

ORIGINAL RESEARCH

Disease Expression and Outcomes in Black and White Adults With Hypertrophic Cardiomyopathy

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BACKGROUND: There is limited research on hypertrophic cardiomyopathy (HCM), which is the most common inherited cardiac disorder, in diverse populations, including Black individuals. Current literature lacks comprehensive data on HCM disease expression, comorbidities, and outcomes in this historically disadvantaged group. The purpose of this study was to examine structural HCM characteristics, comorbidities, and outcomes in a Black and White cohort with HCM.

METHODS AND RESULTS: The study was a subgroup analysis from a longitudinal, prospective study on HCM, with supplemental chart review. The sample included adults (≥ 18 years) with a clinical diagnosis of HCM, who self-identified as Black/African American or White. The study sample comprised 434 individuals; 57 (13.1%) were Black, and 180 (41.5%) were women. Black patients were younger than White patients, 54.6 (13.4) versus 62.5 (14.8) years, $P=0.001$. Black patients were more likely to have sub-basal and diffuse hypertrophy, 22 (38.6%) versus 56 (14.9%), $P<0.001$, 6 (10.5%) versus 15 (4%), $P=0.017$, mid-LV obstruction, 7 (12.3%) versus 21 (5.5%), $P=0.025$, and cardiac fibrosis $\geq 15\%$, 10 (22.2%) versus 19 (8.8%), $P=0.009$, than White patients. Black patients were more likely to experience appropriate implantable cardioverter defibrillator interventions, 5 (38.5) versus 5 (6.8), $P<0.001$ and were more likely to have ≥ 2 sudden death risk factors. Comorbidities were largely similar between groups, though more Black participants had Class II obesity, 12 (21.8) versus 30 (8.1), $P<0.001$. Both groups had similar rates of genetic testing usage.

CONCLUSIONS: This study underscores the need for continued research of HCM in Black populations, including tailored approaches to diagnosis and precise evaluation of cardiac anatomy.

Key Words: health disparities ■ heart anatomy ■ hypertrophic cardiomyopathy ■ outcome ■ risk factor

See Editorial by Lakdawala

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder with a global prevalence of 1:200 to 1:500.¹ It is highly variable in disease expression, course and outcomes.² Despite an abundance of literature on disease expression, course, and outcomes there is a paucity of data on these variables in the context of different racial/ethnic groups. To date, the United States and European clinical HCM guidelines have not adequately addressed minority populations.^{3–5} Research examining HCM expression, disease course, and outcomes across races

and ethnic groups is sparse; especially in traditionally underserved populations, such as Hispanic/Latin and Black groups. The current literature exploring HCM differences between Black and White individuals is limited^{6–10}; a persistent challenge is the small overall numbers of Black participants with HCM in the cohorts studied. Further, the existing literature does not address rarer structural HCM characteristics in this population, characteristics that may have bearing on HCM disease course and outcomes. The purpose of this study was 2-fold: to describe HCM disease expression in a Black

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CLINICAL PERSPECTIVE

What Is New?

- Black patients with hypertrophic cardiomyopathy (HCM) are underrepresented in HCM specialty care.
- In this study, the Black cohort was more likely to have sub-basal and diffuse hypertrophy, mid-LV obstruction, and a high degree of cardiac fibrosis, all HCM characteristics associated with worse disease progression and prognosis.
- Precise evaluation of cardiac anatomy is necessary in the diagnostic work-up of Black patients with suspected HCM to tailor treatment approaches to optimize outcomes in this population; obesity was highly prevalent in both Black and White patients with HCM, and Black patients were more likely to have moderate obesity.

What Are the Clinical Implications?

- Risk of preventable comorbidities, including obesity, should be routinely addressed with patients with HCM.
- Genetic testing remains an integral component of HCM care and genetic testing use in Black populations should be further explored.

Nonstandard Abbreviations and Acronyms

BB	beta blocker
HCM	hypertrophic cardiomyopathy
IRB	Institutional Review Board
NYHA	New York Heart Association

cohort compared with a White cohort and to examine associations between structural HCM phenotype, comorbidities, and outcomes between groups.

METHODS

This study was a subgroup analysis of an ongoing prospective longitudinal data set study from a specialized HCM center located in a large, urban, academic institution in the northeastern United States. The data that support the findings of this study are available from the corresponding author upon reasonable request. The primary study has institutional review board approval with informed consent given by all participants. The inclusion criteria for this analysis was adults (≥ 18 years), with a confirmed clinical diagnosis of HCM: unexplained left ventricular hypertrophy (LVH) of ≥ 15 mm,⁵ that self-identify as either Black/African American or

White.¹¹ Individuals were excluded if they had had prior invasive interventions for HCM that would have altered their native cardiac structure, such as cardiac surgery, and alcohol septal ablation, and there was no imaging available before their intervention. The analysis also included medical records review to supplement missing data from the original data set.

Data Collection and Study Variables

We examined data for 502 consecutively enrolled subjects, who comprised referred patients to the specialty HCM center between July 2015 and November 2019. We excluded 68 individuals (67 White, 1 Black) with prior obstruction-relieving interventions, such as myectomy and alcohol septal ablation, who had no available imaging of their native anatomy pre-intervention for review. We analyzed data for 434 individuals, with 57 (13.1%) identifying as Black/American and 377 (86.9%) as White/Caucasian.

Demographic variables, including sex, age, and race/ethnicity and age at initial HCM center evaluation were examined. Age was used to identify trends in age at diagnosis between the population of interest and the comparison group. Data on New York Heart Association (NYHA) class at the time of presentation for HCM care was also captured from the medical record. Descriptive data on cardiac structure were collected from imaging studies, including echocardiograms and cardiac magnetic resonance (CMR). Echocardiographic data were examined to describe LVH magnitude and distribution, ejection fraction, presence of obstruction and special anatomic features, such as apical aneurysms, anomalous papillary muscles, and complete systolic emptying. Individuals were considered obstructed if they had mid-cavitary or left ventricular outflow tract gradients ≥ 30 mm Hg, whether at rest or with provocation (Valsalva, standing, or exercise). LVH distribution was categorized as sub-basal, basal, and diffuse. Sub-basal LVH included thickening in the apical, apical-mid, and mid-ventricular segments. Basal LVH constituted asymmetric septal hypertrophy of the basal septum segments which represent the most common, “typical” presentation of HCM. Diffuse LVH included thickening throughout all ventricular segments. CMR data were primarily examined for identifying the presence of fibrosis and quantifying fibrosis burden. Fibrosis burden was quantified using the Chan et al recommendations.¹² In addition, we also captured the ejection fraction and maximal LV wall thickness of those individuals who had undergone cardiac CMR testing. We also examined HCM related medications.

Genetic testing data were also captured, from data set entries and electronic chart review to identify patterns of genetic testing usage, as well as identify

genetic testing yield; the distribution of pathogenic variants, likely-pathogenic variants, variants of unknown significance, or negative results. This sample comprised of patients undergoing routine HCM clinical care; thus, genetic testing was performed via CLIA-certified commercial laboratories using standard American College of Medical Genetics variant classification criteria.¹³ Likely-pathogenic variants and variants of unknown significance were further reviewed in ClinVar,¹⁴ the National Institutes of Health-supported, publicly accessible database of reported variants related to disease.

Outcome data included sudden HCM-related death or appropriate defibrillator shock or anti-tachycardia pacing, all-cause mortality, and interventions. For this analysis, major HCM interventions included obstruction relieving interventions (cardiac surgery—myectomy±mitral valve repair/replacement, alcohol septal ablation, and mitral clip procedures), and implantable cardioverter defibrillator (ICD) placement for primary prevention. Traditional and enhanced sudden death risk factors¹⁵ were described in those individuals with ICDs, including massive hypertrophy (LVH ≥ 30 mm), unexplained syncope, family history of sudden death in a first degree relative ≤ 50 years old, ventricular tachycardia on ambulatory monitoring, significant fibrosis ≥ 15 mm, LV ejection fraction less than 50% and apical aneurysm.⁵

Comorbid conditions included hypertension, obesity class, and BMI, sleep apnea, atrial fibrillation, history of coronary artery disease, history of stroke/transient ischemic attack, and diabetes mellitus. These comorbid conditions were chosen as they are common within the general population and have implications for patients with HCM.^{16–24} Hypertension disproportionately and more severely affects Black individuals,²² and contributes to the development of LVH.^{16,22} Obesity is also more prevalent in the Black population overall¹⁷ and can contribute independently to cardiac remodeling and development of LVH.²⁴

Statistical Analysis

Stata 16 software²⁵ was used for statistical analysis. Descriptive statistics were used to evaluate descriptive data. Means and SDs were calculated for normally distributed continuous variables, and medians and interquartile ranges were used for non-normally distributed continuous variables. Frequency distributions were used for categorical variables. Associations were established with unpaired t-tests for normally distributed continuous variables, Mann Whitney *U* tests for non-normally distributed variables. Chi-square tests were used for categorical variables, with Fisher exact tests used as needed

for expected frequencies < 5 . We used ordinal and binomial logistic regression to examine relationships between race, HCM phenotype, and outcomes while controlling for comorbidities. For both aims significance was met if *P* value was ≤ 0.05 and CIs were 95% where appropriate.

Missing data points were excluded from analysis. Some parameters naturally had missing data as not every individual in the sample had undergone every testing modality. If the total number of analyzed individuals in certain parameters deviated from the original sample, this was noted.

RESULTS

Demographics and Baseline Structural HCM Characteristics

A total of 434 individuals met the inclusion criteria with *n* (%); 57 (13.1%) were Black and 180 (41.5%) were women. Follow-up 2.2 (1.2), mean (SD) years, Black participants were significantly younger than White participants, 54.6 (13.4) versus 62.5 (14.8) years, $P=0.001$. Men were overrepresented in both groups. Black participants were less likely to be categorized as functionally unlimited, or NYHA I, 13 (22.8%) versus 129 (35.5%), $P=0.030$. However, both groups had similar rates of advanced functional limitations, NYHA III–IV.

Echocardiography Data

Maximal LV wall thickness and ejection fraction were similar between the groups. However, there were significant differences in LVH distribution between the Black and White cohort. Sub-basal and diffuse hypertrophy were significantly more prevalent in the Black cohort: sub-basal—22 (38.6%) versus 56 (14.9%), $P<0.001$; diffuse—6 (10.5%) versus 15 (4%), $P=0.017$. Basal hypertrophy was significantly less prevalent in Black patients compared with White patients, 29 (50.9%) versus 306 (81.2%), $P<0.001$. Both groups had similar proportions of non-obstructed individuals and individuals with provokable obstruction (Valsalva, standing, or exercise). However, Black patients had significantly more mid-ventricular obstruction, 7 (12.3%) versus 21 (5.5%), $P=0.025$ and less left ventricular outflow tract obstruction at rest, 17 (29.8%) versus 171 (45.1%), $P=0.015$. Black and White patients had similar prevalence of special anatomic features, such as anomalous papillary muscles and complete systolic emptying. There was a trend towards higher presence of apical aneurysms in Black patients, 17 (12.3%) versus 18 (4.8%), $P=0.055$, though this did not meet statistical significance (Figure; Table 1).

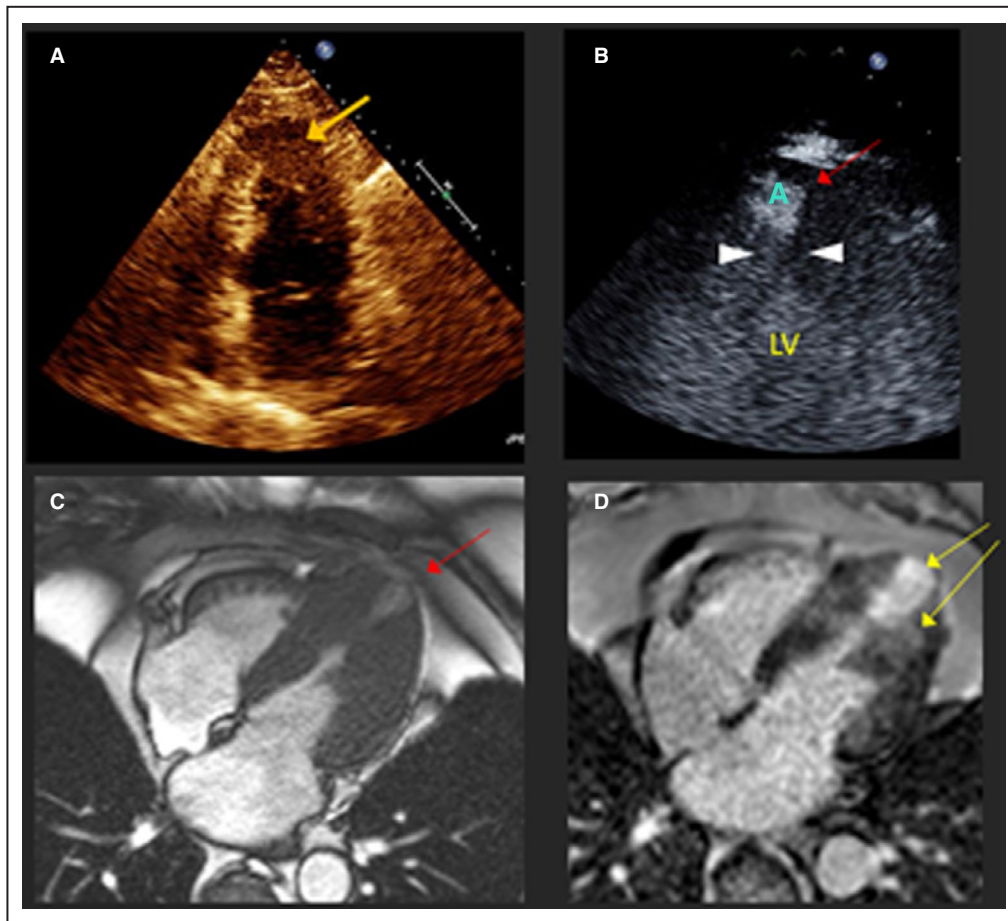


Figure 1. Apical akinetetic aneurysm in a 65-year-old man with hypertrophic cardiomyopathy. **A**, Apical 4-chamber echocardiogram shows apical thickening (orange arrow) but aneurysm is not visualized due to foreshortening. Intravenous contrast is recommended for all patients with apical hypertrophic cardiomyopathy to detect aneurysm. **B**, Same patient after intravenous echo contrast. Red arrow, A=apical aneurysm; left ventricular cavity; white arrowheads point to mid-left ventricular obstruction attributable to systolic complete emptying at that level. **C**, Same patient, 4-chamber view cardiac magnetic resonance showing mid-left ventricular hypertrophy, obstruction, and thin-walled apical aneurysm. **D**, Delayed late gadolinium enhancement consistent with apical and mid-left ventricular fibrosis, yellow arrows. CMR indicates cardiac magnetic resonance; and LV, left ventricular.

CMR Data

More Black than White patients had CMRs, 45 (79%) versus 215 (57.6%), $P=0.009$. In this subgroup, there were no differences in ejection fraction, though maximal LV wall thickness differed, with Black patients having a greater LV maximal thickness, mean (SD), 22.2 mm (6.4) versus 18.9 mm (4.7), $P=0.017$. The presence of cardiac fibrosis overall was noted in similar proportions between both groups. However, significantly more Black patients with HCM had fibrosis comprising $\geq 15\%$ of the myocardium than White patients with HCM, 10 (22.2%) versus 19 (8.8%), $P=0.009$ (Table 1; Figure).

Medical Therapy

Beta blockers were the most common HCM-related medications in both groups. However, the Black cohort was much more likely to be treated with

non-dihydropyridine calcium channel blockers alone, or in combination with beta blockers, 9 (15.8%) versus 17 (4.5%), $P=0.003$, and 15 (26.3%) versus 34 (9%), $P<0.001$, respectively. However, the Black HCM cohort was less likely to be treated with disopyramide \pm beta blockers \pm calcium channel blockers, than the White HCM cohort, 5 (8.8%) versus 77 (20.4%), $P=0.036$ (Table 2). This difference is consistent with the finding of lower prevalence of resting left ventricular outflow tract obstruction in the Black HCM cohort. The use of anticoagulants between groups was largely consistent with the prevalence of atrial fibrillation in the sample.

Comorbidities

Both groups in this sample had a similar number of attendant comorbidities. There was a trend towards less atrial fibrillation and hyperlipidemia in Black patients

Table 1. Demographics and Structural HCM Characteristics

Sample n=434; Black, 57 [13.1], White, 377 [86.9] Patients	Black, n [%]	White, n [%]	P Value
Age (y), mean (SD)	54.6 [13.4]	62.5 [14.8]	0.000
Sex (men)	30 [52.6]	224 [59%]	0.375
NYHA Class I	13 [28.8]	129 [35.5]	0.030
NYHA Class II	22 [38.6]	124 [34.2]	0.258
NYHA Class III and IV	22 [38.6]	110 [30.3]	0.105
Max echocardiography LVH, mm, mean (SD)	19.1 [5.9]	18.4 [4.9]	0.838
Ejection fraction (echo), mean (SD)	71.1 [6.1]	69.6 [6.9]	0.866
LVH distribution (echo data)			
Basal LVH	29 [50.9]	306 [81.2]	0.000
Sub-basal LVH	22 [38.6]	56 [14.9]	0.000
Diffuse LVH	6 [10.5]	15 [4.0]	0.017
Special anatomic features [echo data]			
Complete systolic emptying	9 [15.8]	30 [7.9]	0.169
Apical aneurysm	7 [12.3]	18 [4.75]	0.055
Anomalous papillary muscle	10 [17.5]	59 [15.6]	0.916
Obstruction (echo data)			
No obstruction	20 [35.1]	116 [30.6]	0.247
LVOT obstruction at rest (≥30 mm Hg)	17 [29.8]	171 [45.1]	0.015
Provocable LVOT obstruction (Valsalva, standing, exercise)	13 [22.8]	71 [18.7]	0.232
Mid-LV obstruction	7 [12.3]	21 [5.5]	0.025
Cardiac MRI data			
CMR (had)	45 [79.0]	215 [57.6]	0.009
Max CMR LVH, mm, mean (SD)	22.2 [6.4]	18.9 [4.7]	0.017
Fibrosis (yes)	36 [80.0]	142 [67.3]	0.121
Fibrosis ≥15% (yes)	10 [22.2]	19 [8.8]	0.009

CMR indicates cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; mid-LV, mid-ventricular; MRI, magnetic resonance imaging; and NYHA, New York Heart Association.

but this did not reach statistical significance. Presence of a hypertension diagnosis was similar between groups. Body mass index (BMI) was available in 55 individuals of the Black HCM cohort and 372 of the White HCM cohort. Both groups had similar BMI, 30.4 (5.5) versus 28.8 (5.4), $P=0.979$. Overweight and obesity were highly prevalent in both groups, 47 (85.5%) of Black patients and 293 (78.8%) of White patients had a BMI of ≥ 25 , $P=0.125$. However, Black patients had a

significantly higher proportion of Class II obesity (BMI, 35.0–39.9) than White patients, 12 (21.8%) versus 30 (8.1%), $P<0.001$ (Table 3).

Outcomes and Interventions

In the follow-up period (mean, 2.2 [1.2] years), there were no deaths among Black patients; 4 deaths (1 sudden death, 2 cardiac-related but not sudden death, and 1 non-cardiac) occurred in the White HCM cohort. These events occurred in older White patients (>age 70 years). Black and White patients had similar rates of ICD insertion for primary prevention, 13 (22.8%) versus 76 (20.2%), $P=0.644$. Of the individuals in both cohorts who had implanted ICDs, Black patients had a significantly higher rate of appropriate ICD interventions (anti-tachycardia pacing or shock) than White patients, 5 (38.5%) versus 5 (6.6%), $P<0.001$ (Table 4). Of the 5 individuals in the Black HCM cohort who had appropriate ICD interventions, 3 individuals had ventricular tachycardia storm with multiple ICD shocks, with 1 individual requiring extra corporeal membrane

Table 2. Distribution of Medical Therapy Between Groups

Medical Therapy	Black, n (%)	White, n (%)	P Value
BB alone	25 [43.6]	215 [57.0]	0.062
CCB alone*	9 [15.8]	17 [4.5]	0.003
BB+CCB	15 [26.3]	34 [9.0]	<0.001
Disopyramide±BB±CCB	5 [8.8]	77 [20.4]	0.036
None	3 [5.3]	34 [9.0]	0.344
Anticoagulants	6 [10.5]	92 [24.4]	0.128

BB indicates beta-blockers; and CCB, calcium-channel blockers.

*Fisher exact.

Table 3. Comorbid Conditions

	Black, n [%]	White, n [%]	P Value
No. of comorbidities, mean (SD)	1.8 [1.4]	1.9 [1.4]	0.310
Coronary artery disease	4 [7.0]	37 [9.9]	0.501
Stroke/transient ischemic attack	2 [3.5]	15 [4]	0.865
Sleep apnea	4 [7.0]	43 [11.5]	0.312
Hypertension	32 [56.1]	176 [47.6]	0.201
Atrial fibrillation	6 [10.5]	79 [21.1]	0.061
Hyperlipidemia	22 [38.6]	195 [52.1]	0.057
Diabetes mellitus	7 [12.3]	23 [6.2]	0.090
BMI, mean (SD)	30.4 [5.5]	28.8 [5.4]	0.979
Underweight (BMI, <19.9)	1 [1.8]	2 [0.5]	0.148
Normal weight (BMI, 20–24.9)	7 [12.7]	77 [20.7]	0.082
Overweight (BMI, 25–29.9)	23 [41.82]	150 [40.3]	0.416
Class I obesity (BMI, 30–34.9)	10 [18.2]	91 [24.5]	0.149
Class II obesity (BMI, 30–39.9)	12 [21.8]	30 [8.1]	0.001
Class III obesity (BMI, 40+)	2 [3.64]	22 [5.91]	0.248

BMI indicates body mass index.

oxygenation hemodynamic support and multiple anti-arrhythmic agents before ventricular tachycardia was suppressed. More detailed HCM characteristics of individuals with appropriate ICD interventions are shown in Table 5.

Table 4. Outcomes and Interventions

Follow-Up Period, 2.2 [1.2] y, Mean (SD)	Black, n [%]	White, n [%]	P Value
Outcomes			
Appropriate ICD shocks/ATP	5 [38.5]	5 [6.8]	0.001
Sudden death from HCM	0 [0]	1 [0.3]	
Cardiac death	0 [0]	2 [0.5]	
Non-cardiac death	0 [0]	1 [0.3]	
Interventions			
ICD (primary prevention)	13 [22.8]	76 [20.2]	0.644
Obstruction relieving interventions	15 [26.3]	108 [28.7]	0.716
Type of obstruction-relieving interventions			
Myectomy	15 [100] [†]	101 [93.5] [†]	0.940
Alcohol septal ablation	0 [0]	4 [3.7] [†]	0.568
Mitral clip	0 [0]	3 [2.8] [†]	0.655

ATP indicates anti-tachycardia pacing; HCM, hypertrophic cardiomyopathy; and ICD, implantable cardioverter defibrillator.

[†]Percentage calculations are based on n of individuals undergoing obstruction relieving interventions, n=15 Black individuals, n=108 White individuals.

All patients with ICDs had them implanted for primary prevention of sudden death and had at least 1 of the sudden death predictors as outlined by the most recent American Heart Association/American College of Cardiology HCM guidelines.⁵ Specific sudden death risk factor data were available for 72 of the 76 White patients with ICDs and for all 13 Black individuals with ICDs. A higher proportion of the Black cohort had massive hypertrophy and ≥2 sudden death risk factors than the White cohort, 7(46.7%) versus 5(6.9%), *P*<0.001, and 10 (66.7%) versus 17 (23.6%), *P*=0.001. Other risk factors were not statistically significantly different in this

Table 5. Characteristics of Subgroup With Appropriate ICD Interventions

	Black, n=5	White, n=5
Age, median [IQR]	45 [44–64]	48 [48–58]
Sex (men)	2 [40.0]	3 [60.0]
Massive LVH ≥30 mm	2 [40.0]	1 [20.0]
Syncope	0 [0.0]	1 [20.0]
SCD in family	4 [80.0]	0 [0.0]
VT on ambulatory monitoring	2 [40.0]	2 [40.0]
Apical aneurysm	1 [20.0]	1 [20.0]
HCM with LV systolic dysfunction EF<50%	0 [0.0]	0 [0.0]
Fibrosis ≥15%	1 [20.0]	0 [0.0]
Secondary prevention	0 [0.0]	1 [20.0]
Sudden death risk factors ≥2	2 [40.0]	1 [20.0]
LVH distribution		
Sub-basal LVH	0 [0.0]	1 [20.0]
Basal LVH	2 [40.0]	3 [60.0]
Diffuse LVH	3 [60.0]	1 [20.0]
Obstruction		
At rest (LVOT gradient ≥30 mm Hg)	0 [0.0]	3 [60.0]
With provocation	1 [20.0]	0 [0.0]
Mid-LV obstruction	1 [20.0]	1 [20.0]
No obstruction	3 [60.0]	1 [20.0]
Genetic profile and corresponding genes		
Pathogenic/likely-pathogenic variant	3 [60.0] [MYH7 and MYBPC3 x2] [*]	1 [20.0] [MYH7]
Variant of unknown significance	3 [60.0] [TNNI3, MYL3, AGL, SOS2] [*]	1 [20.0] [MYBPC3]
No variant found	0 [0.0]	1 [20.0]
Did not have genetic testing	1 [20.0]	2 [40.0]

EF indicates ejection fraction; AGL, amylo-alpha-1,6-glucosidase, 4-alpha-glucanotransferase; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; IQR, interquartile ranges; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MYH7, myosin heavy chain 7; MYBPC3, myosin binding protein C3; MYL3, myosin light chain 3; SCD, sudden cardiac death; SOS2, SOS ras/rho guanine nucleotide exchange factor 2; TNNI3, troponin I3, cardiac type; and VT, ventricular tachycardia.

^{*}Two individuals had both pathogenic and variants of unknown significance.

subgroup analysis. Only 40 individuals of the White cohort had CMRs before ICD insertion, and 12 of 13 individuals of the Black ICD cohort. Sudden death risk factors for both groups are shown in Table 6. We evaluated additional clinical factors, beyond the guideline recognized factors, that may be associated with ICD implantation, such as LVH distribution and type of obstruction. However, none were significantly associated with ICD insertion. In Chi-square analysis we did not find significant associations with phenotype, including LVH distribution, presence and type of obstruction, or fibrosis presence or burden, comorbidities, race, or sex.

Black and White patients had similar proportions of obstruction-relieving interventions. All Black patients in this study had myectomies as a method of obstruction-relieving intervention and so did 93.5% of White patients. Five white patients underwent alcohol septal ablation or mitral clip procedure (Table 4).

Structural HCM Characteristics and NYHA Class

There was no statistically significant association between presence of fibrosis or significant fibrosis ($\geq 15\%$) and LVH distribution in this sample. Further, there were no significant associations between fibrosis and type of obstruction. NYHA class was variable among those with significant fibrosis, without a clear pattern. Of the 29 individuals with fibrosis $\geq 15\%$, 11 (37.9%) were NYHA Class I, 8 (27.6%) were NYHA Class II, and 10 (34.5%) had NYHA Class III functional limitations. None had NYHA Class IV limitations. NYHA class was also variable among those

with sub-basal and diffuse hypertrophy. NYHA data were available in 74 of the 78 individuals with sub-basal hypertrophy, 25 (33.8%) were NYHA class I, 22 (29.7%) NYHA Class II, 23 (31.1%) NYHA Class III, 4 (5.4%) NYHA Class IV. Among the 21 individuals with diffuse hypertrophy, 5 (23.8%) were NYHA Class I, 11 (52.4%) were NYHA Class II, and 5 (23.8%) were NYHA Class III. No individuals with diffuse hypertrophy had NYHA Class IV functional limitations. Neither fibrosis $\geq 15\%$ nor LVH distribution had significant association with NYHA class.

Genetic Profile

Genetic testing data were available in 51 individuals of the Black HCM cohort and 376 individuals of the White HCM cohort. Less than half of each group had genetic testing, 23 (45.1%) Black patients versus 162 (43.1%) White patients, and there were no differences in genetic testing usage between groups. In absolute numbers, Black patients had more pathogenic, likely pathogenic, and variants of unknown significance than White patients, though this trend did not reach statistical significance (Table 7). In Black patients, pathogenic and likely pathogenic HCM variants were noted in the MYH7 and MBPC3 genes, whereas pathogenic and likely pathogenic HCM variants in White patients were noted in a wider variety of genes: ACTC1, GAA, MYH7, MBPC3, MYL3, TPM1, TNNI3, and TNNT2.

DISCUSSION

Black patients represented 13.1% of the sample studied which was below the average population statistics

Table 6. Sudden Death Risk Factors in Those With ICDs

ICD Insertion	Black, n [%]	White, n [%]	P Value
Individuals with ICD, n [%] of total cohort	13 [22.8]	76 [20.2]	
SCD factors documented, n [%] of cohort with ICD inserted	13 [100]	72 [94.7]	
Demographics and sudden death risk factors			
Age (y), median [IQR]*	57 [45–64]	60 [47–65.5]	0.685
Sex (men)	6 [46.2]	45 [62.5]	0.268
Massive thickness, LVH ≥ 30 mm	5 [38.5]	5 [6.9]	0.001
Syncope [‡]	1 [7.7]	10 [13.9]	0.468
SCD in family [‡]	5 [38.5]	21 [29.2]	0.357
VT on ambulatory monitoring	9 [69.2]	35 [48.6]	0.171
Apical aneurysm [‡]	3 [23.1]	9 [12.5]	0.267
HCM with LV systolic dysfunction EF $<50\%$ [‡]	0 [0]	3 [4.2]	0.604
Individuals with CMR before ICD insertion	12 [92.3]	40 [55.6]	0.012
Fibrosis $\geq 15\%$ [‡]	4 [33.3]	10 [25]	0.409
Secondary prevention	0 [0]	1 [1.4]	0.847
≥ 2 sudden death risk factors [‡]	8 [61.5]	17 [23.6]	0.010

CMR indicates cardiac magnetic resonance; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; IQR, interquartile ranges; LV, left ventricular; LVH, left ventricular hypertrophy; SCD, sudden cardiac death; and VT, ventricular tachycardia.

*Mann-Whitney *U* test.

[‡]Fisher exact test.

Table 7. Genetic Testing Usage and Results

	Black, n [%]	White, n [%]	P Value
Genetic testing (yes)	23 [45.1]	162 [43.1]	0.785
Variant of unknown significance	5 [21.7]	26 [16.1]	0.251
Negative	8 [34.8]	87 [53.7]	0.045
Positive and likely pathogenic variants	10 [43.5]	49 [30.3]	0.102

of the study region.²⁶ However, this is consistent with the existing literature, where Black patients in the HCM study samples are also underrepresented.^{6,8–10} Black participants are underrepresented in clinical research overall despite efforts to increase participation.^{27,28} Women were also underrepresented in both study groups, which is also consistent with historical trends.²⁹ The reasons for this underrepresentation in the setting of HCM research have not been fully explored. However, most literature on HCM originates from specialty HCM centers and individuals must often navigate a complex and challenging healthcare system before they are seen in experienced HCM clinics.^{5,30} Research exploring the social determinants of HCM health may provide insights into improving representation of Black individuals in the clinical and research setting.

Structural HCM Characteristics and Genetic Profiles

Black patients were more likely to have apical hypertrophy than their White counterparts, which is consistent with the existing literature.^{6,8} However, Black patients were also more likely to have apical-mid and mid-ventricular LVH, as well as diffuse hypertrophy, which has previously not been reported in this population. As such, Black patients may be less likely to present with the “classic” HCM phenotype, which may contribute to delays in diagnosis and treatment. Further, while the existing literature shows that Black patients are less likely to be obstructed than White patients, we did not observe that in our sample. We found that Black individuals had significantly more mid-ventricular obstruction, which is also a novel finding. The discrepancy between our findings and the existing literature may be because mid-ventricular obstruction has been under-evaluated and under-recognized in existing research—echocardiograms often require the use of contrast which may not be a common practice in all echocardiography laboratories; thus, individuals with mid-ventricular obstruction may be categorized as having no obstruction.³¹ Our findings underscore the

importance of differentiating and appropriately diagnosing mid-ventricular obstruction given its association with poor outcomes.³²

More Black patients than White patients had CMR. Since baseline sudden death risk from HCM declines with age (especially after 60 years),^{33,34} a possible explanation for this difference in usage may be related to the age difference between groups, as Black patients were significantly younger. Thus, it is possible that they were undergoing a more comprehensive sudden death risk evaluation. In this regard, Black patients were more likely to have significant fibrosis ($\geq 15\%$), shown to be a risk for arrhythmia, and sudden death events.^{12,35}

Less than half of the study sample underwent genetic testing. This finding is consistent with the existing literature on HCM genetic testing usage in Black patients, which ranges from 38.7% to 50.4%,^{6,8} though it is lower than expected for HCM genetic testing usage in White patients, which ranges between 50.4% to 62.1% in White patients.^{8,10} Admittedly, the literature examining HCM genetic testing usage rates between Black and White HCM patients is itself significantly limited in number and may be specific to the study sites. It is possible that the more equitable use of genetic testing between groups in this sample may be because of the lower rate of HCM genetic testing usage in White patients rather than an increase in genetic testing usage in Black patients. The drivers in patient decision making for HCM genetic testing usage are not well understood and this lack of data may limit success in any future interventions aimed at improving the utilization of HCM genetic testing. Research examining the factors affecting decision making in genetic testing usage among both Black and White patients with HCM is warranted in general. However, this research is especially important for Black populations with HCM to reduce disparities beyond genetic testing usage alone.

Although Black patients had higher rates of pathogenic, likely pathogenic, and variants of unknown significance these did not meet statistical significance. It is possible that referral patterns may have affected the higher rates of these results among Black patients with HCM in this sample. It is important that genetic testing results for Black patients with HCM be closely examined. Genomic reference databases are not diverse, thus limiting precise variant interpretation in minority populations.^{36,37} Further, there is precedent for reclassification of pathogenic HCM variants in a sample of Black patients with HCM, that were subsequently deemed benign.⁷ In addition to the individuals with clinical HCM, genetic misclassification can affect family screening and impact the trajectory of family members that may be either cleared from screening or identified as having a high risk of developing HCM attributable to cascade screening based on inaccurate data. Improving genetic testing usage among Black

patients with HCM will also benefit genomic reference databases by increasing representation of minority populations.

Outcomes and Sudden Death Risk Factors

Both groups in the study cohort had low mortality which is consistent with the existing literature. However, Black patients had a significantly higher rate of appropriate ICD ATP therapy or discharges. This is despite Black and White patients having similar rates of ICD insertion for primary prevention. We examined sudden risk factors for ICD insertion in both groups and Black patients were more likely to have massive LVH and have ≥ 2 sudden death risk factors than White patients. The proportion of Black and White individuals with ICDs who also had significant fibrosis did not differ, yet this may be because of the lower number of White patients who had undergone CMR before ICD insertion, limiting the statistical results. ICD interventions were not significantly associated with structural HCM characteristics, including fibrosis, or demographics. This may be because of the overall low number of events in the study groups. Racial disparities in the use of ICD implantation have narrowed overall³⁸ though they still exist. The reasons for this disparity are not well understood and require further evaluation, including decisional factors.

Efforts to refine models for sudden cardiac death risk from HCM and identify the most pertinent risk factors are ongoing.^{15,39} One of the largest studies evaluating sudden death factors in HCM is the HCMR (Novel Markers of Prognosis in Hypertrophic Cardiomyopathy) registry (NCT01915615), a multi-center longitudinal observational study with 2755 patients with HCM.⁴⁰ Registry participants comprised a low-risk cohort.⁴¹ Most participants did not have obstruction and few had either significant fibrosis ($\geq 15\%$), 2%, apical aneurysms, 3%, or massive hypertrophy, 2.3%.⁴⁰ In contrast, both cohorts for the present study had a higher prevalence of these HCM characteristics. The sample in the HCMR registry was less diverse, with 7.5% Black patients that as we have shown have a higher incidence of ICD discharges. Further, clinical, echocardiography, and CMR data were only dichotomized between a White and minority group, with the minority group encompassing Black, Asian, Hispanic, and other individuals, in aggregate. Despite a much lower overall sample size, our study suggests there may be significant differences in sudden death risk factors between Black and White cohorts with HCM.

Medical Therapy and Interventions

The HCM-specific medical therapy for both groups was consistent with current guideline recommendations.⁵ Moreover, it was consistent with phenotypic

presentation, specifically in the use of disopyramide, which was more prevalent in the White cohort, which was also more likely to have left ventricular outflow tract obstruction at rest. Calcium channel blocker therapy alone, or in combination with a beta blocker, was more common in the Black HCM cohort which was more likely to have diffuse and sub-basal hypertrophy and mid-LV obstruction. There is a need for contemporary examination of the use of verapamil in individuals with this less common HCM phenotype.

Comorbidities

Both groups had a similar number of comorbid conditions though Black patients were significantly younger. Further, there was no difference in prevalence of comorbidities between the 2 groups, except Class II obesity (BMI, 35–39.9) which was more prevalent in the Black cohort. Notably, despite the high prevalence of risk factors for coronary artery disease and stroke/transient ischemic attack, specifically obesity and hypertension in the general population, these conditions were relatively uncommon in both groups. Further, comorbidities were not associated with mortality outcomes, though it is likely that the low numbers of deaths and appropriate ICD interventions in the sample overall, limited statistical power for such analysis. More research is needed to explore comorbid conditions in Black patients with HCM, including the role of age and the degree of successful management of the attendant comorbidities.

Limitations

There were several limitations for this study. First, this was an analysis of an existing prospective database. Although there were missing datapoints in some of the variables of interest, this was minimized through chart reviews. The subjects enrolled in the study were individuals who were getting care at a specialty HCM center. The potential of referral bias limits the generalizability of the results to a wider HCM population who may not receive care at a specialty center. The subjects enrolled in the study had already navigated the healthcare system to obtain specialty care suggesting that patient characteristics may differ from a general patient population. Further, race was self-identified in this sample. Thus, the inherent bias present in any self-identification characterization was also present in our study. Further, we examined the use of HCM-related medical therapy in the groups after they had established care in the HCM specialty center. It is possible that they had been on other therapy before presentation to specialty care. Additionally, we recognize that medical therapy is not static and may change depending on disease progression.

CONCLUSIONS

This study provides much needed data about the disease expression, course, and outcomes of Black patients with HCM, specifically addressing less common cardiac HCM characteristics that have not been reported in this population previously. The underrepresentation of Black participants in our study, which is consistent with the extant research, underscores the need for continued research of HCM in this population. Further, there is a need to explore HCM in Black patients in care settings beyond specialty HCM centers that can contribute to a wider scope of understanding of HCM course and outcomes in this population. To address health disparities experienced by Black patients with HCM our data suggests the need for tailored approaches for the diagnosis of this condition, including precise delineation of cardiac anatomy.

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