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Outcomes of Cardiac Resynchronization Therapy in Heart Failure Patients and Effect of MAGGIC-HF Score on Prognosis

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Abstract

Objectives: Cardiac resynchronization therapy (CRT) has recently become a significant treatment option in patients with heart failure (HF), who do not respond to optimal medical treatment. In this study, we aimed to evaluate the long-term prognosis of CRT and to determine the relationship between the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC-HF) risk score and CRT.

Materials and Methods: One hundred and ten consecutive patients who underwent CRT between 2015 and 2019 were analyzed retrospectively. Baseline characteristics of the patients were recorded and clinical parameters including laboratory, electrocardiographic and echocardiographic were compared before CRT implantation and during patient follow-up. The patients were classified as surviving patients and patients without survival according to the 2-year clinical outcome. The improvement in echocardiographic parameters observed at the 6th month after CRT in surviving patients was defined as a positive response to CRT.

Results: The patients with survival had lower pulmonary artery systolic pressure (PASP) (34.66±18.31 vs 46.50±15.86 p=0.01) and higher left ventricular ejection fraction (LVEF) than patients without survival (27.00±5.86 vs 23.89±5.32 p=0.04). After 6 months from CRT implantation, the improvement of LVEF and PASP and decrease in left ventricular

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Abstract

diameters were found in patients with survival (p=0.015). In addition, there was a weak correlation between MAGGIC risk score levels and hospitalizations in this study population (p=0.031, r=208)

Conclusion: Predictors of long-term survival in CRT treatment are basal LVEF and PASP levels. Basal LVEF is important in the positive response to CRT.

Keywords: Cardiac resynchronization therapy, heart failure, prognosis

Introduction

Heart failure (HF) is still an important health problem today. Despite the positive improvements in treatment, it is associated with poor prognosis and mortality[1]. Cardiac resynchronization treatment (CRT) is one of the invasive treatment methods widely used in patients with HF in recent years, and many studies have shown that CRT is an effective treatment method for increasing quality of life and functionality and improving survival. CRT is recommended for patients with unresponsiveness to medical treatment, poor New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) <35% and QRS duration ≥130 ms[2,3]. However, the benefit required from CRT may not be seen in 1/3 of the patients. Therefore, it is important to identify patients who will not benefit from CRT due to high cost-effectiveness[4]. Before CRT implantation, examining the clinical-demographic characteristics of patients who respond positively to CRT and evaluating echocardiographic, electrocardiographic and laboratory parameters may play an important role in the selection of candidates for this treatment. In addition, various HF risk models may be used to determine the survival after CRT and positive response to CRT in patients with HF. One of these risk models is the MAGGIC-HF (Meta-Analysis Global Group in Chronic Heart Failure) risk score model developed by the Global Group of Meta-Analysis, which can be used in HF patients with both reduced ejection fraction and preserved ejection fraction[5]. In this study, we aimed to determine the positive response to CRT and predictors affecting survival and to evaluate the prognostic significance of the MAGGIC risk score calculated before CRT.

Materials and Methods

Study Population

This retrospective observational study was carried out with HF patients who underwent CRT implantation at Pamukkale University Medical Faculty Hospital between January 2015 and January 2019. CRT was applied to patients with LVEF <35% and NYHA class II-III and Iva, who were resistant to optimal medical therapy in the last 3 months, with a QRS duration ≥130 ms in Left bundle branch block (LBBB) morphology or a QRS duration ≥150 ms without LBBB morphology. Before CRT, the MAGGIC-HF risk scores of the patients were calculated and the NYHA functional class was determined by at least 2 experienced cardiologists who were blind to the study. HF was classified in three groups, as ischemic, non-ischemic and other causes according to the underlying etiology. Ischemic HF was defined as HF due to a previous myocardial infarction and severe coronary artery disease with or without intervention. The clinical and demographic characteristics, comorbidities, medications, preoperative and post-operative indicators of the patients and the data collected during the follow-up visits were recorded and stored for later analysis. However, patients who could not be followed up according to the data obtained from the records or who had a lack of data were excluded from the study and finally, the study was carried out with 110 patients.

The subjects were classified as patients with survival within the first 2 years after CRT (group 1, n=91) and patients without survival (group 2, n=19). Patients who survived after CRT were divided into two subgroups as those who responded positively to CRT (group 1a, n=44) and those who did not (group 1b, n=47) and a 10% increase in LVEF after the CRT procedure was defined as a positive response[6]. Preoperative clinical data including laboratory, electrocardiographic and echocardiographic parameters and MAGGIC-HF risk scores of the groups were compared to determine the positive response to CRT and factors affecting survival. Preoperative and postoperative six-month periods of the patients with survival were reanalyzed to determine which parameters were associated with the positive response to CRT.

This study was approved by Pamukkale University Faculty of Medicine Hospital Denizli, Turkey Ethics Review Board in accordance with the Declaration of Helsinki (decision no: 60116787-020/34161, date: 09.06.2020), and informed consent was obtained from all registered patients.

CRT Implantation

The left ventricle pacing was implanted into the lateral or posterolateral vein after the coronary sinus was cannulated with a guide sheath using the left subclavian approach. The right atrial lead was placed in the right atrial appendage and the right ventricular lead was placed in the right ventricular apex or right ventricular outflow tract. Fluoroscopy was used to evaluate the final position of the left ventricular pacing lead, and optimization of device parameters before discharge was provided for each patient.

Clinical Data

Peripheral venous blood samples of the patients were collected for standard blood tests after 8-12 hours of fasting. The resting electrocardiogram data of the patients before and after CRT implantation and during follow-up were analyzed. The QRS duration was defined as the longest measured QRS time in any lead. 2D transthoracic echocardiographic imaging was performed with Vivid 7 GE echocardiography device before and after CRT implantation. Left atrial diameter, left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) were measured using the M-mode method. LVEF was calculated by the bi-plane Simpson method and pulmonary artery systolic pressure (PASP) was calculated by the modified Bernoulli equation by adding the estimated right atrial pressure to the tricuspid regurgitation jet flow velocity.

Clinical Outcomes

The mortality due to HF and all causes within two years after CRT implantation was defined as the primary outcome. The improvements in echocardiographic parameters after CRT implantation were defined as the secondary outcome.

Statistical Analysis

The analysis of all data was performed using SPSS v.21.0 for Windows (SPSS, Inc., Chicago, Ill., USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as frequency and percentage. The Shapiro-wilk test was used to check the normality of continuous data, the student's t-test for variables that were compatible with normal distribution, and the Mann-Whitney U test for variables not compatible with normal distribution. Comparison of categorical variables was performed by the chi-square analysis and the statistical significance level (alpha) was considered as 0.05.

Results

Baseline Demographic and Clinical Characteristics of the Study Population

Baseline demographic and clinical characteristics of the groups are shown in Table 1. There are no significant differences in mean age, distribution of gender and comorbidities such as hypertension, diabetes, coronary artery diseases, cerebrovascular diseases and chronic

Table 1. Baseline characteristics of study population

Variables	Group 1 (n=91)	Group 2 (n=19)	p-value
Demographics			
Mean age, (years)	62.43±12.46	63.89±7.93	0.630
Male gender, n (%)	64 (70)	11 (58)	0.440
Body mass index (kg/m^2)	29.70±3.80	29.60±4.00	0.766
HF characteristics			
HF duration, week	45.50±30.80	49.20±26.90	0.362
Ischemic HF, (n) %	53 (58)	11 (58)	0.821
Non ischemic HF, n (%)	16 (16)	4 (21)	0.558
Other causes of HF, n (%)	21 (25)	4 (21)	0.721
NYHA II, n (%)	11 (12)	1 (5)	0.418
NYHA III, n (%)	76 (84)	16 (84)	0.566
NYHA IVa, n (%)	4 (4)	3 (11)	0.102
ICD/Pacemaker history, n (%)	7 (8)	2 (11)	0.630
Comorbidities			
Hypertension, n (%)	67 (74)	12 (63)	0.546
Diabetes, n (%)	32 (35)	7 (37)	0.763
Dyslipidemia, n (%)	34 (37)	4 (21)	0.218
Current smoking, n (%)	29 (32)	5 (26)	0.732
COPD, n (%)	5 (5)	-	0.309
Previous stroke, n (%)	3 (3)	1 (5)	0.641
CAD, n (%)	70 (77)	13 (68)	0.669
Laboratory			
Creatinine, (mg/dL)	1.14±0.43	1.28±0.46	0.23
BUN, (mg/dL)	24.16±12.30	24.17±13.06	1.00
Sodium, (mEq/L)	138.13±3.40	137.00**±3**.16	0.19
C-reactive protein, (mg/L)	1.05±1.62	1.61±2.40	0.22
Echocardiographic			
LVEF, (%)	27.00±5.86	23.89±5.32	0.04
LVEDD, (mm)	64.59±8.23	66.67±9.59	0.34
LVESD, (mm)	53.01±8.80	56.78±10.36	0.11
PASP, (mmHg)	34.66±18.31	46.50±15.86	0.01
Medications			
Beta blockers, n (%)	82 (90)	16 (84)	0.866
ACEI/ARB/ARNI, n (%)	75 (82)	14 (73)	0.642
Aldosterone antagonist, n (%)	70 (77)	14 (74)	0.899
Other diuretics, n (%)	58(63)	12 (63)	0.855
Anti-aggregants, n (%)	66 (64)	14 (74)	0.645
Statins, n (%)	41 (45)	6 (32)	0.359
Digitalis, n (%)	23 (25)	5 (26)	0.824
Ivabradine, n (%)	16 (18)	4 (21)	0.642
Electrocardiogram			
Sinus rhythm, n (%)	74 (81)	15 (79)	0.840

Table 1. continued

Atrial fibrillation, n (%)	17 (19)	3 (16)	0.840
QRS duration >150 msn, n (%)	28 (31)	5 (26)	0.801
QRS duration >130 msn, n (%)	63 (67)	13 (68)	0.845
LBBB morphology, n (%)	86 (95)	15 (79)	0.097
RBBB morphology, n (%)	2 (2)	2 (11)	0.066
MAGGIC score	24.41±5.70	25.06±4.70	0.650

HF: Heart failure, NYHA: New York Heart Association, ICD: Implantable cardioverter defibrillator, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, PASP: Pulmonary artery systolic pressure, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, ARNI: Angiotensin receptor neprilysin inhibitor, LBBB: Left bundle branch block, RBBB: Right bundle branch block, MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure, n: Number

obstructive pulmonary diseases. (p>0.05) Also, the laboratory findings, electrocardiographic parameter, medications, HF properties such as duration, etiology and NYHA functional class did not show significant differences in HF patients with survival and without survival. (p>0.05) However, LVEF was significantly higher and PASP was significantly lower in patients with survival compared to patients with no survival. (LVEF, 27.00±5.86, 23.89±5.32, p=0.04; PASP, 34.66±18.31, 46.50±15.86, p=0.01, respectively). Also, the MAGGIC risk score did not differ between the groups (p>0.05).

Comparison of the Preoperative and Postoperative 6-month Periods of Patients with Survival After CRT

Comparing the patients with a positive response to CRT (group 1a) and those without (group 1b), the negative response to CRT was shown more frequently in patients with a history of DM and hyperlipidemia and previous pacemaker/implantable cardioverter defibrillator (ICD) history. In addition, the patients who responded positively to CRT had higher LVEF (31.57±9.25, 25.96±5.99; p<0.001) (Table 2).

When the 6-month periods before and after CRT of the surviving patients were compared, it was found that LVEDD, LVESD, and PASP decreased and LVEF increased in the 6th month, and the improvements in these parameters were statistically significant (p=0.015) (Figure 1-4). In the two-year follow-up after CRT implantation, the mean hospitalization time was 1 day and there was a

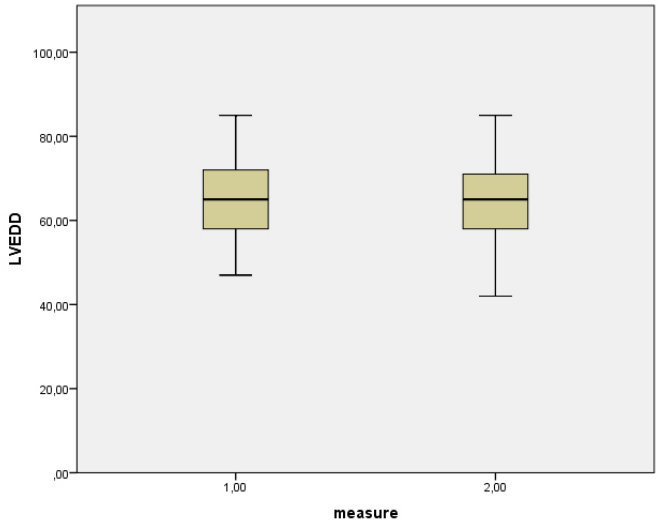

Figure 1. Comparison of preoperative and postoperative 6-month LVEDD measurements of survival patients
LVEDD: Left ventricular end diastolic diameter

significant but weak correlation between the MAGGIC-HF risk score and re-hospitalizations (p=0.031, r=208) (Table 3).

Discussion

The regression in LVDD, LVSD, PASP and the increase in LVEF were the parameters showing CRT positive response in this study. The two main determinants of survival in CRT were preoperative PASP level and basal LVEF. The MAGGIC-HF risk score was insufficient to predict prognosis in the post-CRT period. Among the surviving patients, patients who responded positively

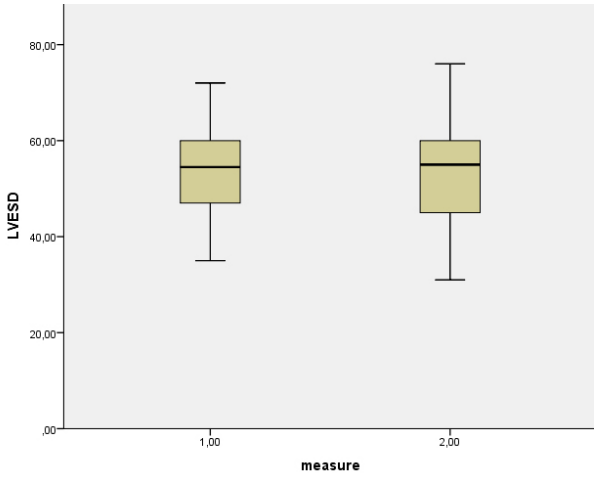

Figure 2. Comparison of preoperative and postoperative 6-month LVESD measurements of survival patients

LVESD: Left ventricular end systolic diameter

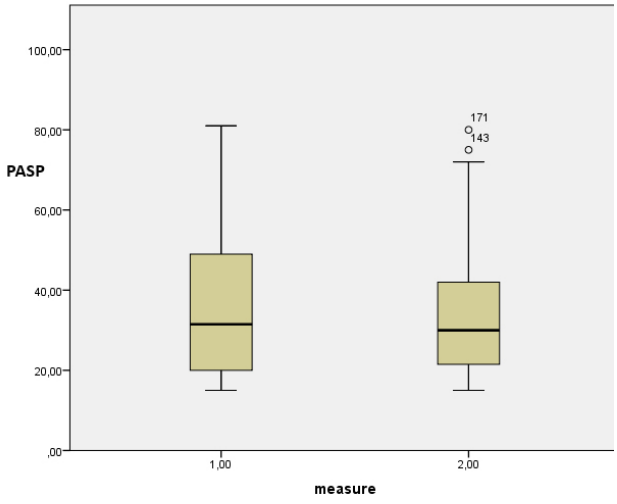

Figure 3. Comparison of preoperative and postoperative 6-month PASP measurements of survival patients

PASP: Pulmonary artery systolic pressure

to CRT had less DM, hyperlipidemia and pacemaker implantation. Besides, basal LVEF was higher in patients who responded positively to CRT.

CRT implantation improves prognosis in patients with HF. However, the randomized controlled studies have shown that the mortality is between 15% and 18% in the 12-24 month period after CRT and this rate increases more in longer periods[7]. Low LVEF is still associated with increased mortality, and basal LVEF should be considered

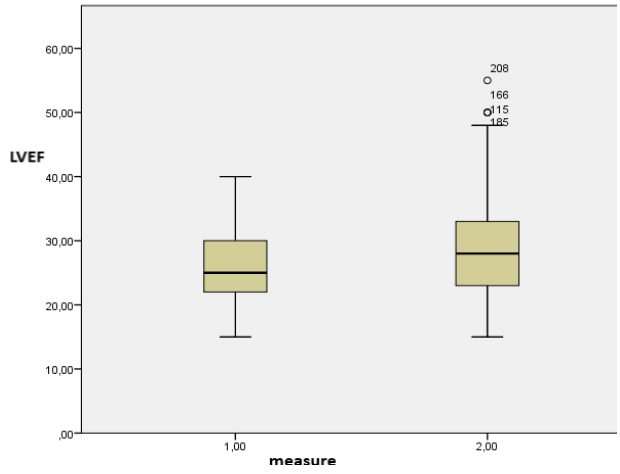

Figure 4. Comparison of preoperative and postoperative 6-month LVEF measurements of survival patients

LVEF: Left ventricular ejection fraction

to determine candidates for CRT implantation[8]. Small previous studies have shown that patients with severe symptoms but higher baseline LVEF exhibit better clinical and echocardiographic improvement[9,10]. In the MADIT-CRT study, patients were classified into three groups as <25%, 26-30% and >30% according to LVEF, and the group with the lowest LVEF had high mortality ratio and recurrent HF. Although the clinical benefit seen from CRT was independent of basal LVEF, the group with LVEF >30% provided more improvements from CRT[11]. In our study, similar to randomized controlled studies, the two-year mortality rate was 17%. In our study, one of the important parameters for survival and positive response to CRT was basal LVEF and the patients with high LVEF showed a more positive response to CRT. However, PROSPECT and REVERSE studies have suggested that the clinical and echocardiographic benefit seen from CRT is independent of LVEF, unlike the MADIT-CRT study and our study[12,13]. The contradictory results obtained from the studies may base on the different definitions of the patients included in the study, like clinical and demographic characteristics or positive response to CRT, the differences of NYHA functional class, and inclusion criteria.

Table 2. Baseline characteristics of the study population with CRT responses

Variables	Group 1a (n=44)	Group 1b (n=47)	p-value
Demographics			
Mean age, (years)	60.24±11.50	63.86±11.95	0.250
Male gender, n (%)	28 (64)	36 (77)	0.140
Body mass index (kg/m^2)	28.20±3.50	29.00±4.40	0.824
HF characteristics			
HF duration, week	44.70±25.10	50.20±27.50	0.362
Ischemic HF, (n) %	23 (52)	31 (66)	0.191
Non ischemic HF, n (%)	9 (20)	7 (15)	0.731
Other causes of HF, n (%)	12 (27)	9 (19)	0.264
NYHA II, n (%)	6 (14)	5 (11)	0.892
NYHA III, n (%)	38(86)	41 (87)	0.922
NYHA IVa, n (%)	0	1 (2)	0.899
ICD/Pacemaker history, n (%)	1 (2)	6 (13)	0.030
Comorbidities			
Hypertension, n (%)	30 (68)	37 (79)	0.446
Diabetes, n (%)	9 (20)	23 (49)	0.006
Dyslipidemia, n (%)	8 (18)	26 (55)	0.004
Current smoking, n (%)	12 (27)	17 (36)	0.710
COPD, n (%)	2 (5)	3 (6)	0.522
Previous stroke, n (%)	2 (5)	1 (2)	0.410
CAD, n (%)	33 (75)	37 (79)	0.864
Laboratory			
Creatinine (mg/dL)	1.17±0.47	1.14±0.40	0.720
BUN (mg/dL)	22.45±9.42	25.20±13.74	0.240
Sodium (mEq/L)	137.96±4.09	137.88±2.64	0.906
C reactive protein (mg/L)	1.15±1.79	1.18±1.79	0.940
Echocardiographic			
LVEF (%)	31.57±9.25	25.96±5.99	<0,001
LVEDD (mm)	65.24±8.56	64.96±8.31	0.87
LVESD (mm)	53.49±9.23	54.15±8.92	0.71
PASP (mmHg)	36.88±18.95	36.89±18.19	0.96
Medications			
Beta blockers, n (%)	39 (89%)	41 (87%)	0.514
ACEI/ARB/ARNI, n (%)	34 (77%)	41 (87%)	0.497
Aldosterone antagonist, n (%)	37 (84%)	33 (70%)	0.899
Other diuretics, n (%)	27 (61%)	31 (66%)	0.894
Anti-aggregants, n (%)	28 (64%)	38 (81%)	0.070
Statins, n (%)	15 (34%)	26 (55%)	0.05
Digitalis, n (%)	14 (32%)	9 (19%)	0.88
Ivabradine, n (%)	10 (23%)	6 (13%)	0.124
Electrocardiogram			

Table 2. continued

Sinus rhythm, n (%)	37 (84)	37 (79)	0.872
Atrial fibrillation, n (%)	7 (16)	10 (21)	0.710
QRS duration >150 msn, n (%)	15 (34)	13 (28)	0.668
QRS duration >130 msn, n (%)	29 (66)	34 (72)	0.375
LBBB morphology, n (%)	43 (98)	46 (98)	0.902
RBBB morphology, n (%)	1 (2)	1 (2)	0.896
MAGGIC score	23.87±5.467	24.95±5.558	0.286

HF: heart failure, NYHA: New York Heart Association, ICD: Implantable cardioverter defibrillator, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, PASP: Pulmonary artery systolic pressure, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, ARNI: Angiotensin receptor neprilysin inhibitor, LBBB: Left bundle branch block, RBBB: Right bundle branch block, MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure, n: Number, CRT: Cardiac resynchronization therapy

Table 3. Relationship between MAGGIC risk score and hospitalization in surviving patients

		MAGGIC risk score	**Hospitalization day**
Hospitalization	**Pearson correlation**	**0.208**	**1**
	Sig. (2-tailed)	0.031	-
	n	108	108

MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure, n: Number

In patients with a positive response from CRT, at the end of the first month, LVDD, LVSD and left ventricle volumes decrease and this improvement continues up to 12 months in approximately 65-75% of the patients. In the MIRACLE and Multicentre InSync™ Randomized Clinical Evaluation-Implantable Cardioverter Defibrillator (MIRACLE-ICD) studies, a significant increase in LVEF was observed with a decrease in left ventricular end systolic-diastolic volume and linear diameters in the patient group with CRT[14]. In our study, similar to the MIRACLE and MIRACLE-ICD studies, there was a significant decrease in LVDD and LVSD and a significant increase in LVEF, and these results were evaluated as a positive response to CRT in patients with survival. The clinical response of HF patients to CRT may differ. Yu et al.[15] could not identify the association of left ventricular end-systolic volume (LVESV) reduction after CRT with NYHA functional class, quality of life, and 6-minute walk test, but in another study, a decrease of <15% in LVESV resulted in better clinical improvement[16]. However, this situation may associate with placebo effects of CRT. Therefore, we did not include clinical improvement indicators after CRT implantation to avoid a subjective evaluation in our study. In the REVERSE study, it was shown that the ratio of re-hospitalization was decreased and the hospitalization's duration was shortened after CRT[17]. Similar to this study, the hospitalization's duration was average of one day in our study.

Several studies have shown that the factors such as impaired renal function, presence of AF, poor NYHA functional class, gender, HF etiology, presence of LBBB and QRS duration >150 ms affect CRT response and prognosis[18,19]. However, Ghanem et al.[20] did not find any relationship between demographic-clinical variables and CRT response. Similar to this study, there was no relationship between demographic-clinical variables with CRT response and clinical outcome in our study.

The increased PASP and right ventricular dysfunction have also been associated with adverse clinical outcomes after CRT[21]. Previous studies have shown that patients with PASP levels higher than 50 mmHg have a worse prognosis. However, little is known about how it affects

the long term after CRT. In a study, Bašinskas et al.[22] classified the patients as PASP <50 mmHg and PASP >50 mmHg before CRT implantation and evaluated their CRT response and survival. As a result, the group with higher PASP levels had more deaths and re-hospitalizations. In another study, PASP levels above 39.5 mmHg were associated with increased mortality after CRT, but this result was not confirmed by Cox regression analysis[22,23]. In our study, similar to these studies, one of the important parameters affecting survival and CRT positive response was increased PASP levels and it was closely related to mortality. The decline of PASP was considered as CRT positive response in our study, but this result may be secondary to the improvement of left ventricular functions.

Although various HF risk score models have been developed to evaluate prognosis, to predict survival, and to determine who will benefit from organ transplantation or assist support devices in patients with HF, their reliability is poor on the patient basis and their performance is limited in the estimation of prognosis[24]. We used the MAGGIC risk score, which is one of the HF risk score models, in this study. We showed that MAGGIC score did not provide sufficient long-term prognostic information in HF patients.

Study Limitations

This study had some limitations. This study was designed as a retrospective study and had a relatively small sample. Also, the alterations of HF therapy follow-up may affect the clinical outcome and CRT response in patients. Other limitations included not using modern echocardiographic parameters such as tissue doppler and strain imaging, which are more sensitive and specific, and not evaluating functional mitral regurgitation, which is one of the CRT response indicators.

Conclusion

The strongest predictors of survival in patients implanted with CRT are basal LVEF and PASP. Furthermore, basal LVEF is one of the most important factors in the benefit seen from CRT regardless of underlying HF etiology. However, multi-center, randomized controlled large studies are needed to determine candidate patients for CRT and to see long-term results of CRT.

Ethics

Ethics Committee Approval: This study was approved by Pamukkale University Faculty of Medicine Hospital Denizli, Turkey Ethics Review Board in accordance with the Declaration of Helsinki (decision no: 60116787-020/34161, date: 09.06.2020).

Informed Consent: Informed consent was obtained from all registered patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.N., G.Ş., Concept: G.N., G.Ş., Design: G.N., G.Ş., Data Collection or Processing: G.N., G.Ş., Analysis or Interpretation: S.Ç., G.G., Literature Search: G.N., S.Ç., Writing: G.N., S.Ç., G.Ş., G.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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