly higher in patients with decreased SII values compared to those with increased SII values (141.1±4.7 vs. 135.7±3.7, p<0.001) during 6-month CRT.

Table 2. Laboratory findings before and 6 months after cardiac resynchronization therapy (CRT).

Parameters	Before CRT			6 months after CRT		
	N	Mean±SD	Median (min-max)	N	Mean±SD	Median (min-max)
Hemoglobin (g/dL)	77	13.0±2	12.9(8-17)	78	16.1±27.1	13.2(8-252)
WBC (10^3/μL)	76	8.1±2.4	7.9(3.8-13.1)	75	8.4±2.8	8(4-24.1)
Platelet (10^3/μL)	78	236.4±66.6	229(92-436)	78	221.3±68.5	217.5 (67-431)
Neutrophil (10^3/μL)	72	5.3±1.7	4.9 (2-9.3)	72	5.5±2.6	5(2.3-22.8)
Lymphocyte (10^3/μL)	74	2.0±0.7	1.9(0.6-3.9)	72	2.1±1.1	2(0.4-7)
Monocyte (10^3/μL)	76	0.7±0.3	0.7 (0-1)	78	0.8±0.6	0.7 (0-5)
Eosinophil (10^3/μL)	77	0.2±0.2	0.1(0-1)	78	0.4±1.6	0.1(0-14)
Urea (mg/dL)	78	47.8±29.1	40(13-215)	76	50.7±36.8	41.8(1-295)
Creatinine (mg/dL)	77	1.3±0.9	1.1(1-8)	77	2.6±11.4	1.1(0-101)
GFR (mL/min/1.73m^2)	71	68.1±23.9	75(5-110)	74	64.3±27.2	64.5(7-215)
AST (IU/L)	75	24.7±25.0	20(1-1)	74	45±194.7	18.5(8-1693)
ALT (U/L)	76	25±21.6	17 (5-125)	72	20.8±18.1	16 (5-115)
Cholesterol (mg/dL)	52	174.1±38.6	167.5 (112-262)	25	180±46	179 (104.275)
Triglyceride (mg/dL)	51	149.7±79.3	131 (16-431)	23	166.5±103.2	134 (56-453)
HDL (mg/dL)	52	46.6±13.3	46 (23-94)	25	47.1±11.4	43 (34-69)
LDL (mg/dL)	52	94.9±35.6	90.8 (29-179)	25	103.1±43.5	107 (27-200)
Uric acid (mg/dL)	20	6.7±1.6	6.9 (5-11)	14	7.2±2.7	6.9 (3-13)
ESR (mm/h)	7	30.4±37.9	16(2-112)	5	33.2±28.3	30 (4-75)
CRP (mg/L)	46	12±16.1	5.2 (1-74)	47	11±22.6	5.4 (0-152)
Troponin (ng/L)	36	227.5±1078.3	31.2 (0-6512)	23	64.6±61.3	40 (14-191)
DDimer (ug/mL FEU)	6	3.7±2.5	4.2(0-7)	7	0.9±0.5	0.7(0-2)
BNP (ng/L)	26	9429.7±7865.2	8119 (130-25410)	30	5241.2±7158.7	1586.5(229-24651)

WBC: White blood cell; GFR: Glomerular filtration rate; AST: Aspartate transaminase; ALT: Alanine transaminase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TSH: thyroid stimulating hormone; T3: triiodothyronine; T4: thyroxine; ESR: Erythrocyte sedimentation rate; BNP: B-type natriuretic peptide; CRP: C-reactive protein.

Correlation between SII and echocardiography parameters

Based on percent change from baseline values, SII was correlated positively with LVEDV (r=0.518, p<0.001), LVESV (r=0.541, p<0.001),

RVES area (r=0.397, *p*=0.001), RVED area (r=0.265, *p*=0.035), BNP (r=0.502, *p*=0.040) and NYHA (r=0.475, *p*<0.001), and was correlated negatively with LVEF (r=-0.530, *p*<0.001), RV FAC (r=-0.368, *p*=0.003), TAPSE (r=-0.385, *p*=0.001) and baseline QRS (r=-0.440, *p*<0.001) (Table 6).

Univariate and multivariate analyses for determinants of response to CRT

In the univariate analysis, decrease in SII (% change: median -23.5 vs. 54.6 in responders and non-responders, respectively, *p*<0.001), RVES area (-17.5 vs. -2.9, *p*<0.001), RVED aera (-3.7 vs. 0.0, *p*<0.001) and TAPSE (-18.0 vs. –15.0,*p*=0.008) but increase in RV FAC (18.6 vs. 4.2, *p*<0.001) from baseline were associated with increased likelihood of response to CRT (Table 7).

Table 3. Echocardiography findings before and 6 months after cardiac resynchronization therapy (CRT).

Parameters	Before CRT			6 months after CRT		
	N	Mean±SD	Median (min-max)	N	Mean±SD	Median (min-max)
EF	78	23.9±5.4	21(15-35)	76	34.1±9.5	35(15-55)
LVEDV	78	247.6±60.8	255.5(108-358)	76	209±53	215(98-308)
LVESV	78	187.9±51.6	184(78-291)	76	149.1±48	142.5(56-265)
LVD (diastolic)	77	6.4±0.5	6.4(5-7)	76	6.1±0.5	6(5-7)
LVD (systolic)	78	5.3±0.5	5.3(4-6)	76	5±0.5	4.9(4-6)
IVS	78	1±0.1	1(1-1)	76	1±0.1	1(1-1)
PW	78	1±0.1	1(1-1)	75	1±0.1	1(1-1)
LA	78	4.6±0.4	4.5(4-6)	76	4.5±0.6	4.4(1-6)
MY	78	2.6±0.7	3(1-4)	76	1.9±0.5	2(1-3)
Ty anulus	78	3.8±0.2	3.8(3.4)	76	3.7±0.2	3.7(3-4)
TY	78	2.9±0.4	3(2-4)	76	2.3±0.6	2(1-3)
AY	78	0.3±0.5	0 (0-2)	76	0.4±2.3	0(0-20)
E	78	90.5±14.8	92(64-123)	76	77±14.9	75.5(50-115)
A	77	68.4±14.0	66(41-97)	71	65.6±13.5	65(40-95)
E/A	77	1.4±0.3	1.4(1-2)	71	1.2±0.3	1.2(1-2)
LV lat E	78	8.2±1.2	8.5(6-12)	76	9.8±1.3	10(7-13)
LV lat A	77	10.1±1.1	10.2(8-13)	71	9.7±1.1	10(7.13)
LV lat S	78	7.7±1.2	8(6-10)	76	8.1±1.2	8.5(6-10)
LV med E	78	7.3±1.1	7.5(5-10)	76	8.3±1.2	8.1(5-11)
LV med A	77	9.7±1.2	10(7-13)	71	9.6±1.2	10(7-13)
LV med S	78	7.1±1.2	7.2(5-10)	77	7.4±1.2	8(5-10)
RV E	78	57.3±11.0	57(36-86)	76	65.1±12.4	65.5(40-95)
RV A	77	44.6±9.1	45(30-66)	71	51.8±10	54(32-75)
RV lat E	78	8.6±1.1	8(6-12)	76	11±1.7	11(8-15)
RV lat A	77	10.7±1.1	10.8(9-14)	71	12.5±1.4	12.6(10-16)
RV lat S	78	9.2±1.1	9(7-11)	76	11.3±11.6	11.5(8-15)
RVED area	78	29.6±2.7	29.6(24-38)	76	28.4±2.5	28.2(25-36)
RVES area	78	17.5±2.7	17.2(13-25)	76	15.1±2.8	14.3(10-23)
TAPSE	78	17±2.2	18(12-21)	78	0±0	0(0-0)
FAC	78	40.8±6.8	40.5(21-54)	76	47±7.2	47.6(23-60)
PASP	78	47.8±9.9	45(28-70)	76	35.6±8.5	35(20-60)

EF: Ejection fraction; LVED: Left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; IVS: Interventricular septum; E-wave: trans-mitral early diastolic rapid filling; A-wave: atrial contraction late filling; E/A: Ratio of trans-mitral early to late peak velocities; E': Peak early diastolic velocity; A': Peak late diastolic velocity; S: Peak systolic velocity; LV: Left ventricle; RV: Right ventricle; lat: lateral; med: medial; TAPSE: tricuspid annular plane systolic excursion; PSAP: Pulmonary artery systolic pressure; RVES: Right ventricular end-systolic; RVED: Right ventricular end-diastolic; FAC: Fractional area change.

Multivariate logistic regression analysis revealed that decrease in SII (OR 0.982,95% CI: 0.970 to 0.995, *p*=0.006) and TAPSE (OR 0.602, 95% CI. 0.396 to 0.916, *p*=0.018) during treatment as the only significant determinants of good response to CRT in HF patients (Table 7).

Table 4. SII and CRT-response parameters (LVESV, EF and NYHA) before and after CRT.

Parameters		**Before CRT**			**6 months after CRT**			***p* value**
		n	mean±SD	median(min-max)	n	mean±SD	median(min-max)	
SII		78	688.1±363.8	591.2(11.9-1661.3)	78	735.9±545.3	611.1(3.9-3471.9)	*0.179*
EF		78	23.9±5.4	21(15-35)	76	34.1±9.5	35(15-55)	***<0.001***
LVESV		78	187.9±51.6	184(78-291)	76	149.1±48	142.5(56-265)	***<0.001***
NYHA score		78	3.1±0.4	3(2-4)	76	2.0±0.8	2(1-3)	***<0.001***
Class, n(%)	Class I	0(0.0)			24(30.1)			
	Class II	2(2.6)			29(37.2)			
	Class III	67 (85.9)			23(29.5)			
	Class IV	9(11.5)			0(0.0)			
Response to CRT					n(%)			
NHYA		remained unchanged			19(24.4)			
		improved by at least one NYHA class			57(73.1%)			
LVESV (decreased by ≥15%)					51(65.4)			
EF (increased by≥10%)					54(69.2)			
SII change from baseline to 6-month CRT					n(%)			
Decreased					48(61.5)			
Increased					30(38.5)			

SII: Systemic immune-inflammation index; EF: Ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association class

Table 5. SII values with respect to CRT-response parameters (LVESV, EF and NYHA).

Parameters		**SII, median(min-max)**		**SII (change form baseline)**		**SII (% change)**
		Before CRT	**After CRT**	**Decreased (n=48)**	**Increased (n=30)**	**Median (min-max)**
LVESV	No response (n=25)	497.5(72.4-1275.0)	764.7(111.9-2403.4)	5(20.0)	20(80.0)	36.7(-30.9-753)
	Decreased by ≥15% (n=51)	677.7(11.9-1661.3)	546.9(3.9-1220.7)	43(84.3)	8(15.7)	-20.8(-75.5-177.5)
	p value	**0.016**	**0.017**	**<0.001**		**<0.001**
EF	No response (n=22)	517.4(72.4-1275.0)	789.6(111.9-2403.4)	4(18.2)	18(81.8)	33.0(-30.9-753)
	Increased by≥10%) (n=54)	670.2(11.9-1661.3)	550.1(3.9-1220.7)	44(81.5)	10(18.5)	-20.0(75.5-177.5)
	p value	0.097	**0.018**	**<0.001**		**<0.001**
NYHA	No response (n=19)	237.3(178.1-1065.1)	621.3(232.0-2403.4)	4(21.1)	15(78.9)	29.2(-30.9-753.3)
	Improved (n=57)	675.2(11.9-1661.3)	553.3(3.93-1220.7)	44(77.2)	13(22.8)	-18.6(-75.5-177.5)
	p value	0.067	**0.020**	**<0.001**		**<0.001**

SII: Systemic immune-inflammation index; LVESV: left ventricular end-systolic volume; EF: Ejection fraction; NYHA: New York Heart Association class.

Table 6. Correlation between percent change in SII and echocardiography parameters.

Parameters	**SII (% change)**	
% change	**r**	***p value***
EF	-0.530	***<0.001***
LVEDV	0.518	***<0.001***
LVESV	0.541	***<0.001***
FAC	-0.368	***0.003***
RVES area	0.397	***0.001***
RVED area	0.265	***0.035***
TAPSE	-0.385	***0.001***
BNP	0.502	***0.040***
NYHA	0.475	***<0.001***
Baseline QRS	-0.440	***<0.001***

SII: Systemic immune-inflammation index; EF: Ejection fraction; LVED: Left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; FAC: Fractional area change; RVES: Right ventricular end-systolic; RVED: Right ventricular end-diastolic; TAPSE: Tricuspid annular plane systolic excursion; NYHA: New York Heart Association class; BNP: B-type natriuretic peptide; r: correlation coefficient; Spearman correlation analysis.

Table 7. Univariate and multivariate analyses for determinants of response to CRT.

Parameters	**Univariate analysis**			**Multivariate logistic regression analysis**			
% change	**Response to CRT**			**Response to CRT**			
	No	**Yes**	***p* value**	**Exp(B)**	**95% CI**		***p* value**
	Median (min-max)	**Median (min-max)**			**LB**	**UB**	
SII	54.6(-30.9-753.3)	-23.5(-75.5-177.5)	**<0.001**	0.982	0.970	0.995	***0.006***
RVES area	-2.9(-25.9-6.8)	-17.5(-33.8-1.3)	**<0.001**	0.799	0.615	1.039	*0.094*
RVED area	0(-4.6-4.1)	-3.7(-15-3.5)	**<0.001**	0.839	0.508	1.384	*0.491*
TAPSE	-15(-21-(-12))	-18(-21-(-13))	**0.008**	0.602	0.396	0.916	***0.018***
RV FAC	4.2(-8.2-45.8)	18.6(-1.3-105.0)	**<0.001**	0.938	0.850	1.036	*0.206*
Constant				0.00			*0.021*

SII: Systemic immune-inflammation index; RVES: Right ventricular end-systolic; RVED: Right ventricular end-diastolic; TAPSE: Tricuspid annular plane systolic excursion; FAC: Fractional area change; CI: Confidence interval: LB: Lower bound; UB: upper bound.

Discussion

Our findings revealed improvements in the NYHA (by at least one class), LVESV (decreased by ≥15%) and EF (increased by≥10%) indicating a good response to 6-month CRT in at least 65% of HF patients, as well as the higher likelihood of the three CRT-response criteria to be met by patients with vs. without decrease in SII levels from baseline under CRT. In addition to its correlation with the CRT-response criteria (EF, LVESV and NYHA), the change from baseline SII was also correlated with baseline QRS width, certain RV echocardiographic parameters (TAPSE, RVES area, RVED area, RV FAC) and serum BNP levels. Multivariate logistic regression analysis revealed the decrease in SII from baseline to 6th month of CRT as the only significant determinants of response to CRT in HF patients.

CRT is considered an effective nonpharmacologic therapy associated with improved cardiac function and quality of life as well as lower risk of HF hospitalizations and mortality among HF patients with reduced EF and ventricular dyssynchrony manifests as LV conduction delay [1,23]. Nonetheless, as supported by our findings, the non-response rate to CRT remains around 30% in the setting of HF, despite its efficacy in remodeling of the LV leading to improved LV function via decreased dimensions and increased EF [1,4,23].

SII, as a newly defined prognostic index that integrates three circulating immune cells (neutrophils, lymphocytes and platelets), is suggested to have a prognostic value in patients with cardiovascular disease [17,20,21,24] as well as in the follow-up of patients with ICDs for HF reduced with ejection fraction (HFrEF) [22] and those with CRT device implantation [2].

In a multivariate regression analysis in 4,066 critically ill patients with HF, the authors reported that after adjusting for possible confounders (i.e., age, heart rate, and albumin), the high level of SII effectively predicted high 30- and 90-day and hospital mortalities, as well as the high risk of occurrence of major cardiovascular events (MACEs) [17]. Similarly, in a past study with 5602 CAD patients, the authors reported that a higher SII score (≥694.3) was independently associated with increased risk of developing cardiac death (HR: 2.02), nonfatal MI (HR: 1.42), nonfatal stroke (HR: 1.96), MACEs (HR: 1.65) and total major events (HR: 1.53), indicating SII to have a better prediction of major cardiovascular events than traditional risk factors in CAD patients after coronary intervention [20]. Moreover, in a 10-year follow up study on the long-term prognostic impact of SII in 1011 patients with ICD for HFrEF, patients with a higher SII (≥1119) value were reported to have significantly higher long-term mortality and appropriate ICD therapy rates, and the authors considered the likelihood of SII to be an independent predictive marker for both long-term mortality and appropriate ICD therapy in patients with HFrEF [22].

Likewise, our findings indicate SII values to be a potential novel marker for predicting response to CRT in patients with HF, with better treatment response noted in patients with decrease vs. increase in SII from baseline during CRT as reflected by the improved EF, LVESV and NYHA status as well as the concomitantly improved RV function parameters.

Notably, in a past study among 88 HF patients who underwent CRT device implantation, 57.9% of patients were reported to be responders based on echocardiographic CRT response (a decrease in LVESV of ≥15% and/or absolute increase of 5% in EF) at 6-month follow-up after CRT implantation, while the authors also noted presence of significantly lower baseline SII levels but higher lymphocyte count, LVEF and QRS width in responders vs. non-responders to

CRT [2]. The authors concluded that based on multivariate logistic regression analysis, a SII cut-off value of ≤973.3 measured within 24-48 hours prior to CRT implantation along with LVEF and QRS width were independent predictors for response to CRT, emphasizing that SII may be used as a novel, simple and reliable inflammatory biomarker in the prediction of response to CRT in patients with HF [2].

Notably, in the current study, higher baseline SII values seems to be associated with increased likelihood of LVESV response per se, while SII values after 6 months of CRT were significantly lower among responders vs. non-responders for each of the response criteria (LVESV, EF, NYHA). Hence, our findings seem to emphasize the role of monitoring SII values after CRT implantation, and the association of a decrease rather than an increase in SII values from baseline to 6th month of CRT with a higher chance of having a good response to CRT in HF patients.

These findings seem consistent with consideration of SII as a marker reflecting a combination NLR and PLR [19] as well as the association of lower NLR and PLR also with a good response to CRT in patients with HF [25,26]. Indeed, the concomitant rise in SII in patients with increased NLR, PLR and hs-CRP levels who had worse clinical outcomes in the follow-up is considered to reflect the deleterious effects of baseline inflammatory condition in patients with HF undergoing CRT [2,4,26]. The decline in SII values under CRT, as found to predict better CRT response in our patients, seems to indicate the amelioration of inflammation and thus achievement of a better treatment response in our HF patients.

In this regard, our findings support the utility of SII as a readily available novel biomarker in addition to older inflammatory biomarkers (i.e., hs-CRP, NLR and PLR) in prediction of response to CRT among HF patients [2], while also emphasize the critical prognostic role of change in SII from baseline under therapy rather than the preimplantation SII in predicting CRT response defined as improved LVESV, EF and NHYA.

The significantly improved NYHA by at least 1 class in 73.1% of our patients after 6-month CRT support the data from a pooled analysis of three studies indicated significant improvements in NYHA by at least one NYHA class in 57% of patients (RR 1.6, 95% CI: 1.1 to 2.5) with CRT [14]. In addition, the higher likelihood of having a decrease in SII values during 6-month CRT in our patients with higher baseline QRS seems notable given the role of morphology of QRS waves in deciding ventricular dyssynchrony for CRT inclusion criteria as well as the consideration of a strong positive correlation between the larger QRS area in the pre-treatment period with better CRT response [11].

Besides its well-known effects on LV function (i.e., improved LVEF, decreased intraventricular mechanical dyssynchrony, and favorable LV remodeling) [27,28], some studies have also suggested the association of CRT with significant improvements in RV size and function in patients with HF [29-32]. In the current study, apart from achievement of CRT response (based on EF, LVESV and NYHA) in at least 60% of patients, SII change during CRT was also correlated with echocardiographic parameters of RV function (negatively with TAPSE and RV FAC, and positively with RVES area and RVED area). This seems notable given that in addition to SII, change from baseline in all of these echocardiographic parameters of RV function also differed significantly among responders (decrease in TAPSE, RVES area and RVED area, increase in FAC) vs. non-responders, whereas only SII and TAPSE remained as predictors of CRT response in the multivariate analysis.

Although TAPSE is considered a relatively simple echocardiographic measure of RV function showing a good correlation with more precise measures of RV systolic function, it only assesses the contribution of RV free wall in prediction of RV global systolic function [1,32-34]. FAC is considered a more global measure of RV systolic function that correlates well with cardiac MRI-derived RVEF, while it reflects a measure of RV response to afterload rather than contractility [32,35]. In the current study, while both TAPSE and RV FAC were negatively correlated with SII change from baseline, increase in RV FAC but decrease in TAPSE during 6-month CRT was associated with higher likelihood of responding to CRT and only TAPSE and SII were found to significantly predict the CRT response. In fact, the effects of CRT on RV function remain controversial, as the previous studies reported both the association of CRT with an improved RV function (as assessed by RV FAC) [30] as well as no significant improvements in TAPSE or RV dimensions in patients who received CRT therapy [36,37]. Also, in a meta-regression analysis of 16 studies in 1764 patients on the relation of baseline RV function (TAPSE, RVEF, RV basal strain or RV FAC) with response to CRT (as assessed by change in LVEF), the authors concluded that baseline RV function as assessed by TAPSE, FAC, basal strain or RVEF does not determine response to CRT after a mean follow up period of 10.5 months [31].

Notably, in a meta-regression analysis of 13 studies in 1541 HF patients to evaluate the relationship of CRT on various echocardiographic parameters of RV function, 9-month CRT therapy was reported to be associated with significant increases in TAPSE and RV FAC, whereas after meta-regression analysis for age, QRS duration, and baseline LVEF as covariates, the authors concluded that there was no significant improvement in any of the parameters of RV function after CRT [32]. Hence, significant improvement in the echocardiographic parameters of RV function (TAPSE, RV basal strain, RV FAC) after CRT was concluded to be not independent of baseline clinical variables but statistically dependent on age, QRS duration and baseline LVEF [32].

The positive correlation between SII and BNP in the current study seems to support the previously reported data on the association of elevated baseline BNP with a 68% increased risk of HF or death in HF patients allocated to CRT-D, as well as the association of lower 1-year BNP levels with a significantly higher echocardiographic response to CRT-D and a lower risk of HF or death, compared to the subgroup where BNP levels remained high [38]. Other studies also reported evidence for the usefulness of BNP (lower levels measures at either baseline or during the early period after CRT implantation) as a predictor of the CRT response (defined as ≥15% decrease in LVESV) [4,39,40].

In addition to natriuretic peptides such as BNP, the markers of collagen synthesis (i.e., PINP) as well as the inflammatory markers (especially CRP, gal-3, and CT-apelin) are also considered amongst the biomarkers with promising results in predicting left ventricular remodeling and response to CRT implantation [3]. However, the currently available data on potential biomarkers with definite prognostic value in identifying CRT response in HF patients remain inconclusive, given the limited number of available biomarker studies with use of different definitions for the CRT response in these studies, most of which also focused on the effect of postprocedural marker measurement rather than the baseline and preprocedural measurements on follow-up outcomes [3,4].

In this regard, providing data on the association of SII with response to CRT based on

comprehensive analysis involving baseline and follow up SII values as well as the change from baseline in relation to the three response criteria (EF, LVESV and NYHA), our findings indicate the likelihood of monitoring SII levels after CRT implantation to be used to improve risk assessment in HF patients, enabling a beneficial reverse remodeling process after implantation via timely implementation of advanced treatments (i.e., cardiac transplantation or mechanical circulatory support) for the survival of patients [3,4].

Nonetheless, the etiology of CRT non-response is considered to be multifactorial, necessitating a multifaceted approach to address and prevent the risk of non-response along with the proper preoperative patient selection, electrode implantation and postoperative optimization [4,11,23].

Conclusions

In conclusion, our findings revealed a good response to CRT by at least 65% of HF patients, along with the decrease in SII and TAPSE during treatment period as significant determinants of a good response to CRT. Monitoring the change in SII levels after CRT implantation rather than the pre-implantation baseline SII values seems to better predict the CRT response in terms of improved LVESV, EF and NHYA among HF patients. Accordingly, our findings seem to indicate the favorable utility of SII, as a non-invasive readily available marker, in predicting response to CRT and thus enabling a beneficial reverse remodeling process via timely implementation of advanced treatments in HF patients. Larger scale prospective studies simultaneously addressing several biomarkers in relation to standardized CRT response criteria are needed to identify the optimal biomarker to predict the response to CRT in HF patients.

Funding: *The author(s) received no financial support for the research, authorship, and/or publication of this article.*

Conflict of Interest: *The authors declare that they have no conflict of interest.*

Ethical Statement: *The study protocol was approved by Local Ethics Committee. (Date of Approval: 15/12/2021, Reference No: 2021-23/7)*

References

[1]Ojo A, Tariq S, Harikrishnan P, et al. Cardiac Resynchronization Therapy for Heart Failure. Interv Cardiol Clin. 2017; 6(3): 417-426.

[2]Karauzum K, Karauzum I, Celikyurt U, et al. A lower systemic immune-inflammation index level is associated with response to cardiac resynchronization theraphy. Turk J Clin Lab. 2020; 11(3): 186-192.

[3]Asgardoon MH, Vasheghani-Farahani A, Sherafati A. Usefulness of Biomarkers for Predicting Response to Cardiac Resynchronization Therapy. Curr Cardiol Rev. 2020; 16(2): 132-140.

[4]Heggermont W, Auricchio A, Vanderheyden M. Biomarkers to predict the response to cardiac resynchronization therapy. Europace. 2019; 21(11): 1609-1620.

[5]Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129-2200.

[6]Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: The MIRACLE ICD Trial. JAMA. 2003; 289(20): 2685-2694.

[7]Cazeau S, Ritter P, Lazarus A, et al. Multisite pacing for end-stage heart failure: early experience. Pacing Clin Electrophysiol. 1996; 19(11 Pt 2): 1748-1757.

[8] Linde C, Abraham WT, Gold MR, et al. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: Results from the REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) study. J Am Coll Cardiol. 2010; 56(22): 1826-1831.

[9]Al Jaroudi W, Chen J, Jaber WA, et al. Nonechocardiographic imaging in evaluation for cardiac resynchronization therapy. Circ Cardiovasc Imaging. 2011; 4(3): 334-343.

[10]Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol. 2004; 44(9): 1834-1840.

[11]Zhu H, Zou T, Zhong Y, et al. Prevention of non-response to cardiac resynchronization therapy: points to remember. Heart Fail Rev. 2020; 25(2): 269-275.

[12]Daubert C, Behar N, Martins RP, et al. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. Eur Heart J. 2017; 38(19): 1463-1472

[13]Rickard J, Michtalik H, Sharma R, et al. Predictors of response to cardiac resynchronization therapy: a systematic review. Int J Cardiol. 2016; 225: 345-352.

[14]McAlister F, Ezekowitz J, Wiebe N, et al. Cardiac Resynchronization Therapy for Congestive Heart Failure: Summary. 2004 Nov. In: AHRQ Evidence Report Summaries. Rockville (MD): Agency for Healthcare Research and Quality (US); 1998-2005. 106. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11907/

[15]Curtis AB. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med. 2013; 369(6): 579.

[16]Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. Circ Res. 2015; 116(7): 1254-1268.

[17]Tang Y, Zeng X, Feng Y, et al. Association of Systemic Immune-Inflammation Index With Short-Term Mortality of Congestive Heart Failure: A Retrospective Cohort Study. Front Cardiovasc Med. 2021; 8: 753133.

[18]Wang BL, Tian L, Gao XH, et al. Dynamic change of the systemic immune inflammation index predicts the prognosis of patients with hepatocellular carcinoma after curative resection. Clin Chem Lab Med. 2016; 54(12): 1963-1969.

[19]Zhang Y, Lin S, Yang X, et al. Prognostic value of pretreatment systemic immune-inflammation index in patients with gastrointestinal cancers. J Cell Physiol. 2019; 234(5): 5555-5563.

[20]Yang YL, Wu CH, Hsu PF, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary

artery disease. Eur J Clin Invest. 2020; 50(5): e13230.

[21] Tosu AR, Kalyoncuoglu M, Biter HI, et al. Prognostic value of systemic immune-inflammation index for major adverse cardiac events and mortality in severe aortic stenosis patients after TAVI. Medicina (Kaunas). 2021; 57(6): 588.

[22] Hayıroğlu Mİ, Çınar T, Çinier G, et al. Evaluating systemic immune-inflammation index in patients with implantable cardioverter defibrillator for heart failure with reduced ejection fraction. Pacing Clin Electrophysiol. 2022; 45(2): 188-195.

[23] Naqvi SY, Jawaid A, Goldenberg I, et al. Non-response to Cardiac Resynchronization Therapy. Curr Heart Fail Rep. 2018; 15(5): 315-321.

[24] Strassheim D, Dempsey EC, Gerasimovskaya E, et al. Role of inflammatory cell subtypes in heart failure. J Immunol Res. 2019; 2019: 2164017.

[25] Agacdiken A, Celikyurt U, Sahin T, et al. Neutrophil-to-lymphocyte ratio predicts response to cardiac resynchronization therapy. Med Sci Monit. 2013; 19: 373-377.

[26] Balci KG, Balci MM, Sen F, et al. The role of baseline indirect inflammatory markers in prediction of response to cardiac resynchronisation therapy. Kardiol Pol. 2016; 74(2): 119-126.

[27] Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002; 346(24): 1845-1853.

[28] Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005; 352(15): 1539-1549.

[29] Bleeker GB, Schalij MJ, Nihoyannopoulos P, et al. Left ventricular dyssynchrony predicts right ventricular remodeling after cardiac resynchronization therapy. J Am Coll Cardiol. 2005; 46(12): 2264-2269.

[30] Campbell P, Takeuchi M, Bourgoun M, et al. Right ventricular function, pulmonary pressure estimation, and clinical outcomes in cardiac resynchronization therapy. Circ Heart Fail. 2013; 6(3): 435-442.

[31] Sharma A, Bax JJ, Vallakati A, et al. Meta-analysis of the relation of baseline right ventricular function to response to cardiac resynchronization therapy. Am J Cardiol. 2016; 117(8): 1315-1321.

[32] Sharma A, Lavie CJ, Vallakati A, et al. Changes in parameters of right ventricular function with cardiac resynchronization therapy. Clin Cardiol. 2017; 40(11): 1033-1043.

[33] Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010; 23(7): 685-713.

[34] Ghio S, Recusani F, Klersy C, et al. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol. 2000; 85(7): 837-842.

[35] Lai WW, Gauvreau K, Rivera ES, et al. Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. Int J Cardiovasc Imaging. 2008; 24(7): 691-698.

[36] Damy T, Ghio S, Rigby AS, et al. Interplay between right ventricular function and cardiac resynchronization therapy: an analysis of the

CARE-HF trial (Cardiac Resynchronization-Heart Failure). J Am Coll Cardiol. 2013; 61(21): 2153-2160.

[37] Kjaergaard J, Ghio S, St John Sutton M, et al. Tricuspid annular plane systolic excursion and response to cardiac resynchronization therapy: results from the REVERSE trial. J Card Fail. 2011; 17(2): 100-107.

[38] Brenyo A, Barsheshet A, Rao M, et al. Brain natriuretic peptide and cardiac resynchronization therapy in patients with mildly symptomatic heart failure. Circ Heart Fail. 2013; 6(5): 998-1004.

[39] Brouwers C, Versteeg H, Meine M, et al. Association between brain natriuretic peptide, markers of inflammation and the objective and subjective response to cardiac resynchronization therapy. Brain Behav Immun. 2014; 40: 211-218.

[40] McAloon CJ, Ali D, Hamborg T, et al. Extracellular cardiac matrix biomarkers in patients with reduced ejection fraction heart failure as predictors of response to cardiac resynchronisation therapy: a systematic review. Open Heart. 2017; 4(2): e000639.