ORIGINAL ARTICLE

The association of hematological indices with the response to cardiac resynchronization therapy: a single-center study

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Abstract

Background: Cardiac resynchronization therapy (CRT) is an established therapeutic option for patients with heart failure (HF) and left ventricular ejection fraction (LVEF) ≤35 % who meet specific criteria according to current guidelines. However, up to 40 % of patients have no response to CRT. Our study aimed to investigate the association between different hematological and biochemical indices and response to CRT.

Methods: Patients with HF due to ischemic or dilated cardiomyopathy referred to our hospital for CRT implantation from January 2013 to November 2017 were included in the study. Response to CRT was defined as an increase in LVEF ≥10 % or a decrease in left ventricular end-systolic volume (LVESV) ≥15 % at six months of follow-up.

Results: A total of 48 patients (mean age: 66.2 ± 9.5 years, 81.3 % males) were included in the study. Of these HF patients, 29 (60.4 %) had ischemic cardiomyopathy, and 19 (39.6 %) had dilated cardiomyopathy. At six months of follow-up, 37 patients (77.1 %) had responded to CRT. Ten patients (20.8 %) had ventricular tachycardia (VT), 24 (50 %) patients were hospitalized, and two patients (4.2 %) died during the follow-up period. Multivariate analysis demonstrated that age (p =0.03) and creatinine levels (p =0.02) were independent predictors of the response to CRT. No significant associations between hematological markers (white blood cells, neutrophils, lymphocytes, platelets, neutrophil to lymphocyte ratio, red blood cells distribution width) and CRT response were observed.

Conclusions: A smaller increase in LVEF and a smaller decrease in LVESV were predictive for VT occurrence and hospitalizations in patients receiving CRT. No significant association between hematological markers and response to CRT was found. HIPPOKRATIA 2019, 23(3): 118-125.

Keywords: Cardiac resynchronization therapy, heart failure, hematological indices, predictors, responders

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Background

Cardiac resynchronization therapy (CRT) is an established therapeutic option for patients with heart failure (HF) and left ventricular ejection fraction (LVEF) ≤35 % who meet specific criteria according to current guidelines[1,2]. CRT aims to restore atrioventricular, inter- and intra-ventricular synchrony, with the goal of reducing left ventricular (LV) volumes, improving mitral regurgitation, and increasing LVEF. Many randomized controlled trials have demonstrated the beneficial role of CRT, including improvements in exercise capacity, peak VO_2, quality of life, and New York Heart Association (NYHA) functional class, as well as reductions in hospitalizations and all-cause mortality[3,4]. The response to CRT can be assessed according to clinical variables (NYHA, quality of life, 6 min walk test, exercise duration, and metabolic exercise tests); LV remodeling parameters (increase in LVEF, reductions in LV volumes and mitral regurgitation); or patient outcomes (reductions in hospitalizations, morbidity, and all-cause mortality).

Currently, up to 40 % of patients have poor response to CRT[5]. However, the response rates to CRT appear to depend on the pre-defined criteria and vary from 33 % to 96 % at six months of follow-up[6,7]. Identifying simple, easily measurable parameters that are predictive of a patient's response to CRT would be of great clinical importance. Indeed, observational studies have suggested that hematological markers [including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and red cell distribution width (RDW)] can predict response to CRT[8-10]. Our study aimed to investigate the association of hematological and biochemical indices with the response to CRT.

Methods

Study population

A retrospective analysis of prospectively collected data from our Institution was conducted. Patients with HF (due to ischemic or dilated cardiomyopathy) referred to our hospital for CRT implantation, from January 2013 to November 2017, were screened. The inclusion criteria were: 1) NYHA class II-IV HF despite adequate medical treatment (i.e., all classes of HF medications utilized, except for contraindications or serious side-effects); 2) chronic LV systolic dysfunction caused by ischemic or dilated cardiomyopathy (LVEF ≤35 %); 3) QRS duration ≥130 ms; 4) stable paced rhythm ≥95 % post-implantation in patients with atrial fibrillation or sinus rhythm; 5) left bundle branch block (LBBB), and 6) comprehensive echocardiographic evaluation at baseline and six months follow-up. Exclusion criteria were: 1) prior pacemaker or implantable cardioverter-defibrillator; 2) recent (<6 months) acute coronary syndrome and/or coronary revascularization; 3) poor echocardiographic window; 4) chronic hematologic, inflammatory or autoimmune disorders that could influence the hematological indices; 5) inadequate percentage of paced rhythm (<95 %), 6) life expectancy <1 year due to non-cardiac diseases, and 7) a major change in a medication known to impact mortality during follow-up.

All patients were at least 18 years old and provided informed written consent to be included in the Department's prospective database for further studies. The study protocol was approved by the local hospital Ethics Committee (General Hospital of Athens "Evangelismos, Decision number 26076, Date: 02/09/16).

Definitions

The response to CRT was defined as an increase in LVEF ≥10 % or a decrease in left ventricular end-systolic volume (LVESV) ≥15 % at six months of follow-up.

Data collection

The following data were extracted: demographic information [age, sex, weight, height, body mass index (BMI)], clinical information (HF type, smoking status, NYHA class, medications, history of hypertension, diabetes mellitus, and dyslipidemia), electrocardiographic parameters (QRS duration, PR duration, QTc duration, and fragmentation of QRS complex), echocardiographic parameters [LVEF, LVESV, LV end-diastolic volume (LVEDV), LV end-systolic diameter (LVESD), LV end-diastolic diameter (LVEDD), interventricular septum diameter (IVS), posterior wall diameter (PWD), left atrial volume (LAV) and diameter (LAD) at end-systole, right ventricular systolic pressure (RVSP)], and laboratory data [hemoglobin (Hb), hematocrit (Hct), white blood cells (WBC), platelets (PLT), NLR, PLR, platelet to neutrophil ratio (PNR), RDW, creatinine, lactate dehydrogenase (LDH), total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides] of the included patients at baseline (before CRT implantation).

Blood samples and echocardiography

Venous blood samples were collected in the morning on the day of CRT implantation and immediately processed. Blood samples were taken into standardized tubes containing dipotassium ethylene-dinitro-tetra-acetic acid (EDTA) for complete blood count. Echocardiographic examinations were performed with GE Vivid 7 (GE Healthcare, Chalfont St. Giles, United Kingdom) during the last week before CRT implantation in a standardized manner LVEDV, LVESV, LVEF, and LAV were calculated by a modified Simpson biplane method from apical imaging planes. LAD was measured in the parasternal long-axis view.

Device implantation

All devices were implanted by experienced operators (SX, KPL, ME). All patients received a CRT device in combination with a cardioverter-defibrillator. The implantation was performed transvenously by the left subclavian route. Coronary sinus venography was routinely obtained before introducing the LV lead, which was preferably inserted into the lateral or postero-lateral branches of the coronary sinus. The right atrial and right ventricular leads were implanted at the atrial appendage and the apex, respectively. Optimization of the atrioventricular interval was performed by an experienced cardiologist using Doppler echocardiographic measurements of transmitral flow. For patients with permanent atrial fibrillation, biventricular pacing was ensured by optimizing drug therapy to obtain permanent ventricular pacing or radiofrequency ablation of the atrioventricular junction.

Long-term follow-up

After hospital discharge, patients had regular follow-up at six months post-implantation. The primary outcomes included all-cause mortality, hospitalizations for HF, and assessment of LVEF and LVESV to establish the CRT responders. Ventricular tachycardia (VT) (>3 QRS complexes with a rate >100 beats per minute) was defined as a secondary outcome.

Statistical analysis

Data were analyzed on Prism, Version 6.0 (GraphPad, CA, USA) and IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean ± standard deviation (SD) and Boolean variables as proportions. Univariate analyses were conducted for CRT response (all patients, dilated cardiomyopathy subgroup, and ischemic cardiomyopathy subgroup), VT, hospitalizations for HF, and all-cause mortality. For continuous variables, normal distribution was assessed by Shapiro-Wilk's test, and the unpaired independent samples t-test with Welch's correction or Mann-Whitney U test was applied as appropriate. Fisher's exact test (two-tailed, alpha <0.05) was used for dichotomous variables. The chi-squared test for trend (linear by linear) was used for mitral regurgitation at baseline. Variables that provided p-value <0.05 were further evaluated in multivariate analyses using binomial logistical regression. Linear regressions were run to understand the effects of hematological indices on changes in LVESV and LVEF.

Results

Our cohort consisted of 48 patients (mean age: 66.2 ± 9.5 years, 81.3 % male). HF was of an ischemic etiology in 29 patients (60.4 %), while dilated cardiomyopathy was the cause for HF in 19 patients (39.6 %). All patients were followed for six months. Baseline characteristics are shown in Table 1.

Predictors of CRT response

At six months of follow-up, 37 patients (77.1 %) responded to CRT while 11 patients (22.9 %) did not respond to CRT. Univariate analysis showed that age (p =0.01), LAD (p =0.03), LAV (p =0.02), and creatinine levels (p =0.02) were significantly associated with response to CRT. On the other hand, no significant association was found between hematological markers (WBC, neutrophils, lymphocytes, platelets, NLR, RDW) and CRT response (Table 1). A multivariate analysis that included the significant factors from the univariate analysis revealed that age (p =0.03) and creati-

Table 1: Baseline characteristics and follow-up data of the study population. The response to cardiac resynchronization therapy was defined as an increase in left ventricular ejection fraction ≥10 % or a decrease in left ventricular end-systolic volume ≥15% at the 6-month follow-up.

		Non-responders to CRT [n =11 (22.9 %)]	Responders to CRT [n =37 (77.1 %)]	p-value
Characteristics				
Age (years)		59.7 ± 8.9	68.1 ± 8.9	**0.01**
Males		11 (100)	28 (75.7)	0.10
BMI (kg/m^2)		27.0 ± 3.8	26.3 ± 2.7	0.58
QRS width (ms)		155.9 ± 13.2	146.5 ± 16.9	0.07
HF type	Ischemic CMP	4 (36.4)	25 (67.6)	0.09
	Dilated CMP	7 (63.6)	12 (32.4)	
Echocardiographic parameters at baseline				
LVEF (%)		26.4 ± 4.1	26.8 ± 4.9	0.78
LVESV (mL)		181.5 ± 51.6	158.9 ± 40.2	0.20
LVEDD (mm)		69.0 ± 7.0	64.5 ± 6.2	0.07
LVESD (mm)		59.0 ± 7.9	55.5 ± 6.8	0.20
LVEDV (mL)		257.8 ± 47.6	224.3 ± 51.6	0.06
LA diameter (mm)		47.9 ± 3.9	44.7 ± 4.1	**0.03**
LA volume (mL)		94.1 ± 16.3	79.0 ± 19.1	**0.02**
PASP (mmHg)		39.2 ± 5.7	36.6 ± 13.0	0.37
MR	No MR-1+/4+	3 (27.3)	21 (56.8)	0.23
	2+/4+	7 (63.6)	12 (32.4)	
	3+/4+	1 (9.1)	4 (10.8)	
Medications				
ACEIs/ARBs		10 (90.9)	33 (89.2)	1.00
BBs		11 (100)	35 (94.6)	1.00

MRAs	10 (90.9)	34 (91.9)	1.00
Ivavradine	1 (9.1)	0 (0)	0.23
Diuretics	11 (100)	36 (97.3)	1.00
Nitrates	1 (9.1)	3 (8.1)	1.00
Digoxin	2 (18.2)	2 (5.4)	0.22
CCBs	1 (9.1)	1 (2.7)	0.41
Anticoagulants	5 (45.5)	11 (29.7)	0.47
Antiplatelets	7 (63.6)	14 (37.8)	0.17
Anti-arrhythmic drugs	6 (54.5)	17 (46.0)	0.74
Statins	8 (72.7)	18 (48.7)	0.19
Laboratory parameters at baseline			
WBCs (10^6/L)	7,656 ± 1,477	7,374 ± 1,869	0.61
Lymphocytes (10^6/L)	1,675 ± 686	1,911 ± 666	0.33
Platelets (10^6/L)	206,455 ± 67,828	226,838 ± 51,330	0.37
Neutrophils (10^6/L)	5,231 ± 1,576	4,664 ± 1,458	0.30
NLR	3.8 ± 2.3	2.8 ± 1.6	0.21
PLR	143.3 ± 76.1	134.9 ± 62.4	0.74
PNR	42.6 ± 19.3	52.8 ± 18.7	0.14
RDW-SD (fL)	46.0 ± 4.1	44.9 ± 5.1	0.45
RDW-CV (%)	14.9 ± 1.9	14.9 ± 1.9	0.99
Hemoglobin (g/dL)	13.2 ± 1.5	12.9 ± 1.4	0.50
Hematocit (%)	40.0 ± 4.6	38.3 ± 3.9	0.27
Creatinine (mg/dL)	1.55 ± 0.56	1.06 ± 0.21	**0.02**
LDH (U/L)	241.1 ± 95.0	220.1 ± 50.4	0.50
Total cholesterol (mg/dL)	177.9 ± 47.6	165.2 ± 44.9	0.45
HDL (mg/dL)	44.2 ± 22.4	43.3 ± 20.5	0.91
LDL (mg/dL)	110.6 ± 49.7	100.4 ± 42.9	0.55
Triglycerides (mg/dL)	114.8 ± 41.2	114.7 ± 38.1	0.99
Follow-Up			
VT	6 (54.6)	4 (10.8)	**<0.01**
AF	1 (9.1)	7 (18.9)	0.66
Rehospitalizations	10 (90.9)	14 (37.8)	**<0.01**
Death of any cause	2 (18.2)	0 (0)	**0.05**
LVEF (%)	26.3 ± 5.2	41.1 ± 8.6	**<0.01**
LVESV (mL)	175.7 ± 46.1	97.1 ± 28.5	**<0.01**
ΔLVEF (%)	- 0.1 ± 2.8	14.3 ± 7.8	**<0.01**
ΔLVESV (mL)	- 5.7 ± 16.9	- 61.7 ± 39.6	**<0.01**

Continuous data are presented as mean values ± SD while categorical variables as absolute and relative frequencies (percentages). ACEIs/ARBs: angiotensin-converting-enzyme inhibitor/ Angiotensin II receptor blockers, AF: atrial fibrillation, BB: b-blockers, BMI: body mass index, CCB: calcium channel blockers, CMP: cardiomyopathy, CRT: cardiac resynchronization therapy, HDL: high density lipoprotein, HF: heart failure, LA: left atrium, LDH: lactate dehydrogenase, LDL: low density lipoprotein, LVEDD: left ventricular end systolic diameter, LVEDV: left ventricular end diastolic volume, LVESD: left ventricular end systolic diameter, LVESV: left ventricular end systolic volume, MRAs: mineralocorticoid receptor antagonists, NLR: neutrophil to lymphocyte ratio, PASP: pulmonary artery systolic pressure, PLR: platelet to lymphocyte ratio, PNR: platelet to neutrophil ratio, RDW-CV: red blood cells distribution width-coefficient variation, RDW-SD: red blood cells distribution width-standard deviation, VT: ventricular tachycardia, WBC: white blood cells, ΔLVEF: left ventricular ejection fraction difference, ΔLVESV: left ventricular end systolic volume difference.

nine levels (p =0.02) were the only independent predictors of the response to CRT. Linear regression analysis showed that creatinine (p =0.03) and LDH (p =0.03) levels were significantly associated with an LVEF increase during the follow-up while no significant association was found between laboratory markers and LVESV decrease.

Adverse outcomes during follow-up

Ten patients (20.8 %) had VT, 24 patients (50 %) were rehospitalized, and two patients (4.2 %) died during the follow-up period. Univariate analysis showed that a smaller LVEF increase and LVESV decrease during follow-up were significant predictors (p <0.001) for hospitalizations and VT occurrence. Regarding laboratory indices, patients with VT had significantly lower levels of RDW-CV (p =0.005), whereas patients with hospitalizations had higher LDH levels (p =0.01) and paradoxically lower WBC and lymphocyte levels (p =0.04). No significant associations were found for all-cause mortality, likely due to the small number of events.

Subgroup analysis according to HF type
Dilated cardiomyopathy

The dilated cardiomyopathy group consisted of 19 patients (mean age: 67.4 ± 8.8 years, 94.7 % male). During the six months follow-up period, 12 patients (63.2 %) responded to CRT, while seven patients (36.8 %) did not respond to CRT. Univariate analysis showed that age (p =0.01) and PNR (p =0.04) were significantly associated with CRT response (Table 2). However, multivariate analysis did not show any independent predictors of CRT response.

Ischemic cardiomyopathy

The ischemic cardiomyopathy group consisted of 29 patients (mean age: 65.4 ± 10 years, 72.4 % male). During the six months follow-up period, 25 patients (86.2%) responded to CRT, while four patients (13.8 %) did not respond. Univariate analysis did not reveal any significant predictor of CRT response (Table 3).

Discussion

The main findings of our study are: 1) a smaller increase in LVEF and a smaller decrease in LVESV were significantly associated with VT and hospitalization rates during follow-up, and 2) there was no significant association between hematological markers and CRT response.

It is well-established that responders to CRT therapy have a lower incidence of adverse outcomes (mortality, VT, hospitalizations)[11,12]. The potential predictive value of simple laboratory indices has been studied with respect to CRT response and cardiovascular outcomes in CRT patients. For example, RDW is a measure of variability in the size of circulating erythrocytes and is generally used to investigate the differential diagnosis of anemia. RDW has been found to be a strong predictor of prognosis in HF patients[13]. Several observational studies have suggested that RDW may be a predictor of response to CRT. Specifically, a prospective study showed that baseline RDW did not predict LV reverse remodeling (defined as a reduction of LVESV ≥15 % at six months of follow-up). However, stable-high levels of RDW ≥14.5 % and the increase of RDW from <14.5 % to ≥14.5 % were associated with a lower likelihood of LV reverse remodeling and independently predicted the composite outcome of

Table 2: Baseline characteristics of the subgroup of dilated cardiomyopathy patients. The response to cardiac resynchronization therapy was defined as an increase in left ventricular ejection fraction ≥10 % or a decrease in left ventricular end-systolic volume ≥15 % at the six months follow-up.

Characteristics	Response to CRT therapy		p-value
	Non-responders to CRT (n =7, 36.8 %)	Responders to CRT (n =12, 63.2 %)	
Age (years)	60.4 ± 7.8	71.5 ± 6.6	**0.01**
Males	7 (100)	11 (91.7)	1.00
Laboratory parameters at baseline			
Hemoglobin (g/dl)	13.6 ± 1.2	12.6 ± 1.4	0.12
Hematocrit (%)	41.5 ± 3.5	37.6 ± 4.2	0.05
Platelets (10^6/L)	195,857 ± 35,709	231,083 ± 51,156	0.10
RDW-SD (fl)	47.7 ± 4.2	45.4 ± 6.2	0.34
RDW-CV (%)	15.6 ± 2.2	15.2 ± 2.1	0.68
WBC (10^6/L)	8,034 ± 1,539	7,158 ± 1,718	0.27
Lymphocytes (10^6/L)	1,602 ± 771	1,818 ± 660	0.55
Neutrophils (10^6/L)	5,651 ± 1,853	4,667 ± 1,552	0.26
NLR	4.4 ± 2.7	2.9 ± 1.7	0.22
PLR	142.8 ± 55.8	145.3 ± 72.2	0.94
PNR	37.7 ± 12.1	55.2 ± 22.3	**0.04**
LDH (U/L)	215.9 ± 62.7	208 ± 44.7	0.79

Continuous data are presented as mean values ± standard deviation while categorical variables as absolute and relative frequencies (percentages). LDH: lactate dehydrogenase, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PNR: platelet to neutrophil ratio, RDW-CV: red blood cells distribution width-coefficient variation, RDW-SD: red blood cells distribution width-standard deviation, WBC: white blood cells.

Table 3: Baseline characteristics of the subgroup of ischemic cardiomyopathy patients. The response to cardiac resynchronization therapy was defined as an increase in left ventricular ejection fraction ≥10 % or a decrease in left ventricular end-systolic volume ≥15 % at the six months follow-up.

	Non-responders to CRT (n =4, 13.8 %)	Responders to CRT (n =25, 86.2 %)	p-value
Age (years)	58.5 ± 11.7	66.5 ± 9.5	0.27
Males	4 (100)	17 (68)	0.55
Laboratory parameters at baseline			
Hemoglobin (g/dl)	12.6 ± 2.1	13.0 ± 1.4	0.70
Hematocrit (%)	37.5 ± 5.7	38.6 ± 3.7	0.74
Platelets (10^6/L)	225,000 ± 10,9839	224,800 ± 52,339	0.10
RDW-SD (fl)	43.0 ± 1.8	44.6 ± 4.6	0.24
RDW-CV (%)	13.8 ± 0.7	14.8 ± 1.8	0.07
WBC (10^6/L)	6,996 ± 1,275	7,478 ± 1,963	0.54
Lymphocytes (10^6/L)	1,804 ± 589	1,959 ± 678	0.66
Neutrophils (10^6/L)	4,498 ± 542	4,662 ± 1,444	0.69
NLR	2.7 ± 0.8	2.8 ± 1.5	0.88
PLR	144.2 ± 114.2	129.9 ± 58.1	0.82
PNR	51.1 ± 28.3	51.7 ± 17.2	0.97
LDH (U/L)	285.3 ± 134.7	224.9 ± 52.5	0.44

Continuous data are presented as mean values ± SD while categorical variables as absolute and relative frequencies (percentages). LDH: lactate dehydrogenase, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PNR: platelet to neutrophil ratio, RDW-CV: red blood cells distribution width-coefficient variation, RDW-SD: red blood cells distribution width-standard deviation, WBC: white blood cells.

death and HF hospitalization[14]. Moreover, a retrospective study showed that for every 1 % rise in RDW, there was a 19 % rise in all-cause mortality[15]. Patients with elevated RDW demonstrated significantly less improvement in LVEF and reductions in LVEDV and LVESV than patients with normal RDW[15]. Moreover, non-responders to CRT had higher baseline RDW and a greater increase in RDW at six months of follow-up compared to responders[8]. In multivariate analysis, baseline RDW levels were found to be the only predictor of echocardiographic response (defined as a relative increase in LVEF ≥15 % after six months)[8].

The exact pathophysiologic relationship between RDW and cardiovascular outcomes is unknown. However, it has been proposed that an inflammatory environment with increased levels of cytokines, such as in HF patients, can inhibit erythropoietin-induced erythrocyte maturation[8]. Consequently, decreased erythrocyte maturation may result in elevated RDW[8].

Anemia may also influence the outcomes of patients who undergo a CRT device implantation. In particular, anemia at baseline (defined as Hb ≤12 g/dL in women and ≤13 g/dL in men) and a larger decrease in Hb during follow-up were significantly associated with the composite endpoint of HF hospitalization, LV assist device placement, heart transplantation, and all-cause mortality[16]. However, anemia did not influence echocardiographic response to CRT[16].

Inflammation has been recognized as a significant contributor in the pathogenesis of HF, atrial fibrillation, and other cardiovascular diseases. Data from a *post hoc* analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trial demonstrated that subclinical inflammation (as indicated by an increase in WBC count and neutrophils count) is associated with increased risk of death and cardiovascular events in HF patients[17]. Similarly, a pilot study showed that an increase in neutrophils is associated with a higher incidence of sudden unexpected death in HF patients[18]. The NLR, PLR, and WBC counts are simple hematological indices that reflect the inflammatory status. A retrospective analysis found that non-responders to CRT had higher NLR, higher PLR, and lower relative lymphocyte count compared to responders[10]. Furthermore, NRL and relative lymphocyte count were significantly associated with NYHA functional class[10]. NLR's predictive role was also demonstrated by the multivariate analysis in another single-center study with a small sample size[9]. Additionally, high sensitivity C-reactive protein in serum has been found to predict both non-responders and patients at higher risk for cardiac death[19]. CRT seems to have an anti-inflammatory role, which may contribute to the facilitation of LV reverse remodeling. Indeed, CRT responders have a decrease in inflammatory markers (NLR, c-reactive protein, interleukins)[9].

Renal dysfunction is a common comorbidity in patients with HF. A meta-analysis showed that baseline renal dysfunction was associated with all-cause mortality in patients who underwent CRT[20]. The role of renal dysfunction in CRT response is controversial. Some studies found that renal dysfunction did not influence the clinical or echocardiographic response following CRT implantation[21,22], while a large observational study showed that impaired renal function was associated with a lack of echocardiographic response during six months follow-up[23]. Conversely, responding to CRT therapy seems to have a beneficial role in the improvement of renal func-

tion[21]. Renal responders have favorable long-term outcomes[24].

Interestingly, in the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) trial, patients with an elevated ratio of blood urea nitrogen to serum creatinine had a significantly greater reduction in the risk of HF or death following CRT-D therapy compared to those with a low ratio[25]. Sub analysis of the Multicenter InSync Randomized Clinical Evaluation) (MIRACLE) trial showed that HF patients who received CRT had clinical benefit (including increased LVEF and decreased LV volumes) compared to HF patients who did not receive CRT, independent of renal function; however, impaired renal function was associated with diminished response[26]. In addition, the Cardiac Resynchronization - Heart Failure (CARE-HF) trial showed that CRT reduced the risk of the composite end point of death or HF hospitalization, independent of baseline renal function compared to medical therapy alone[27].

Limitations

Given the single-center retrospective study design, the relatively small sample size is the main limitation. The small statistical power of the study likely accounts for the non-significant difference in CRT response with respect to the type of HF. Furthermore, the higher response rates in older patients may also be attributed to the small sample size. Subanalyses of large prospective randomized studies, including MIRACLE[28], CARE-HF[29], REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction)[30], and MADIT-CRT[31] have established that patients with non-ischemic cardiomyopathy have more favorable reverse remodeling compared to patients with ischemic cardiomyopathy. Additionally, since echocardiographic measures collected by a single operator, bias may have been introduced. As laboratory investigations were not performed at the six months follow-up, an analysis of the changes in hematological indices over time could not be performed. Lastly, given that no universal definition of CRT response exists, a direct comparison of the results of this study with the existing data from the literature was difficult.

Conclusions

In conclusion, older age and lower creatinine levels were significant predictors of CRT response; furthermore, a smaller increase in LVEF and a smaller decrease in LVESV at six months of follow-up were significantly correlated with VT and hospitalization rates. Finally, there was no significant association between the CRT response and simple hematological markers.

Conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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