

# Clinical Profile of Patients with Hypertrophic Cardiomyopathy at a University Hospital

## *Perfil clínico de pacientes con miocardiopatía hipertrófica en un hospital universitario*

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### ABSTRACT

**Introduction:** Hypertrophic cardiomyopathy is the most frequent genetic cardiomyopathy and there is no available information on baseline characteristics and outcome of patients with this disease in our country.

**Objective:** To know the clinical profile of patients with hypertrophic cardiomyopathy and to identify predictors of adverse outcome.

**Methods:** One hundred- and forty three patients with hypertrophic cardiomyopathy at the Hospital Italiano of Buenos Aires between 2005 and 2011 were included in the study.

**Results:** Median age was 66 years and 52 % were women. Most patients presented an asymmetric distribution (92%) and 60 % had dynamic obstruction. Mortality was 5.59 % at a median follow-up of 2.11-years [25-75 IQR (0.75- 3.70)]. The most prevalent symptom was dyspnea (36%), followed by angina (17%) and syncope (14%).

Dynamic obstruction, moderate or severe mitral regurgitation, left atrial diameter and female gender were independently associated with dyspnea. Dynamic obstruction was independently associated with angina. Maximum wall thickness was directly and independently associated with syncope, while ejection fraction and left ventricular hypertrophy or negative T in the electrocardiogram presented an inverse relationship. Mortality was independently associated with hospitalization for decompensated heart failure.

**Conclusion:** Similar to previous studies, our population shows that hypertrophic cardiomyopathy is a heterogeneous disease. A prospective study is necessary to validate the risk predictors assessed in this study.

**Key words:** Hypertrophic cardiomyopathy - Diagnosis - Treatment - Prognosis.

### RESUMEN

**Introducción:** La miocardiopatía hipertrófica es la miocardiopatía de origen genético más común y en nuestro medio no hay información disponible acerca de las características basales y de la evolución de los pacientes con esta patología.

**Objetivos:** Conocer el perfil clínico de pacientes con miocardiopatía hipertrófica e identificar predictores de mala evolución.

**Material y métodos:** Se incluyeron 143 pacientes con miocardiopatía hipertrófica en el Hospital Italiano de Buenos Aires entre 2005 y 2011.

**Resultados:** La mediana de edad de la población fue de 66 años y el 52% eran mujeres. La mayoría de los pacientes (92%) presentaron distribución asimétrica, el 60% obstrucción dinámica. Con una mediana de seguimiento de 2,11 años (rango intercuartil 25-75: 0,75-3,70), la mortalidad total fue del 5,59%. El síntoma más frecuente fue la disnea (36%); le siguieron la angina (17%) y el síncope (14%). Las variables que se asociaron en forma independiente con la disnea fueron la obstrucción dinámica, la insuficiencia mitral mayor o igual a moderada, el diámetro de la aurícula izquierda y el sexo femenino. La obstrucción dinámica se asoció en forma independiente con la angina. El espesor máximo presentó una relación directa e independiente con el síncope, mientras que la fracción de eyección y la hipertrofia ventricular izquierda o las T negativas en el electrocardiograma tuvieron una relación inversa. Los pacientes que se internaron por insuficiencia cardíaca descompensada tuvieron mayor mortalidad en forma independiente.

**Conclusiones:** Al igual que en otras series, en nuestra población se objetivó que la miocardiopatía hipertrófica es una enfermedad muy heterogénea. Es necesario realizar un estudio prospectivo para validar los predictores de riesgo evaluados en este trabajo.

**Palabras clave:** Cardiomiopatía hipertrófica - Diagnóstico - Tratamiento - Pronóstico.

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## Abbreviations

CA	LA Left atrial	MI	Mitral regurgitation
EMB	Endomyocardial biopsy	HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter defibrillator	NYHA	New York Heart Association
ECG	Electrocardiogram	IQR	Interquartile range
HT	Hypertension	CMR	Cardiac magnetic resonance
HF	Heart failure	SPECT	Single-photon emission computed tomography

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy and its estimated prevalence is 1 every 500 persons. (1) It is a disease characterized by marked variability, both in its phenotype as in its clinical presentation and prognosis, causing occasional difficulties in its diagnosis and treatment. Echocardiography is the most widely used non-invasive method, but cardiac magnetic resonance imaging (CMR) allows a more detailed study of all the involved segments. (2) Genetic tests confirm the disease in the presence of compatible phenotype by echocardiography or CMR, although in practice their use is limited by low sensitivity and high cost. (3,4) Endomyocardial biopsy (EMB) reveals the histopathologic diagnosis of the disease but it is not routinely indicated. (5)

Treatment depends on symptoms, presence of intraventricular obstruction and risk of sudden death. (5) In this sense, therapeutic options are medical treatment, septal reduction therapy (percutaneous septal alcohol ablation or surgical myectomy), and device implantation (implantable cardioverter defibrillator and pacemaker). In our setting, there is lack of information about baseline characteristics and outcome of HCM patients. (6) The purpose of our study was to gain insight into the clinical profile of HCM patients and to identify predictors of poor outcome.

## METHODS

### Design

Retrospective analysis of HCM patients in a university hospital.

### Study population

A survey of clinical histories was performed in the electronic database of the Hospital Italiano of Buenos Aires to identify patients with HCM who had undergone an echocardiography or CMR study during hospitalization or in the outpatient setting between December 2005 and December 2011. The following words were used to perform the search: "Septal hypertrophic cardiomyopathy", "Apical hypertrophic cardiomyopathy", "Non-obstructive asymmetric septal hypertrophic cardiomyopathy", "Symmetrical hypertrophic cardiomyopathy", and "Dynamic intraventricular obstruction".

Patients < 18 years or who did not meet the established definition of HCM were excluded from the study. Hypertrophic cardiomyopathy was defined as left ventricular hypertrophy diagnosed by echocardiography and/or CMR in the absence of left ventricular dilation and cardiac or systemic disease leading to that degree of hypertrophy, with or without dynamic intraventricular obstruction. (5) In most

cases, HCM was identified by maximum wall thickness  $\geq 15$  mm, except when the phenotype was very characteristic of HCM or in the presence of significant dynamic obstruction and absence of systemic or cardiac disease. (5)

Patients with HCM diagnosis by EMB with or without diagnostic echocardiogram for HCM were also included in the study. The histological criterion for the diagnosis of HCM was presence of myocyte hypertrophy with fiber disarray and interstitial fibrosis. (7)

Dynamic obstruction was defined as baseline or with Valsalva maneuver subaortic or intraventricular gradient  $\geq 30$  mmHg. (5)

Clinical, echocardiographic, CMR and treatment data were collected, as well as data from different cardiovascular events. Echocardiographic and CMR reports were performed by independent physicians who were blinded to clinical data and among them. Echocardiography was performed with a General Electric Vivid Five ultrasound machine and CMR with a SIEMENS AVANTO 1.5 Tesla scanner. Echocardiographic variables were measured following the American Society for Echocardiography recommendations and CMR variables according to the Society of Cardiovascular Magnetic Resonance protocols. (8-10) Coronary lesions were considered to be significant when epicardial vessel obstruction was  $\geq 70\%$ , except for left coronary trunk lesions which were considered to be significant when the obstruction was  $\geq 50\%$ . (11)

### Statistical Analysis

Continuous data were analysed with the t test or Wilcoxon's test according to variable distribution, and categorical data were analysed with the chi-square test or Fischer's exact test, as appropriate. Spearman's correlation coefficient was used to assess correlation between echocardiographic and CMR maximum thickness measurements and the degree of agreement between both methods was assessed with the Bland-Altman test. A multivariate logistic regression analysis was performed to identify predictors of ventricular fibrillation or sustained ventricular tachycardia, dyspnea, angina, syncope and death, with manual input of variables that in the univariate analysis had a p value < 0.1. Only variables presenting a significant association with the event (p<0.05) were used in the model. In addition, the area under the ROC curve was used to assess the discrimination ability of the different models. Finally, a Kaplan-Meier analysis was performed to estimate overall survival. STATA 11.1 was used for statistical analyses and a p value < 0.05 was considered as statistically significant.

## RESULTS

A total of 143 patients, 64% ambulatory and 36% hospitalized for reasons associated or not with HCM, were included in the study. Median age was 66 years [25-75 interquartile range (IQR): 53-74], 52% were fe-

male and prevalence of hypertension (HT) was 59% (Table 1). Most patients (92%) presented asymmetric distribution, 60% dynamic obstruction and median maximum echocardiographic wall thickness was 1.80 cm (25-75 IQR: 1.56-2.10). Median ejection fraction was 62% (25-75 IQR: 60-66) and 41% presented  $\geq$  moderate mitral regurgitation (MR) (see Table 1). Thirty-one patients (22%) underwent CMR, and 75% of them presented late gadolinium enhancement. A good correlation (Spearman's  $r$  coefficient = 0.75,  $p < 0.001$ ) was found between maximum thickness by echocardiography and CMR. The Bland-Altman analysis showed a good degree of agreement between CMR and echocardiography, with acceptable agreement limits between -0.582 and 0.818 cm, and no evidence of CMR overestimation with respect to echocardiography [difference between means of 0.118 cm (95% CI, -0.011 to 0.246 cm),  $p = 0.861$ ] (Figure 1).

At median follow-up of 2.11 years (25-75 IQR: 0.75-3.70) (Figure 2), overall mortality was 8/143 (5.59%), 62.5% of cardiovascular origin. The most prevalent symptom was dyspnea [51/143 (36%)], followed by angina [25/143 (17%)] and syncope [20/143 (14%)] (Table 2).

Thirteen patients (9%) required septal ablation and 5 (3.50%) surgical myectomy; 8 patients (5.59%) received an implantable cardioverter defibrillator for secondary prevention and 3 (2%) underwent cardiac transplantation due to end-stage heart failure (HF) (see Table 2).

Variables independently associated with dyspnea were: dynamic obstruction [OR 2.70 (95% CI 1.10-6.66);  $p = 0.030$ ],  $\geq$  MR [OR 2.46 (95% CI 1.07-5.65);  $p = 0.033$ ], left atrial (LA) diameter [OR 1.10 (95% CI 1.03-1.17) per each mm increase;  $p = 0.001$ ] and female gender [OR 2.70 (95% CI 1.12-6.66);  $p = 0.027$ ] (Table 3). The discrimination ability of this combination of variables to identify patients with dyspnea presented an area under the ROC curve of 0.799 (see Table 3)

Maximum thickness (per each mm increase) and concentric HCM phenotype were independently associated with ventricular fibrillation/ventricular tachycardia [OR 1.27 (95% CI 1.08-1.51;  $p = 0.005$ ) and OR 11.20 (95% CI 2.07-60.48;  $p = 0.022$ ), respectively; see Table 3].

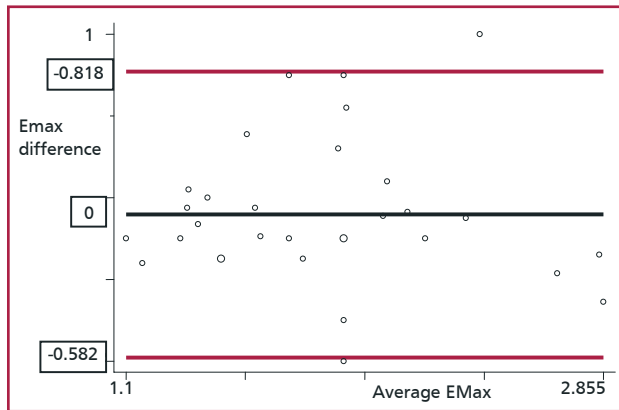
Dynamic obstruction was independently associated with angina [OR 4.28 (95% CI 1.38-13.23);  $p = 0.012$ ]. Maximum thickness (per each mm increase) was directly and independently associated with syncope [OR 1.13 (95% CI 1.01-1.27);  $p = 0.029$ ], while there was an inverse association with ejection fraction and left ventricular hypertrophy or electrocardiographic negative T [OR 0.91 (95% CI 0.84-0.99),  $p = 0.031$  and OR 0.30 (95% CI 0.10-0.85),  $p = 0.023$ , respectively; see Table 3].

Patients hospitalized for decompensated HF independently presented higher mortality [OR 10.08 (95% CI 2.22-45.72),  $p = 0.003$ ; see Table 3].

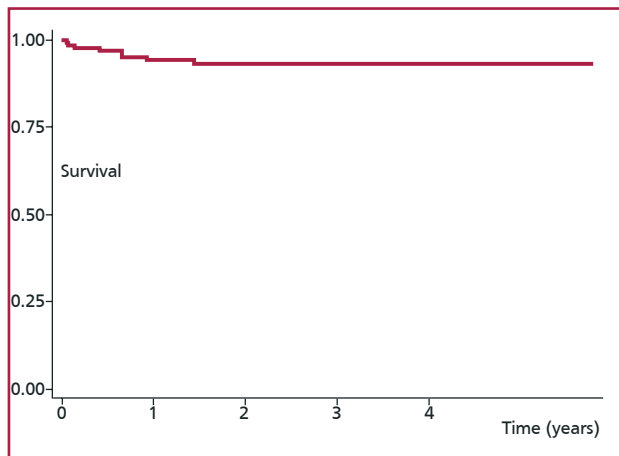
**Table 1.** Clinical variables and diagnostic methods

Age, years	66 (53-74)
Female gender n (%)	75 /143 (52)
HT, n (%)	84/143 (59)
Diabetes, n (%)	8/143 (6)
Creatinine, mg/dL	0.90 (0.79-1.1)
Beta-blockers, n (%)	114/143 (79)
Calcium-blockers, n (%)	41/143 (29)
Amiodarone, n (%)	25/143 (17)
Dynamic obstruction, n (%)	86/143 (60)
Asymmetric distribution, n (%)	132/143 (92)
Phenotype	
Septal, n (%)	123/143 (86)
Apical, n (%)	6/143 (4)
Concentric, n (%)	14/143 (10)
Septal thickness, cm	1.78 (1.55-2.07)
Posterior wall thickness, cm	1.25 (1.15-1.35)
Maximum thickness, cm	1.80 (1.56-2.10)
LV mass index, gr/m <sup>2</sup>	174 (144-207)
Ejection fraction, %	62 (60-66.1)
E wave velocity, m/s	0.80 (0.62-1.06)
A wave velocity, m/s	0.75 (0.6-0.98)
E/A ratio	1.20 (0.77-1.49)
Deceleration time, ms	220 (190-290)
LA diameter, cm	4.50 (4.1-5)
MR, degree:	
0: absence, n (%)	34/143 (24)
1: mild, n (%)	50/143 (35)
2: moderate, n (%)	18/143 (13)
3: moderate to severe, n (%)	25/143 (17)
4: severe, n (%)	16/143 (11)
MR $\geq$ moderate, n (%)	59/143 (41)
MR mechanism, organic (%), n (%)	12/109 (11)
CMR, n (%)	31/143 (22)
Maximum thickness by CMR, cm	1.80 (1.45-2.20)
Gadolinium enhancement, n (%)	23/31 (75)
EMB, n (%)	5/143 (3.50)
ECG, pattern:	
LV hypertrophy/ negative T waves	99/143 (70 %)
Bundle branch block	19/143 (13 %)
Pacemaker rhythm	10/143 (7 %)
Normal	15/143 (10 %)

Continuous variables were expressed as median and 25-75 interquartile range. Categorical variables were expressed as percentages. HT: Hypertension, LV: Left ventricular. LA: Left atrial, MR: Mitral regurgitation. CMR: Cardiac magnetic resonance. EMB: Endomyocardial biopsy. ECG: Electrocardiogram



**Fig. 1.** Agreement between CMR and electrocardiographic maximum thickness. Bland-Altman analysis depicting mean difference (black line) and limits of agreement (red lines). The y axis shows Emax difference, i.e. the maximum thickness difference between cardiac magnetic resonance and echocardiographic measurements. The x axis shows average Emax: cardiac magnetic resonance maximum thickness + echocardiographic maximum thickness) / 2



**Fig. 2.** Overall population survival

**DISCUSSION**

This retrospective study provides insight into some of the clinical features, diagnostic methods and treatments administered to patients with HCM in our setting. In most cases the diagnosis was made noninvasively by echocardiography, except in five cases in which EMB was performed (three patients underwent heart transplantation for end-stage HF). Most patients in whom HCM was diagnosed by EMB showed concentric hypertrophy and septal thickness was significantly lower than in those in whom EMB was not performed (median septal thickness 1.30 cm vs. 1.80 cm,  $p = 0.0256$ ). Moreover, although 59% of the included population had HT as a risk factor, probably related to patient age, most presented asymmetrical distribution of hypertrophy with a marked predominance of septal thickness and obstructive pattern in 60% of cases. This type of remodeling is closer to the

**Table 2.** Events, symptoms and therapeutic interventions

Death, n (%)	8/143 (5.59)
Cardiovascular death, n (%)	5/8 (62.50)
Congestive heart failure, n (%)	24/143 (17)
VF/VT, n (%)	8/143 (5.60)
NSVT, n (%)	14/143 (9.80)
Atrial fibrillation, n (%)	27/143 (19)
CA, n (%)	37/143 (26)
Coronary artery disease, n (%)	13/37 (35)
Stroke, n (%)	7/143 (4.90)
Dyspnea, n (%)	51/143 (36)
Angina, n (%)	25/143 (17)
Syncope, n (%)	20/143 (14)
Septal ablation, n (%)	13/143 (9)
Myectomy	5/143 (3.50)
Definitive pacemaker, n (%)	12/143 (8)
Implantable cardioverter defibrillator, n (%)	8/143 (5.59)
Coronary angioplasty, n (%)	7/143 (5)
CABG, n (%)	3/143 (2)
MVR, n (%)	7/143 (5)
Heart transplantation, %	3/143 (2)

VF / VT: Ventricular fibrillation/ventricular tachycardia. NSVT: Non-sustained ventricular tachycardia. CA: Coronary angiography. CABG: Coronary artery bypass graft surgery. MVR: Mitral valve replacement.

possibility of a genetic cardiomyopathy, though confirming genetic analyses were not performed in this study. The prevalence of HT in different studies of symptomatic HCM patients is variable and ranges from 25% and 54 % of cases. (12, 13)

In the analysis per patient, a very good agreement between CMR and echocardiography was observed in maximum thickness measured in 31 participants. The high agreement between the two methods can be partly explained because a large percentage of our sample was represented by septal HCM which is easier to evaluate by echocardiography. It is also possible that the analysis per segment increases the discrepancy between both methods. A study shows that CMR overestimates echocardiography measurements; even in lateral segments, thickness obtained by the former method can be 20 % higher, due to the difficulties arising with echocardiography to measure the lateral wall. (14)

The annual overall mortality in this study was 2.8 per year, probably low for this condition although 75 % of patients presented late gadolinium enhancement. The only independent predictor of death was hospitalization for decompensated HF. These patients had greater LA dilation, higher MR, more need for septal reduction therapy and increased demand for cardiac transplantation. Maron et al. recently pub-

**Table 3.** Predictors of ventricular arrhythmias and symptoms: multivariate analysis

Event / Symptom	Predictor/s	OR (95 % CI)	p	AUC
VF/VT	Maximum thickness, per each mm	1.27 (1.08-1.51)	0.005	0.797
	Concentric phenotype	11.20 (2.07-60.48)	0.022	
Death	Hospitalization for decompensated HF	10.08 (2.22-45.72)	0.003	0.741
Dyspnea	Dynamic obstruction	2.70 (1.10-6.66)	0.030	0.799
	≥ moderate mitral regurgitation	2.46 (1.07-5.65)	0.033	
	LA diameter, per each mm	1.10 (1.03-1.17)	0.001	
	female gender	2.70 (1.12-6.66)	0.027	
Angina	Dynamic obstruction	4.28 (1.38-13.23)	0.012	0.644
Syncope	Maximum thickness, mm	1.13 (1.01-1.27)	0.029	0.690
	Ejection fraction	0.91 (0.84- 0.99)	0.031	
	ECG: LVH or negative T	0.30 (0.10-0.85)	0.023	

VF/VT: Ventricular fibrillation/ventricular tachycardia. LA: Left atrial. ECG: Electrocardiogram. LVH: Left ventricular hypertrophy. AUC: area under the ROC curve. HF: Heart failure.

lished results of a HCM cohort aged over 60 years and found that survival at 5 and 10 years was 77 % and 54 %, respectively. (15) Life expectancy in this study was lower compared to that of the overall United States population. Perhaps most importantly is the fact that most deaths were unrelated to HCM and that the authors acknowledge that the traditional risk factors for this disease have a more limited value than in younger patients. (15)

The predictive ability of the variables explored identified dyspnea better than the rest of the symptoms. In this regard, the presence of dynamic obstruction, equal or higher than moderate MR, female gender and LA diameter were independent predictors of dyspnea. Other studies reported that in HCM, female gender was independently associated with symptomatic progression to New York Heart Association (NYHA) FC III-IV dyspnea or death from HF or stroke compared to male gender. (16,17) With regard to the degree of dynamic obstruction associated with greater progression of symptoms, one of the studies reported that patients who had an obstruction  $\geq 30$  mmHg had an independent and increased risk of symptomatic progression to NYHA FC III -IV or death from HF or stroke (RR:2.7;  $p < 0.001$ ). (17)

Angina was independently associated with dynamic left ventricular outflow tract obstruction. In the literature, angina has been associated with increased oxygen demand related to enhanced wall stress due to increased left ventricular mass and also to a decrease of oxygen supply associated with a reduction of coronary flow reserve. The latter could be explained by non-atherosclerotic coronary disease of the intramural arteriolar wall and in some cases by the presence of muscular bridges. (18) So far, an association between increased gradient and angina has not been established, but it would probably lead to enhanced wall stress causing increased oxygen consumption as well as decreased supply as a result of reduced stroke volume. This study did not explore the relationship between ischemia and angina, or between ischemia and other adverse events, since the presence of ischemia

was not systematically assessed in all patients. In one study, the degree of microvascular dysfunction was a strong predictor of clinical worsening and death. (19) According to another study, adverse remodeling and systolic dysfunction at follow-up could explain poor outcome in severe microvascular dysfunction. (20) However, guidelines establish that SPECT or stress echocardiography is not indicated to detect silent ischemia in asymptomatic HCM patients (Class III, Level of evidence C). (5)

Only 13 patients (9 %) of the study population had significant coronary artery disease diagnosed by coronary angiography and 10 of them required surgical or angioplasty revascularization. The indication for coronary angiography was decided by the treating physician guided by symptoms and/or by the need of coronary anatomy information as part of the evaluation for septal reduction therapy. In our study, the frequency of septal reduction therapy was similar to that of other series, with an estimated 5% of HCM patients requiring percutaneous or surgical intervention to relieve the dynamic obstruction. (21)

Syncope was the least frequent symptom and was associated with greater maximum thickness, lower echocardiographic ejection fraction and presence of bundle branch block, pacemaker rhythm or normal ECG. It should be mentioned that only 10% of the population had a normal ECG. Patients who presented with syncope, had greater need of ICD and pacemaker implantation compared to those not presenting syncope [30% vs. 1.63% ( $p < 0.001$ ) and 25% vs. 5.69% ( $p = 0.004$ ), respectively]. In the study by Spirito et al., 10% of the population with HCM had syncope of unknown origin and 3.44 % presented with neurally-mediated syncope. Patients with syncope of unknown origin occurring within 6 months of the initial assessment had a fivefold increased risk of sudden death compared with patients without syncope, across all age strata. (22).

Several limitations of this study are related to the retrospective design. Firstly, many variables were dichotomously coded and thus useful information was

lost. It would have been important to know the functional class of dyspnea as well as the various electrocardiographic patterns or the extent of late gadolinium enhancement. Some studies show more adverse patient outcome with greater degree of gadolinium enhancement. (23) Secondly, LA size was considered according to anteroposterior diameter instead of LA volume. In the study by Losi et al., the latter parameter was a predictor of sudden death, heart transplantation or septal reduction therapy in HCM patients. (24) Thirdly, the role of HCM family history and natriuretic peptides was not assessed. Recently, a prospective study showed that patients who were in the second and third BNP tertile presented higher mortality than patients in the lowest tertile [HR4.88 ( $p = 0.006$ ) and HR 6.98 ( $p = 0.0003$ ), respectively]. (25)

Finally, in this study there are several reasons that hamper the representativeness of the population studied. Firstly, there may be a bias reference that reflects only part of the disease spectrum. But perhaps more importantly is the fact that an over-diagnosis or sub-diagnosis cannot be ruled out due to the acknowledged difficulties in the diagnosis of HCM, and considering that EMB was performed only in a very low number of patients and that in no case genetic testing was done. Nevertheless, consistent with the known prevalence of this disease and the volume of patients treated at our center, it is possible to hypothesize that according to the "filters" used for the search and inclusion of patients, the criteria were more specific than sensitive, so it may be inferred that many patients diagnosed with HCM were not included in this work.

## CONCLUSIONS

As in other series, we observed that in our population HCM is a very heterogeneous disease in its presentation, phenotype and progression. A prospective study is needed to validate the risk predictors evaluated in this study.

## Conflicts of interest

None declared.

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