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Predictors and Prognosis of End-Stage Hypertrophic Cardiomyopathy

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ABSTRACT

Background: Burned-out hypertrophic cardiomyopathy (BO-HCM) is complicated by substantial adverse events. However, few studies have focused on clinical or echocardiographic features and their prognostic values among patients with BO-HCM.
Objective: This study evaluated the clinical manifestations and prognostic value of echocardiography in patients with BO-HCM.
Methods: The present retrospective study evaluated 401 consecutive patients referred to the echocardiography ward of Rajaie Cardiovascular Center for evaluation of HCM during the period from January 2010 to February 2018. Three hundred six patients who completed the follow-up were included: 78 (25.4%) had BO-HCM and an EF of < 50% (group 1), and 228 (74.5%) had a normal EF in their baseline TTE (group 2). Among the group 2 population, 183 patients had a preserved EF of > 50% (group 2B), and 45 became BO-HCM at the end of their follow-up (group 2A). Clinical data were analyzed, including medical history, electrocardiography, and echocardiography. Generalized estimating equation (GEE) regression was performed to assess the association between patient characteristics and burned-out HCM.
Results: An atrial fibrillation (AF) rhythm was more common in the groups with BO-HCM (groups 1 and 2A) (32.8 vs. 14%; P = 0.002), as were Frequent premature ventricular contractions (PVCs) (13.98 vs. 5%; P = 0.040). Moderate or severe systolic anterior motion (SAM) was significantly more common in group 2B (LVEF > 50%) compared with group 1 and 2A, who had an EF of ≤ 50% (32.3% vs. 7.6%; P = 0.006). The S-wave of the right ventricle was significantly lower in groups 1 and 2A (9.73 vs. 11.8 cm/s; P < 0.001). Systolic pulmonary artery pressure (SPAP) was significantly higher in groups 1 and 2A (38.28 vs. 29.74 mmHg, P < 0.001). The differences in the prevalence of asymmetrical septal hypertrophy (ASH), left ventricular outlet (LVOT) obstruction, pericardial effusion (PE), diastolic dysfunction, and mitral regurgitation (MR) were insignificant between all groups.
Conclusions: Among the patients suffering from HCM, the presence of AF rhythm, frequent PVCs, significant RV dysfunction, and absence of systolic anterior motion (SAM) of mitral valve leaflets have prognostic value and might be considered predictors for progression to BO-HCM.

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1. Introduction

Hypertrophic cardiomyopathy (HCM) is a common genetic disease characterized by a hypertrophied (septal thickness > 15 mm), non-dilated, left ventricular (LV) cavity with normal or supernormal systolic function without identifiable causes like long-standing hypertension and aortic stenosis (1, 2). However, in a small number of HCM patients, the progression of myocardial fibrosis leads to impaired systolic and diastolic functions of both the left and right ventricles. This so-called "end-stage HCM" or "burned-out HCM" (BO-HCM) is characterized by progressive LV wall thinning, increased LV end-systolic dimensions, decreased or loss of preexisting left ventricular outflow tract (LVOT) gradients, and a decline of the left ventricular ejection fraction (LVEF) below 50% (2, 3), attracting considerable interest due to the high risk of substantial cardiovascular mortality (4). The burned-out phase affects 4.9% of patients with HCM and has an unfavorable clinical outcome (5-7). These patients have an approximate annual mortality rate of 11%, not only from heart failure and thromboembolic complications but also from a substantial incidence of sudden cardiac death (4, 6, 8). Previous studies described the association between atrial fibrillation and BO-HCM (4, 9). However, many risk factors for cardiovascular mortality in BO-HCM remain obscure. Accordingly, the prognostic factors of end-stage HCM patients need to be clarified to identify patients requiring early management.

2. Objectives

This study aimed to evaluate the clinical characteristics, prognosis, and risk factors of HCM patients.

3. Methods

3.1. Study Patients

This retrospective study evaluated 401 consecutive patients referred to the echocardiography ward of Rajaie Cardiovascular Center for evaluation of HCM during the period from January 2010 to February 2018. Ethical approval for this study was obtained from the Iran University of Medical Sciences (IR.RHC.REC.1400.030). Patients were excluded for the following reasons: A history of surgical or ablative septal reduction therapy, a history of coronary artery disease or documented coronary arterial narrowing (≥ 50% stenosis of at least one major artery by angiography), or a lack of follow-up TTE.

All transthoracic echocardiographic studies were performed on Philips EPIQ devices. All ultrasonography systems were equipped with 1 – 5 MHz TTE transducers and continuous wave, pulsed-wave Doppler and color Doppler imaging. Subjects were examined in the left lateral supine position. All echocardiographic examinations were recorded, and we reanalyzed patient data for further evaluation. In all echo studies, patients were evaluated with 2-D and Doppler. Analysis of LVEF was done with visual assessment and the Simpson biplane method. Mitral regurgitation (MR) and tricuspid regurgitation (TR) severity were analyzed by visual assessment, Doppler, and PISA methods. HCM was diagnosed with transthoracic echocardiography (TTE) or cardiac magnetic resonance imaging as hypertrophied, non-dilated LV (maximum LV wall thickness [MLVWT] ≥ 15 mm in adult patients) in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy. Patients were followed for a mean period of 5 years, and echocardiography experts performed a final index TTE to determine the changes in HCM characteristics. BO-HCM was defined by the detection of an LVEF < 50% on echocardiography during follow-up. Echocardiography was performed using Philips EPIQ ultrasound equipment. The magnitude of LV hypertrophy was assessed from two-dimensional images per the recommendation of the American Society of Echocardiography.

3.2. Group Assignment

The study population was divided into two groups based on the initial TTE, including those patients who already had BO-HCM and an LVEF of less than 50% (group 1) and those whose EF was ≥ 50% (group 2). Furthermore, the latter group was divided into two subgroups, based on the follow-up TTE, including a subgroup whose EF decreased to less than 50% (group 2A) and another subgroup of patients whose EF remained preserved at above 50% (group 2B).

3.3. Echocardiographic Definitions and Measurements

The echocardiographic assessment included evaluation of left ventricular ejection fraction (LVEF), systolic anterior motion (SAM) of the anterior mitral valve, moderate-to-severe RV dysfunction based on the peak systolic velocity (Sm) of the RV, severity of diastolic dysfunction, systolic pulmonary arterial pressure (SPAP), asymmetrical septal hypertrophy (ASH), left ventricular outlet (LVOT) obstruction, pericardial effusion (PE), and mitral regurgitation (MR).

3.4. Follow-up

Patients were followed by TTE performed at our outpatient clinic at a yearly interval for a mean period of 5 years to determine the changes in HCM characteristics.

3.5. Statistical Analysis

Continuous variables are expressed as mean ± SD when normally distributed and median (interquartile range) when non-normally distributed. Categorical variables are expressed as numbers and percentages. The two groups were compared regarding the continuous variables using a t-test or a non-parametric test (Wilcoxon test) when the data were non-normally distributed. In addition, Fisher's exact test was used to compare the two groups concerning the categorical variables. Generalized estimating equation (GEE) regression was performed to assess the association between the patient's characteristics and BO-HCM. The clinical features with $P < 0.05$ in the univariate GEE analysis were included in the multivariate model to identify the independent predictors.

4. Results

4.1. Study Population

This study included 401 adult patients with a diagnosis of HCM confirmed by TTE. Although 101 patients (23.2%) were excluded due to a lack of informed consent or refusing

follow-up echocardiography, the remaining patients were followed for a mean of 5 ± 1.2 years. Finally, 306 patients who completed the follow-up were included in the study; 78 (25.4%) patients were among those who already had BO-HCM and an EF of < 50% in their baseline TTE (group 1), and 228 (74.5%) were those who had a normal EF in their baseline TTE (group 2). Additionally, among the group 2 population, 183 patients had a preserved EF of > 50% (group 2B), and 45 developed BO-HCM by the end of their follow-up (group 2A). Demographic features of the patients in the various groups are summarized in Tables 1-3.

4.2. Electrocardiogram Findings

At the beginning of the study, the prevalence of the atrial fibrillation (AF) rhythm was higher in the group with BO-HCM (group 1) (32.8 vs. 14%; P = 0.002), whereas the prevalence of a sinus rhythm was significantly higher in group 2 (95.2 vs. 88.9%; P = 0.04). Furthermore, frequent premature ventricular contractions (PVCs) were more prevalent in group 1 (13.98 vs. 5%; P = 0.04). During the follow-up, similar to the evaluations at baseline, the prevalence of a sinus rhythm was significantly higher in the patients with LVEF 50% (subgroup 2B) (74.4% vs. 51.3%; P = 0.01), while the AF rhythm was more common in subgroup 2A (reduced LVEF) (48.7% vs. 24.4%) (Table 2; Table 3).

4.3. Echocardiographic Findings

Transthoracic echocardiography demonstrated that moderate or severe systolic anterior motion (SAM) was significantly more common in group 2B (LVEF 50%) compared with group 1 (32.3 vs. 7.6%; P = 0.006). In addition, diastolic dysfunction was more severe in group 1 (17.9 vs. 6.8%; P = 0.07). The S-wave of the RV, according to tissue Doppler imaging (Sm RV), was significantly lower in group 1 (9.73 cm/s vs. 11.8cm/s; P < 0.001). The systolic pulmonary artery pressure (SPAP) was also significantly higher in group 1 (38.28 vs. 29.74 mmHg; P < 0.001). The differences in the prevalence of ASH, LVOT obstruction, PE, diastolic dysfunction, and MR were statistically insignificant between the two study groups in the first analysis (groups 1 and 2) (Table 4; Table 5).

Table 1. Demographic Characteristics of the Patients with Hypertrophic Cardiomyopathy

		Patients (n = 306)
Gender	Male	42.6%
	Female	57.4%
Age (years)		52.9

Table 2. Gender, ECG Features, and NYHA Class among Patients with Hypertrophic Cardiomyopathy in the Baseline Analysis

		Baseline Analysis		
		Normal EF (n = 228)	Burned-out HCM (n = 78)	P value
Gender	Male	56%	59.2	0.571
	Female	44%	40.8	
ECG features	Atrial fibrillation	14%	32.8%	0.002
	PVC in the first ECG	5%	13.2%	0.042
Past medical history	Diabetes mellitus	11.1%	11.9%	0.840
	Hypertension	35.7%	31.5%	0.482
NYHA functional class	I, II	71.7%	66.7%	
	III, IV	28.3%	33.3%	0.540
Family history of HCM		28.3%	19.4%	0.915

Abbreviations: ECG, electrocardiography; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; PVC, premature ventricular complex; NYHA, New York Heart Association

Table 3. Gender, ECG Features, and NYHA Class among Patients with Hypertrophic Cardiomyopathy in the Follow-up Analysis

		Follow-up Analysis		
		Normal EF (n = 183)	Burned-out HCM (n = 45)	P value
Sex	Male	54.7%	59	0.550
	Female	45.3%	41	
ECG features	Atrial fibrillation	24.4%	48.7%	0.007
	PVC in the first ECG	5%	13.2%	0.042
Past medical history	Diabetes mellitus	10.6%	7.7%	0.533
	Hypertension	29.1%	29.9%	0.910
NYHA functional class	I, II	73.7%	70.6%	
	III, IV	26.3%	29.4%	0.841
Family history of HCM		17.2%	15.4%	0.742

Abbreviations: ECG, electrocardiography; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; PVC, premature ventricular complex; NYHA, New York Heart Association

Table 4. Echocardiography Findings of Patients with Hypertrophic Cardiomyopathy with Preserved or Reduced Ejection Fraction

Echocardiography Indices	Severity	Baseline Analysis			Follow-up Analysis			
		Normal EF	BO-HCM	P value	Normal EF		BO-HCM	P value
SAM	No, mild	78	92.4	0.006	74.5		93.4	0.001
	Moderate, severe	32.3	7.6		25.5		6.7	
ASH	Yes	85.2%	83%	0.731	90.2%		85%	0.421
LVOT obstruction (MG >30 mmHg)	Yes	75.7%	66.7%	0.563	71.4%		71.4%	0.990
RVH	Yes	14.4%	26.5%	0.021	21.1%		13%	0.222
RV dysfunction	No, mild	98%	62.3%	< 0.001	No, mild	99.1%	89.5%	<0.001
	Moderate, severe	1.8%	11.8%		Moderate, severe	0.9%	10.4%	
Pericardial effusion	No, mild	97%	95.6%	0.526	98.2%		87.3%	0.003
	Moderate, severe	3%	4.4%		1.8%		12.7%	
Diastolic dysfunction	No, mild	92.4%	86.2%	0.166	93.2%		82.1%	0.071
	Moderate, severe	7.6%	13.8%		6.8%		17.9%	
Mitral regurgitation	No, mild	66.3%	57.3%	0.131	41.5%		34.8%	0.381
	Moderate, severe	33.7%	42.7%		58.5%		65.2%	
Aortic regurgitation	No, mild	94.2%	87.5%	0.030	89.3%		85.3%	0.402
	Moderate, severe	5.8%	12.5%		10.7%		14.7%	

Abbreviations: SAM, systolic anterior motion of anterior mitral valve leaflet; ASH, asymmetric septal hypertrophy; LVOT, left ventricular outflow tract; RVHRV, Right ventricular hypertrophy; RV, right ventricle; EF, ejection fraction; BO-HCM, burned-out hypertrophic cardiomyopathy

Table 5. Echocardiographic and Demographic Predictors of Burned-out HCM

Predictor	Odds Ratio (95% Confidence Interval)	P value
Age	1.02 (1.002 - 1.0471)	0.030
Family history of HCM	1.14 (0.4690 - 2.8100)	0.762
Mild RV dysfunction	2.37 (1.1399 - 4.9337)	0.021
Systolic pulmonary artery pressure	1.02 (0.9952 - 1.0597)	0.097

Abbreviations: HCM, hypertrophic cardiomyopathy; RV, right ventricle

5. Discussion

This cross-sectional study was performed to determine the prevalence, risk factors, predictors, and prognosis of burned-out hypertrophic cardiomyopathy (BO-HCM). In some variables, the results were significantly different from those reported in previous studies. The prevalence of BO-HCM (LVEF ≤ 50%) was 27.2% among participants. This rate was higher than in previous studies. Maron et al. reported a 10% prevalence (10, 11), while Harris et al. reported a prevalence of even less than 3.5%. In addition, Melacini et al. reported the highest rate among all studies (17%) (12, 13). However, their results were based on the symptoms of heart failure.

In the present study, patients with reduced and preserved EF were not different in terms of gender and age. This finding contradicts the findings of Harris et al., who reported that patients in the final stage of HCM were younger than other patients with HCM. At the same time, Maroon et al. found no clear association between symptoms of heart failure, end-stage HCM, and age (14).

The results of our study showed no difference between the gender of patients in terms of age and symptoms. This finding is inconsistent with the results reported by Van Drill et al., who showed that women with HCM were older than men of the same age at diagnosis (15-17). In addition, Van Drill et al. reported that women had higher degrees of diastolic dysfunction, lower exercise capacity, more symptoms, and worse survival (15, 18). Our findings did not show a significant difference in the gender of patients in the prevalence of burned-out HCM. In contrast, not only did our female cases have smaller LV and RV sizes in systole and diastole, but they also had smaller e′-septal, e′-lateral, and E-wave velocities of mitral valve inflow rates. There was also no difference between the two groups in terms of diastolic dysfunction, NYHA function class, and fibrosis in magnetic resonance imaging of the heart, a finding that is inconsistent with the results reported by Van Drilt Al (1, 15).

In our study, the overall prevalence of AF in patients with HCM was approximately 32%, which is higher than the rates reported by Olivotto et al. (5, 19) and Maron et al. (14). In both studies, the prevalence of AF was approximately 20%, roughly four times higher than the prevalence in normal individuals. In our study, the prevalence of AF was higher than previously reported. However, cases with a maximum LVEF of 50% were greater than cases with an LVEF of more than 50% (32.8% vs. 14%). At the first visit, there was no association between symptom severity and the presence of AF rhythm, while patients with AF rhythm had significantly more symptoms at follow-up.

Previous studies reported a significant relationship between a family history of HCM and burned-out HCM (20). Our results showed no relationship between cases with burned-out HCM and a family history of HCM. The use of beta-blockers was also significantly lower in this group of patients. The contradictory results for carvedilol are probably because it is commonly used by patients with heart

failure. Beta-blockers are thought to help reduce burnout in patients with HCM. Undoubtedly, randomized controlled trials are needed to analyze this point further.

Due to valvular abnormalities in HCM, unlike MR, aortic insufficiency (AI) was significantly more severe in the first analysis in patients with burned-out HCM (group 1). Among the valvular disorders, only AI was directly related to NYHA performance class. More than half of patients with HCM suffered from mild to severe RV dysfunction, which was also reflected in the Sm-RV as an indicator of RV function. In addition, RV dysfunction was more severe in cases with burned-out HCM. Sm-RV was also significantly lower in these patients compared to cases with LVEF greater than 50% (9.73 cm/s vs. 8.11 cm/s). In addition, the RV was larger in group 1 patients than in other patients. PAP was also significantly higher in these patients (38.28 vs. 29.74 mmHg). According to our results, RV and PAP were not associated with symptom severity. However, the severity of RV dysfunction was directly related to NYHA performance class. Previous studies have placed little emphasis on RV disorders, RV function parameters, and diastolic function parameters (e.g., e-septal, e′-lateral, and inflow E and A wave) in patients with HCM (Table 5). In our study, the prevalence of burned-out HCM (LVEF < 50%) was 25.4%, which is higher than the rate reported by all previous studies. This study may have overestimated the prevalence because it was conducted at a tertiary center, or the prevalence may be rising. During the study period, 181 patients received implantable cardioverter-defibrillators (ICD). Septal myectomy was performed on eight patients. Fifteen patients expired during the follow-up.

5.1. Limitations

This study has several limitations. First, as mentioned previously, the follow-up of 101 patients was not completed, so they were excluded from the study. Second, our study was performed in a referral hospital, and selective bias was inevitable. Third, genetic analysis was not undertaken in this study despite the increasing value of genetic testing in HCM (21). Fourth, late enhancement analysis by cardiac magnetic resonance imaging was not available in our study, and its prognostic significance was overlooked. Finally, the follow-up time was relatively short. Therefore, more detailed data on a larger multicenter scale are encouraged to evaluate the detailed risk factors related to end-stage HCM.

5.2. Conclusion

Among patients suffering from HCM, the presence of an AF rhythm or frequent PVCs on ECG, significant RV dysfunction, and the absence of systolic anterior motion of mitral valve leaflets have prognostic value and might be considered predictors for progression to BO-HCM.

5.3. Ethical Approval

Ethical approval for this study was obtained from the Iran University of Medical Sciences (IR.RHC.REC.1400.030).

5.4. Informed Consent

Written informed consent was obtained from all the participents.

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Authors' Contribution

M.A.S.A., A. Al, S.K., Z.R., M.K., Se. J., and Sa. J. conceived and designed the study and drafted the manuscript. Z.S., M. Baz., N.S., and M.S. helped design the study, performed parts of the statistical analysis, and helped draft the manuscript. K.R., R. Az., R. An., M. Bar., Z.H., D.K., A. Ab., H.B., A.G., and M.M. reevaluated the clinical data, revised the manuscript, performed the statistical analysis, and revised the manuscript.

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We have no competing interests to declare.

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