

Original Article

Genotypic and phenotypic characterization of hypertrophic cardiomyopathy at the Sociedad de Cirugía de Bogotá - Hospital de San José, Bogotá, 2023-2025

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Accepted: September 19, 2026
Online: September 22, 2026

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Funding

Self-funded.

Conflicts of interest

None.

Cite as

Cely-Cristancho HJ, Vargas-Vergara D, Rincón-Viloria FD, Cervantes de la Hoz F, Casallas-Vega A, Olaya-Sánchez A, et al. Genotypic and phenotypic characterization of hypertrophic cardiomyopathy at the Sociedad de Cirugía de Bogotá - Hospital de San José, Bogotá, 2023-2025. Arch Peru Cardiol Cir Cardiovasc. 2026;7(3):181-188. doi: 10.47487/apcyccv.v7i3.649.



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ABSTRACT

Objectives. To characterise the clinical, imaging, and genetic profile of patients with hypertrophic cardiomyopathy treated at a university hospital in Bogotá between 2023 and 2025. To propose an institutional pathway for multimodal assessment and family screening, informed by the study findings and expert opinion. **Materials and methods.** We conducted a retrospective, cross-sectional observational study of adults treated at a university hospital, reported in accordance with the STROBE guidelines. We reviewed 182 medical records identified using International Classification of Diseases, 10th Revision (ICD-10) codes. After excluding 120 duplicate, repeated, incomplete, insufficient, or ineligible records, a convenience sample of 62 patients was included. Clinical, family history, imaging, and genetic variables were analysed using descriptive statistics and unadjusted exploratory comparisons according to genetic test results. **Results.** The median age was 69 years (interquartile range [IQR]: 46-75), and 50% of patients were women. Hypertension was the most common comorbidity (51.6%), and two patients had amyloidosis (3.2%). Asymmetrical septal hypertrophy was the predominant morphological pattern (27 of 46 patients; 58.7%). Both echocardiography and cardiac magnetic resonance imaging were available for 46.8% of patients. Median late gadolinium enhancement was 12%, and extensive fibrosis was observed in 6.5%. Genetic testing results were available for 47 patients (75.8%), of whom 10.6% had pathogenic or likely pathogenic variants. A family history of hypertrophic cardiomyopathy was more common in this group ($p < 0.001$), which also had a higher left ventricular outflow tract gradient, a greater frequency of obstruction of 50 mmHg or more, systolic anterior motion of the mitral valve, and a higher left ventricular ejection fraction. Because only five patients had pathogenic or likely pathogenic variants, these comparisons were interpreted as exploratory. **Conclusions.** The cohort showed clinical, imaging, and genetic heterogeneity, with a high prevalence of hypertension and the presence of infiltrative phenocopies. These findings support the implementation of an institutional pathway integrating family pedigree assessment, echocardiography with strain imaging, cardiac magnetic resonance imaging with fibrosis quantification, clinical genetic evaluation, and family screening.

Keywords: Cardiomyopathy, Hypertrophic; Genotype; Phenotype; Magnetic Resonance Imaging; Genetic Testing (Source: MeSH-NLM).

RESUMEN

Caracterización genotípica y fenotípica de la miocardiopatía hipertrófica en la Sociedad de Cirugía de Bogotá - Hospital de San José, Bogotá, 2023-2025

Objetivos. Caracterizar el perfil clínico, imagenológico y genético de pacientes con miocardiopatía hipertrófica atendidos entre 2023 y 2025 en un hospital universitario de Bogotá. Proponer, a partir de los hallazgos y de la opinión de expertos, una ruta institucional de evaluación multimodal y tamizaje familiar. **Materiales y métodos.** Estudio observacional, retrospectivo y transversal en adultos atendidos en un hospital universitario, reportado de acuerdo con la declaración STROBE. Se revisaron 182 registros identificados mediante códigos CIE-10. Después de excluir 120 registros duplicados, repetidos, incompletos, insuficientes o no elegibles, se incluyó una muestra por conveniencia de 62 pacientes. Se analizaron variables clínicas, familiares, imagenológicas y genéticas mediante estadística descriptiva y comparaciones exploratorias no ajustadas por resultado genético. **Resultados.** La mediana de edad fue de 69 años (RIQ: 46-75) y el 50% fueron mujeres. La hipertensión arterial fue la comorbilidad más frecuente (51,6%) y hubo dos casos de amiloidosis (3,2%). El patrón septal asimétrico predominó (27/46; 58,7%). La evaluación con ecocardiograma y resonancia estuvo disponible en el 46,8%; la mediana de realce tardío fue del 12% y la fibrosis extensa se observó en el 6,5%. La genética estuvo disponible en 47 pacientes (75,8%) y las variantes patogénicas o probablemente patogénicas representaron el 10,6% de los estudiados. El antecedente familiar fue más frecuente en este último grupo ($p < 0,001$), que además mostró mayor gradiente del tracto de salida, obstrucción de 50 mmHg o más, movimiento sistólico anterior de la válvula mitral y fracción de eyección del ventrículo izquierdo. Debido a que solo cinco pacientes tuvieron variantes patogénicas o probablemente patogénicas, estas comparaciones se interpretaron como exploratorias. **Conclusiones.** La cohorte mostró heterogeneidad clínica, imagenológica y genética, con hipertensión frecuente y fenocopias infiltrativas. Los hallazgos respaldan una ruta institucional que integre familiograma, ecocardiograma con strain, resonancia con cuantificación de fibrosis, genética clínica y tamizaje familiar.

Palabras clave: Cardiomiopatía Hipertrófica; Genotipo; Fenotipo; Imagen por Resonancia Magnética; Pruebas Genéticas (Fuente: DeCS-BIREME).

Introduction

Hypertrophic cardiomyopathy (HCM) is a myocardial disease characterised by left ventricular hypertrophy that is not explained by abnormal loading conditions. Its clinical presentation is heterogeneous, ranging from asymptomatic disease to dynamic left ventricular outflow tract (LVOT) obstruction, heart failure, atrial fibrillation, ventricular arrhythmias, and sudden cardiac death ^(1,2). The prevalence of the classic HCM phenotype has been estimated at approximately 1 in 500 adults, whereas estimates incorporating genetic data and subclinical cases suggest a prevalence of approximately 1 in 200 ^(3,4).

Diagnostic assessment requires integration of personal and family history, clinical examination, electrocardiography, echocardiography, and cardiac magnetic resonance (CMR) imaging, particularly when the phenotype is uncertain, acoustic windows are poor, tissue characterisation is required, or phenocopies of left ventricular hypertrophy are suspected ^(1,2,5). A peak LVOT gradient of ≥ 30 mmHg at rest or with provocation defines obstruction. In symptomatic patients, a gradient of ≥ 50 mmHg is the haemodynamic threshold for considering invasive treatment after optimisation of medical therapy and assessment at a specialist centre ^(1,2,6).

The genetic basis of HCM predominantly involves sarcomeric genes, particularly MYBPC3 and MYH7, although variant interpretation requires standardised criteria and periodic reassessment ⁽⁷⁻⁹⁾. International registries have shown that pathogenic sarcomeric variants are associated with a greater lifetime disease burden ⁽¹⁰⁾. Sudden cardiac death risk stratification should be individualised and incorporate clinical, familial, electrocardiographic, and imaging findings ⁽¹¹⁾.

CMR provides morphological and tissue characterisation. The extent of late gadolinium enhancement (LGE) has been associated with arrhythmic risk and adverse events, although it should be interpreted within the overall clinical context rather than as an isolated marker ⁽¹²⁻¹⁶⁾. Moreover, the heterogeneity of HCM requires differentiation between sarcomeric disease, hypertrophy secondary to loading conditions, and infiltrative or metabolic phenocopies ^(17,18). Published data from Latin America remain limited, supporting the need for local registries to describe access to advanced imaging, genetic testing, and family screening strategies ⁽¹⁹⁾.

The primary objective of this study was to characterise the clinical, imaging, and genetic profiles of patients with HCM treated between 2023 and 2025 at the Sociedad de Cirugía de Bogotá -Hospital de San José. The secondary objective was to propose an institutional pathway for multimodal assessment and family screening based on the study findings and expert opinion.

Materials and methods

Study design

We conducted a retrospective observational cross-sectional study. The manuscript was prepared in accordance with the

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement ⁽²⁰⁾. The study covered 2023-2025 and was conducted at the Sociedad de Cirugía de Bogotá - Hospital de San José.

Population

The source population comprised adults aged ≥ 18 years who received care for a diagnosis of HCM or phenocopies included in its differential diagnosis. Patients were initially identified using ICD-10 codes I42.1-I42.2. A phenotype consistent with HCM was defined as a maximum wall thickness of ≥ 15 mm in one or more left ventricular segments that was not explained solely by loading conditions. Phenocopies were defined as infiltrative, metabolic, or non-sarcomeric genetic diseases capable of producing a left ventricular hypertrophy phenotype, in accordance with current clinical guidelines ^(1,2). The study aimed to characterise the HCM phenotype and its differential diagnosis and therefore included both sarcomeric and non-sarcomeric aetiologies. A convenience sample comprising all eligible records from the study period was used.

Medical records were reviewed by the study authors, and discrepancies were resolved by consensus. Eligibility was verified using the available clinical information and imaging reports. No centralised rereading of all images was performed. Consequently, cases lacking complete quantitative parameters were retained when a documented clinical diagnosis was available, and findings were interpreted with consideration of the risk of misclassification.

Variables

Clinical variables included age, sex, family history of HCM or sudden cardiac death, comorbidities, amyloidosis or infiltrative phenocopies, treatment, New York Heart Association (NYHA) functional class, syncope, resuscitated sudden cardiac arrest, non-sustained ventricular tachycardia, and implanted devices. Atrial fibrillation was not included in the structured analytical dataset; therefore, its frequency could not be estimated, and this omission was considered a limitation. Imaging variables included morphological pattern, maximum wall thickness, LVOT gradient, obstruction at thresholds of ≥ 30 mmHg and ≥ 50 mmHg, systolic anterior motion of the mitral valve (SAM), left ventricular ejection fraction (LVEF), mitral regurgitation, LGE, apical aneurysm, global longitudinal strain (GLS), imaging modality, and completeness of the imaging report. Genetic variables included genetic test results classified according to American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG/AMP) criteria, the gene involved, clinical genetics assessment, and the use of cardiomyopathy-targeted next-generation sequencing panels. Denominators varied according to the availability of each variable.

LGE was expressed as a percentage of left ventricular mass and considered extensive when it involved $\geq 15\%$. GLS was defined as the percentage of longitudinal myocardial deformation reported using speckle-tracking imaging; less negative values indicate poorer deformation. Imaging reports were considered sufficiently complete when all essential variables prespecified for the study could be retrieved and of limited completeness

when one or more were missing. This classification assessed the information available for research and did not replace a technical audit of image quality.

Procedures or interventions

Data were obtained from the institutional database and available clinical reports. Values of 0 for age, LVEF, GLS, biomarkers, and maximum wall thickness were considered implausible because they did not represent physiologically possible or valid measurements in this context; these values were recoded as missing. Imaging assessment included transthoracic echocardiography, CMR, or both, depending on availability. Genetic testing was categorised as negative or yielding variants of uncertain significance (VUS), yielding pathogenic or likely pathogenic variants (P/LP), or not performed, according to ACMG/AMP criteria. Cardiomyopathy-targeted next-generation sequencing panels included MYH7. No experimental interventions were performed.

Ethical aspects

The study involved a retrospective review of medical records and institutional reports, with no intervention involving participants. It was classified as research without risk under Colombian Resolution 8430 of 1993. Data were anonymised for analysis. The study protocol (ID 19059) was approved through expedited review by the Human Research Ethics Committee (CEISH) of Hospital de San José - FUCS because it was classified as research without risk. The decision was ratified in minutes no. 08 of session no. 08, held on May 13, 2026, and communicated in official letter CEISH 194-2026 dated May 14, 2026.

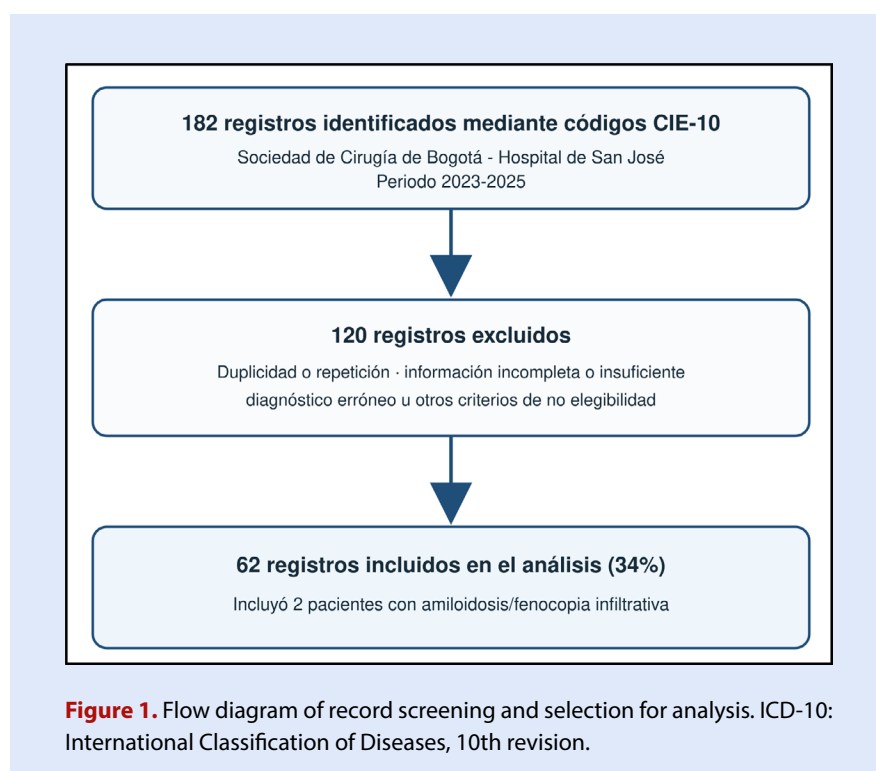
Statistical analysis

Descriptive analyses were performed. Before selecting summary measures and inferential tests, the distributions of continuous variables were assessed using the Shapiro-Wilk test. Continuous variables were reported as medians and interquartile ranges (IQRs), and categorical variables as counts and percentages calculated using the available denominator. Exploratory comparisons between two groups used the Mann-Whitney U test (Wilcoxon rank-sum test) for continuous variables and Fisher's exact test for categorical variables. Exact conditional odds ratios with 95% confidence intervals (CI) were estimated for the main categorical comparisons. No multivariable models or adjustments for multiple comparisons were performed; therefore, all between-group analyses were interpreted as exploratory and hypothesis-generating. A p-value of <0.05 was considered statistically significant. Analyses were performed using Stata version 18.0.

Results

Of 182 records identified using the ICD-10 codes of interest, 120 were excluded because of duplicate or repeated entries, incomplete information, incorrect diagnoses, absence of diagnostic criteria, or other reasons for ineligibility. A total of 62 patients (34%) were included, including two with amyloidosis or an infiltrative phenocopy (**Figure 1**).

The cohort comprised 62 patients, with an even sex distribution. The median age was 69 years (IQR: 46-75), and patients older than 65 years predominated among those with available age data. A documented family history of



HCM or sudden cardiac death was present in three patients (4.8%). Hypertension was the most common comorbidity (32/62; 51.6%), followed by diabetes mellitus, chronic kidney disease, obesity, and coronary artery disease. Most patients with available data were in NYHA functional class I-II. Syncope was documented in seven patients and resuscitated sudden cardiac arrest in one. Non-sustained ventricular tachycardia was uncommon, and seven patients had an implantable cardioverter-defibrillator (**Table 1**).

The predominant morphological pattern was asymmetric septal hypertrophy (27/46; 58.7%; 43.5% of the total cohort), followed by concentric hypertrophy. The pattern could not be classified in 16 patients because it was insufficiently documented in the available reports. Median maximum wall thickness was 17 mm; this measurement was unavailable

in 35 patients. Among the 12 patients with a documented LVOT gradient, ten had LVOT obstruction, defined as a peak gradient of ≥ 30 mmHg (83.3%), corresponding to 16.1% of the total cohort. Nine patients had a gradient of ≥ 50 mmHg (75.0% of those with a documented gradient and 14.5% of the total cohort). SAM was present in 14 patients with available data. Median LVEF was 60%, and mitral regurgitation was predominantly absent or mild. Both echocardiography and CMR were available in 29 patients (46.8%). Among patients with quantified LGE, the median extent was 12% of left ventricular mass, and extensive fibrosis was identified in four patients (6.5% of the total cohort). Median GLS was -14.1% (**Table 2**).

Table 1. Demographic and clinical characteristics and family history of the cohort (N = 62)

Variable	n/N (%) or median (IQR)
Age (years), median (IQR)	69 (46-75); missing: 16
Female sex	31/62 (50.0)
Male sex	31/62 (50.0)
Age ≤ 40 years	5/46 (10.9)
Age 41-55 years	8/46 (17.4)
Age 56-65 years	9/46 (19.6)
Age > 65 years	24/46 (52.2)
Family history of HCM or sudden cardiac death	3/62 (4.8)
Hypertension	32/62 (51.6)
Diabetes mellitus	11/62 (17.7)
Coronary artery disease	7/62 (11.3)
Chronic kidney disease	10/62 (16.1)
Obesity	9/62 (14.5)
Amyloidosis or infiltrative phenocopy	2/62 (3.2)
Beta-blocker use	39/62 (62.9)
Calcium channel blocker use	11/62 (17.7)
Antiarrhythmic drug use	3/62 (4.8)
Disopyramide use	0/62 (0.0)
NYHA I-II	33/43 (76.7)
NYHA III-IV	10/43 (23.3)
Syncope	7/61 (11.5)
Resuscitated sudden cardiac arrest	1/61 (1.6)
Non-sustained VT	3/62 (4.8)
ICD	7/62 (11.3)
Pacemaker	1/62 (1.6)
NT-proBNP (pg/mL), median (IQR)	1,830 (656-5,205); missing: 41
High-sensitivity troponin (ng/L), median (IQR)	68 (20-777); missing: 45

Percentages were calculated using the available denominator for each variable. Data are n/N (%) or median (IQR); the percentage symbol is shown in the column heading. IQR: interquartile range. HCM: hypertrophic cardiomyopathy. NYHA: New York Heart Association. VT: ventricular tachycardia. ICD: implantable cardioverter-defibrillator. NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Table 2. Imaging and electrocardiographic findings in the cohort (N = 62)

Variable	n/N (%) or median (IQR)
Asymmetric septal pattern	27/46 (58.7); 43.5 of the total cohort
Apical pattern	4/46 (8.7)
Concentric pattern	14/46 (30.4)
Midventricular pattern	1/46 (2.2)
Maximum wall thickness (mm), median (IQR)	17 (15-20); missing: 35
LVOT gradient (mmHg), median (IQR)	90 (50-95); missing: 50
LVOT obstruction ≥ 30 mmHg	10/62 (16.1)
LVOT obstruction ≥ 50 mmHg	9/62 (14.5)
SAM	14/59 (23.7)
LVEF (%), median (IQR)	60 (50-65); missing: 18
Preserved LVEF ($\geq 50\%$)	33/44 (75.0)
Mildly reduced LVEF (40-49%)	6/44 (13.6)
Reduced LVEF ($< 40\%$)	5/44 (11.4)
Absent or mild mitral regurgitation	61/62 (98.4)
Severe mitral regurgitation	1/62 (1.6)
Normal baseline ECG	45/62 (72.6)
LVH or repolarisation abnormalities	10/62 (16.1)
LGE (% of LV mass), median (IQR)	12 (7-20); missing: 52
Extensive LGE ($\geq 15\%$)	4/62 (6.5)
GLS (%), median (IQR)	-14.1 (-16.1 to -11.7); missing: 41
Echocardiography only	19/62 (30.6)
CMR only	14/62 (22.6)
Echocardiography and CMR	29/62 (46.8)
Imaging report with sufficient completeness	16/62 (25.8)
Imaging report missing one or more variables	46/62 (74.2)

Percentages were calculated using the available denominator for each variable. Data are n/N (%) or median (IQR); the percentage symbol is shown in the column heading. IQR: interquartile range. LVOT: left ventricular outflow tract. SAM: systolic anterior motion of the mitral valve. LVEF: left ventricular ejection fraction. ECG: electrocardiogram. LVH: left ventricular hypertrophy. LV: left ventricular. LGE: late gadolinium enhancement. GLS: global longitudinal strain. CMR: cardiac magnetic resonance.

Data availability was limited for LVOT gradient (missing in 50/62 patients), quantitative LGE (missing in 52/62), and GLS (missing in 41/62). Given the retrospective design, historical reports did not follow a uniform format, and it was not always possible to distinguish measurements that had not been performed from those that had been performed but not documented. Similarly, the absence of a documented morphological pattern in 16 patients and maximum wall thickness in 35 precluded central imaging adjudication. These findings are particularly relevant given the high prevalence of hypertension and the resulting risk of misclassification.

Genetic testing results were available for 47 patients (75.8%). Of these, five had P/LP variants, representing 10.6% of those tested and 8.1% of the total cohort. The genes identified included MYBPC3, ACTC1, MYL2/MYL3, and others. No pathogenic variants were identified in MYH7, TNNT2, or TNNI3. Most patients did not undergo septal reduction therapy; surgical myectomy was documented in three patients, and no alcohol septal ablation was recorded (Table 3).

In the exploratory analysis by genetic test result, a family history of HCM or sudden cardiac death was the main distinguishing finding: it was present in 60% of the P/LP group and 0% of the negative/VUS group ($p < 0.001$; exact conditional odds ratio: ∞ , 95% CI: 4.73 to ∞). The P/LP group also had a higher LVOT gradient, a greater frequency of obstruction at a threshold of ≥ 50 mmHg (exact conditional odds ratio: 10.19, 95% CI: 0.94-150.82), a greater frequency of SAM (exact conditional odds ratio: 18.21, 95% CI: 1.52-1011.56), and a higher median LVEF. NT-proBNP concentrations were lower in the P/LP group, although this finding should be interpreted cautiously given the small sample and limited biomarker

availability. No statistically significant differences were observed in morphological patterns, mitral regurgitation, electrocardiographic patterns, LGE, extensive LGE, or GLS. Estimates were not adjusted for other variables or multiple comparisons and were based on only five patients with P/LP variants; therefore, they represent exploratory trends rather than confirmatory evidence (Table 4).

Medians were compared using the Mann-Whitney U test (Wilcoxon rank-sum test), and categorical variables using Fisher's exact test. Exact conditional odds ratios and their 95% CIs were estimated for the main categorical comparisons. No multivariable adjustments or corrections for multiple comparisons were performed. Variables showing nominally significant differences in this exploratory analysis are presented.

Discussion

This cohort comprised a clinically heterogeneous population with HCM and related differential phenotypes, an even sex distribution, a high prevalence of hypertension, and a median age of 69 years, higher than that reported in several international HCM registries⁽²¹⁾. This older age might reflect local referral patterns, survivor bias, or delayed recognition and increases the likelihood of hypertrophy related to loading conditions, amyloidosis, and other phenocopies. The coexistence of hypertension and the inclusion of patients with amyloidosis therefore require a systematic distinction between primary sarcomeric disease, secondary hypertrophy, and infiltrative phenocopies.

Asymmetric septal hypertrophy was the most common morphological pattern, consistent with the classic description of HCM⁽²²⁾. However, concentric patterns and cases of amyloidosis reinforce the need for sequential imaging assessment, from echocardiography to CMR. Morphological pattern was unavailable in 16 patients and maximum wall thickness in 35, limiting consistent confirmation of the imaging criterion for HCM, particularly given the prevalence of hypertension. Furthermore, only 46.8% underwent both echocardiography and CMR. CMR provides more precise morphological assessment, quantifies fibrosis, and informs the differential diagnosis; its use should therefore be incorporated into protocols for patients with an uncertain phenotype, poor echocardiographic windows, or a need for risk stratification⁽¹⁾.

LVOT obstruction with a gradient of ≥ 50 mmHg was uncommon in the total cohort but was concentrated in the P/LP group, which also had higher gradients, a greater frequency of SAM, and a higher median LVEF. These findings are exploratory because of the small number of patients with P/LP variants, wide CIs, and absence of multivariable adjustment or correction for multiple comparisons. Moreover, LVOT gradient data were missing in 50 patients; therefore, the frequency of obstruction might be underestimated and does not reflect systematic assessment of all patients. Assessment of the LVOT at rest and with provocation, using ≥ 30 mmHg to define obstruction and ≥ 50 mmHg as the threshold relevant to treatment in symptomatic patients, should be explicitly documented in structured echocardiographic reports.

Table 3. Genetic assessment and septal reduction therapy (N = 62).

Variable	n/N (%) or median (IQR)
Genetic assessment available	47/62 (75.8)
Negative/VUS	42/62 (67.7)
P/LP	5/62 (8.1); 5/47 (10.6 of patients tested)
Not performed	15/62 (24.2)
MYBPC3	2/62 (3.2)
MYH7	0/62 (0.0)
TNNT2	0/62 (0.0)
TNNI3	0/62 (0.0)
ACTC1	1/62 (1.6)
MYL2/MYL3	1/62 (1.6)
Other genes	1/62 (1.6)
No clinically relevant variant	1/62 (1.6)
No septal reduction therapy	59/62 (95.2)
Alcohol septal ablation	0/62 (0.0)
Surgical myectomy	3/62 (4.8)

Los porcentajes se calcularon con el denominador disponible para cada variable; las celdas presentan n/N (%) y el símbolo de porcentaje se indica en el encabezado. PP/P: patogénica/probablemente patogénica. VUS: variante de significado incierto.

Table 4. Exploratory comparison of selected variables by genetic status (N = 47)

Variable	Negative/VUS (N=42), n (%) or median (IQR)	P/LP (N=5), n (%) or median (IQR)	p-value
Family history of HCM or SCD	0 (0)	3 (60)	<0.001
NT-proBNP (pg/mL), median (IQR)	1.830 (1.070-5.205)	393 (379-406)	0.019
LVOT gradient (mmHg), median (IQR)	68 (14-92)	99 (94-150)	0.022
LVOT obstruction $\geq$ 50 mmHg	5 (12)	3 (60)	0.029
SAM	7 (17)	4 (80)	0.009
LVEF (%), median (IQR)	56 (43-64)	68 (63-77)	0.023

Although LVEF was preserved in most patients with available data, GLS was impaired in a subgroup, suggesting subclinical systolic dysfunction. However, GLS data were missing in 41 patients and quantitative LGE data in 52, probably because of heterogeneity in historical examinations and reports. These findings therefore do not permit precise estimation of their distributions or robust comparisons by genotype. Prospective incorporation of strain assessment and standardisation of LGE quantification are needed to address this gap.

The diagnostic yield of genetic testing in this cohort (10.6% of patients tested) was lower than that reported in large international cohorts, including a series of 2,912 unselected probands with a detection rate of approximately 32%^(10,23). In addition to age, comorbidities, inclusion of phenocopies, sample size, and the absence of universal testing, this finding might reflect imprecise diagnostic classification in patients without complete imaging confirmation. The panel included MYH7, although no pathogenic variants were identified in this gene; nevertheless, the exact panel composition and testing laboratory should be reported to allow interpretation of its analytical scope. The low frequency of documented family history might also reflect the absence of systematic pedigree assessment, retrospective under-reporting, and the older age of the cohort. Consequently, the association between P/LP variants and family history should be considered hypothesis-generating and supports implementation of a three-generation pedigree, genetic counselling, and cascade family screening.

The proportion of patients with a normal baseline electrocardiogram (72.6%) was substantially higher than that reported in a cohort of 2,485 patients with echocardiographically confirmed HCM, in which approximately 6% had a normal ECG⁽²⁴⁾. This finding might reflect reliance on clinical reports without centralised ECG rereading, under-reporting of non-specific abnormalities, or diagnostic misclassification, particularly among patients with hypertension, phenocopies, or incomplete imaging information. It should therefore not be interpreted as a typical feature of HCM and reinforces the need for prospective diagnostic reassessment.

Based on these findings, we propose an institutional pathway centred on confirming left ventricular hypertrophy, characterising loading conditions, documenting family history, identifying red flags for sarcomeric disease or phenocopies, performing structured echocardiography with GLS and

dynamic LVOT assessment, obtaining CMR when indicated, prioritising clinical genetics assessment and next-generation sequencing panels in selected patients, and initiating cascade family screening (**Figure 2**). This pathway aims to address the identified limitations: heterogeneous reports, missing essential measurements, limited availability of CMR and genetic testing, absence of systematic pedigree assessment, and risk of misclassification.

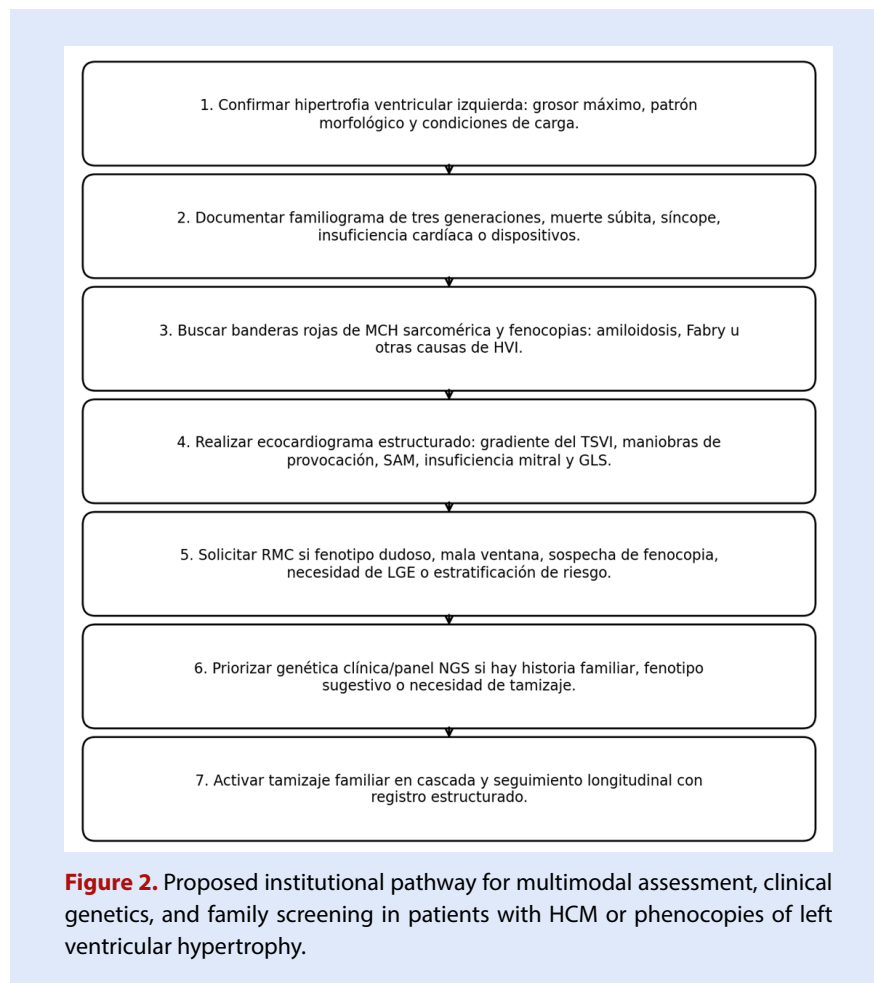
The main limitations were the retrospective, single-centre design and small sample size; exclusion of 120 records without an available breakdown by reason; under-reporting of LVOT gradients, maximum wall thickness, morphological pattern, GLS, quantitative LGE, atrial fibrillation, and family history; non-universal availability of CMR and genetic testing; absence of centralised rereading of images and ECGs; and lack of longitudinal follow-up for clinical events.

Only 25.8% of imaging reports were sufficiently complete to retrieve all prespecified variables. This does not imply that images from the remaining 74.2% were technically inadequate, but it limits consistent retrospective verification of the diagnosis. The high prevalence of hypertension, ECGs reported as normal, and frequent absence of maximum wall thickness measurements increase the risk of misclassification. Including patients with amyloidosis strengthens the assessment of the differential diagnosis but requires interpretation of the findings as those of a cohort with heterogeneous hypertrophic phenotypes rather than an exclusively sarcomeric population. Finally, genetic comparisons were unadjusted, were not corrected for multiple testing, and were based on five patients with P/LP variants; their estimates are imprecise and exclusively exploratory.

HCM in this cohort showed substantial clinical, imaging, and genetic heterogeneity, with a predominant septal phenotype. Hypertension frequently coexisted, and infiltrative phenocopies were also present. LVEF and functional class, when considered in isolation, are insufficient to fully assess disease burden. GLS, LGE quantification, dynamic LVOT assessment, clinical genetics, and family screening should be integrated into an institutional care pathway and prospective registry.

Author contributions

HJCC: conceptualisation, investigation, data curation, project administration, writing-original draft, writing-review and editing, and approval of the final version. **DVV:**



conceptualisation, investigation, supervision, clinical validation, critical review of intellectual content, manuscript editing, and approval of the final version. **FDRV:** investigation, data curation, analysis and interpretation of data, writing-original draft, writing-review and editing, and approval of the final version. **FCH:** investigation, data collection and curation, writing-original draft, writing-review and editing, and approval of the final version. **ACV:** methodology, formal analysis, methodological advice, validation of results, critical review of intellectual content, manuscript editing, and approval of the

final version. **AOS and JLFR:** supervision, clinical validation, interpretation of cardiovascular findings, critical review of intellectual content, manuscript editing, and approval of the final version.

Acknowledgments

The authors thank the Fundación Universitaria de Ciencias de la Salud, Hospital de San José, the Cardiovascular Research Group, and the Office of the Vice-Rector for Research for their academic and methodological support throughout the study.

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