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Association of Race With Disease Expression and Clinical Outcomes Among Patients With Hypertrophic Cardiomyopathy

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IMPORTANCE Racial differences are recognized in multiple cardiovascular parameters, including left ventricular hypertrophy and heart failure, which are 2 major manifestations of hypertrophic cardiomyopathy. The association of race with disease expression and outcomes among patients with hypertrophic cardiomyopathy is not well characterized.

OBJECTIVE To assess the association between race, disease expression, care provision, and clinical outcomes among patients with hypertrophic cardiomyopathy.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included data on black and white patients with hypertrophic cardiomyopathy from the US-based sites of the Sarcomeric Human Cardiomyopathy Registry from 1989 through 2018.

EXPOSURES Self-identified race.

MAIN OUTCOMES AND MEASURES Baseline characteristics; genetic architecture; adverse outcomes, including cardiac arrest, cardiac transplantation or left ventricular assist device implantation, implantable cardioverter-defibrillator therapy, all-cause mortality, atrial fibrillation, stroke, and New York Heart Association (NYHA) functional class III or IV heart failure; and septal reduction therapies. The overall composite outcome consists of the first occurrence of any component of the ventricular arrhythmic composite end point, cardiac transplantation, left ventricular assist device implantation, NYHA class III or IV heart failure, atrial fibrillation, stroke, or all-cause mortality.

RESULTS Of 2467 patients with hypertrophic cardiomyopathy at the time of analysis, 205 (8.3%) were black (130 male [63.4%]; mean [SD] age, 40.0 [18.6] years) and 2262 (91.7%) were white (1351 male [59.7%]; mean [SD] age, 45.5 [20.5] years). Compared with white patients, black patients were younger at the time of diagnosis (mean [SD], 36.5 [18.2] vs 41.9 [20.2] years; $P < .001$), had higher prevalence of NYHA class III or IV heart failure at presentation (36 of 205 [22.6%] vs 174 of 2262 [15.8%]; $P = .001$), had lower rates of genetic testing (111 [54.1%] vs 1404 [62.1%]; $P = .03$), and were less likely to have sarcomeric mutations identified by genetic testing (29 [26.1%] vs 569 [40.5%]; $P = .006$). Implantation of implantable cardioverter-defibrillators did not vary by race; however, invasive septal reduction was less common among black patients (30 [14.6%] vs 521 [23.0%]; $P = .007$). Black patients had less incident atrial fibrillation (35 [17.1%] vs 608 [26.9%]; $P < .001$). Black race was associated with increased development of NYHA class III or IV heart failure (hazard ratio, 1.45; 95% CI, 1.08-1.94) which persisted on multivariable Cox proportional hazards regression (hazard ratio, 1.97; 95% CI, 1.34-2.88). There were no differences in the associations of race with stroke, ventricular arrhythmias, all-cause mortality, or the overall composite outcome.

CONCLUSIONS AND RELEVANCE The findings suggest that black patients with hypertrophic cardiomyopathy are diagnosed at a younger age, are less likely to carry a sarcomere mutation, have a higher burden of functionally limited heart failure, and experience inequities in care with lower use of invasive septal reduction therapy and genetic testing compared with white patients. Further study is needed to assess whether higher rates of heart failure may be associated with underlying ancestry-based disease pathways, clinical management, or structural inequities.

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Supplemental content

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Hypertrophic cardiomyopathy (HCM) is the prototypical genetic cardiomyopathy, caused by dominantly inherited mutations in genes encoding sarcomeric proteins that display age-dependent penetrance and variable clinical expressivity. Although prevalence of sarcomeric mutations is not a priori expected to be different among black individuals with HCM, ancestry-based differences in sarcomeric variants and cardiac remodeling may be associated with the development of HCM and its natural history.[1,2] However, clinical characteristics and outcomes among black patients with HCM have been inadequately studied to date.[3,4]

Although ancestry-based differences in cardiac remodeling may have clinical importance, racial disparities in access to care are potentially as or more consequential. Notable disparities persist in cardiology, and cardiovascular mortality remains highest among black patients,[5] who have a disproportionate burden of heart failure.[6-9] Racial differences in heart failure outcomes in the context of disparate quality of care have been widely documented.[10-16] Using a large multicenter registry, we sought to better understand the association between race and clinical features, natural history, and risk of adverse outcomes among patients with HCM in the United States.

Key Points

Question Is race associated with differential disease expression, inequitable care provision, or disparate clinical outcomes among patients with hypertrophic cardiomyopathy?

Findings In this cohort study of 2467 patients with cardiomyopathy, compared with white patients, black patients with hypertrophic cardiomyopathy were diagnosed at a younger age, were less likely to have sarcomere mutations, and had worse symptoms. Inequities in health care access and delivery were associated with race, with lower rates of genetic testing and invasive septal reduction therapy among black patients with hypertrophic cardiomyopathy.

Meaning The findings suggest that racial differences in disease expression and adverse clinical outcomes exist between black and white patients with hypertrophic cardiomyopathy and that these differences may be associated with inequities in clinical care provision.

Methods

Study Population and Participating Centers

The cohort study included patients with HCM evaluated between 1989 and 2018 at the 7 US centers participating in the Sarcomeric Human Cardiomyopathy Registry (SHaRe).[17] Only US sites were included given the well-documented racial inequities in health care outcomes in the United States.[18] Patients with a site-designated diagnosis of HCM (unexplained left ventricular hypertrophy with maximal left ventricular wall thickness more than 15 mm [13 mm if a family history is noted] or *z* score of at least 3 in pediatric patients, integrating familial or sporadic occurrence and genotype) and adequate clinical information were included. Because of small numbers of patients with other races identified, only patients who self-identified as black or white race were included. Methods regarding data collection in SHaRe have been previously described.[17] Ethical approval was obtained from the Partners HealthCare institutional review board, Boston, Massachusetts, which also waived patient consent because data were deidentified.

Outcome Definitions

Composite outcomes were selected based on clinical relevance and to maximize statistical power. Outcomes were documented at each site by the primary cardiologist during clinical encounters and captured directly into the database. Composite outcomes were defined as follows. Ventricular arrhythmic composite was defined as first occurrence of sudden cardiac death, resuscitated cardiac arrest, or appropriate implantable cardioverter-defibrillator (ICD) therapy or firing (nonantitachycardia pacing). Overall composite was defined as the first occurrence of any component of the ventricular arrhythmic composite end point, cardiac transplant or left ventricular assist device implantation, New York Heart Association (NYHA) class III or IV heart failure, atrial fibrillation, stroke, or all-cause mortality.

Statistical Analysis

Retrospective data were analyzed from the ongoing prospective registry. For descriptive statistics, variables are expressed as mean (SD), median (interquartile range), or counts and percentages as appropriate. For comparisons between groups, the χ^2 test was used for categorical variables and 2-tailed *t* test for continuous variables. Two-sided $P < .05$ was considered to be statistically significant.

Occurrence of incident events after HCM diagnosis was analyzed. Patients with missing data on the presence, absence, or timing of events were dropped from analyses of those outcomes but included in other outcome analyses for which data were available. Ages at first event were compared for patients stratified by race, using hazard ratios (HRs) based on Cox proportional hazards regression. Analyses were performed for selected outcomes restricted to patients who were black and white race with likely pathogenic or pathogenic sarcomeric mutations only.

Given differences in the rates of septal reduction therapies, atrial fibrillation, and baseline and development of NYHA class III or IV heart failure between racial groups, these outcomes were further investigated in a multivariable analysis.

Multivariable logistic regression was performed to investigate the lower rates of septal reduction therapy and atrial fibrillation among black patients on univariate analysis. For the outcome of septal reduction therapies, the severity of obstruction (defined as maximal left ventricular outflow tract gradient [mm Hg] either resting or provoked on echocardiography) was included as an independent covariate. Age and left atrial diameter by echocardiography were included as covariates for the outcome of atrial fibrillation.

The association between race and the development of NYHA class III or IV heart failure was investigated in a multivariable Cox proportional hazards regression model. Covariates were selected a priori based on previous association with

the outcome of interest or pathophysiologic plausibility and included race (black vs white), age at diagnosis, sarcomeric mutation (positive or variant of unknown significance vs absent), obstruction, hypertension (defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg), and body mass index (calculated as weight in kilograms divided by height in meters squared).

Results

Demographics and Clinical Characteristics

A total of 2467 patients met the inclusion criteria at the time of analysis, of whom 205 (8.3%) identified as black (130 male [63.4%]; mean [SD] age, 40.0 [18.6] years) and 2262 (91.7%) identified as white (1351 male [59.7%]; mean [SD] age, 45.5 [20.5] years). Baseline characteristics by race are summarized in **Table 1**. The mean (SD) age of black patients was 5 years younger than that of white patients at diagnosis (mean [SD], 36.5 [18.2] vs 41.9 [20.2] years; $P < .001$) (Table 1 and eFigure in the Supplement). Black patients had higher mean (SD) body mass index at baseline (30.2 [8.1] vs 29.0 [6.9]; $P = .003$), with higher rates of obesity as defined as body mass index of at least 30.0 (50.3% vs 39.5%; $P = .006$).

A background diagnosis of hypertension was more prevalent among black patients (75 [36.6%] vs 594 [26.3%]; $P = .002$), but baseline mean (SD) blood pressure was similar between the 2 groups (128 [17] mm Hg vs 124 [18] mm Hg; $P = .11$). Among those with hypertension, baseline systolic blood pressure (141.6 [19.2] vs 136.9 [18.0] mm Hg; $P = .05$) and maximum wall thickness (17.8 [4.5] vs 17.8 [4.7] mm; $P > .99$) did not differ significantly between black and white patients. Black patients had higher rates of NYHA functional class III or IV heart failure at presentation compared with white patients (36 [22.6%] vs 174 [15.8%]; $P < .001$). European Society of Cardiology sudden cardiac death risk score[19] was low (5-year risk of approximately 2%) and did not differ significantly between the 2 groups (median [IQR], 2.1 [1.5-3.6] vs 2.2 [1.6-3.3]; $P = .96$).

Genetic Characteristics

Most of both black and white patients (96.0%) were first seen after 2006, when genetic testing was clinically available. However, use of genetic testing was significantly lower among black patients compared with white patients (111 [54.1%] vs 1404 [62.1%]; $P = .03$). Of those who underwent genetic testing, black patients were less likely to have a pathogenic or likely pathogenic sarcomeric mutation (29 [26.1%] vs 569 [40.5%]; $P = .006$) and more likely to have a variant of uncertain significance (14 [12.6%] vs 128 [9.1%]; $P = .006$) compared with white patients. The relative frequency of disease gene did not significantly vary by race. For example, among those had pathogenic or likely pathogenic sarcomere mutation on genetic testing, *MYBPC3* mutations most common in black and white patients (22 [75.9%] and 321 [56.4%], respectively; $P = .10$). Similarly, black patients were less likely to have a family history of HCM (54 [26.3%] vs 901 [39.8%]; $P < .001$) and were more often probands (197 [96.6%] vs 2035 [90.4%]; $P = .005$). When restricted to patients who reported a family history of HCM, these findings persisted with lower rates of pathogenic or likely pathogenic sarcomeric mutations (12 [22.2%] vs 366 [40.6%]; $P = .03$) and higher rates of variant of uncertain significance (4 [7.4%] vs 46 [5.1%]; $P = .03$) among black patients.

Baseline Echocardiography

As shown in Table 1, left atrial diameter was significantly smaller among black patients (mean [SD], 42.7 [10.1] vs 44.6 [10.9]; $P = .04$). Left ventricular ejection fraction, maximal left ventricular wall thickness, presence of severe mitral regurgitation, and left ventricular outflow tract gradients were similar between the 2 groups.

Race, Clinical Management, and Adverse Events

We compared the natural history and treatment of patients with HCM at SHaRe sites by race. Median time of care (as defined as time between first and last encounters) was 6.8 years (IQR, 3.0-13.6 years) for black patients and 7.4 years for white patients (IQR, 3.5-15.3 years; $P = .10$).

Clinical Management and Procedures by Race

Invasive septal reduction therapies were performed less frequently in black patients (30 [14.6%] vs 521 [23.0%]; $P = .007$) (**Table 2**), with an unadjusted HR of 0.52 (95% CI, 0.42-0.96) for black patients to receive septal reduction therapy compared with white patients. Of patients who underwent invasive septal reduction therapies, the type of therapy differed between racial groups: black patients had higher rates of myectomy (28 [93.3%] vs 447 [85.8%]) and lower rates of alcohol septal ablation (2 [6.7%] vs 59 [11.3%]). Rates of implantation of ICDs did not vary by race (68 [33.2%] vs 724 [32.0%]; $P = .79$).

Unadjusted Analysis of Clinical Outcomes by Race

Rates of clinical outcomes by race are shown in Table 2, and unadjusted HRs for clinical outcomes by race are summarized in the **Figure**. Atrial fibrillation rates were lower among black patients (35; 17.1%) than among white patients (608 [26.9%]) ($P < .001$), and black race was not associated with increased rate of stroke (10 [4.9%] vs 80 [3.5%]; $P = .43$); 51 black patients (24.8%) and 440 white patients (19.5%) developed NYHA class III or IV heart failure during follow-up ($P = .050$). All-cause mortality was similar between the 2 groups (13 [6.3%] vs 119 [5.3%]; $P = .43$). There was no difference in rates of resuscitated cardiac arrest between the groups (11 [5.4%] vs 74 [3.3%]; $P = .17$). No black patients and 16 white patients (0.7%) experienced sudden cardiac death ($P = .45$).

Black race was not associated with an increased hazard of the ventricular arrhythmia outcome (HR, 0.95; 95% CI, 0.44-2.05; $P = .90$). End-stage remodeling, defined as left ventricular ejection fraction less than 50% (HR, 0.82; 95% CI, 0.44-1.51; $P = .53$) and transplant or left ventricular assist device (HR, 0.55; 95% CI, 0.13-2.26; $P = .40$), was similar between the 2 racial groups (Figure). Overall composite outcome was reached by 91 black patients (44.4%) and 1003 white patients (44.3%) ($P > .99$). Events were most frequently NYHA class III or IV heart failure (in 50 black patients [24.4%] vs 421 white patients

Table 1. Baseline Characteristics of Black and White Patients With Hypertrophic Cardiomyopathy

Characteristic[a]	Black Patients (n = 205)	White Patients (n = 2262)	*P* Value
Male, No. (%)	130 (63.4)	1351(59.7)	.34
Age, mean (SD), y	40.0 (18.6)	45.5 (20.5)	<.001
Age at diagnosis, mean (SD), y	36.5 (18.2)	41.9 (20.2)	<.001
Body mass index, mean (SD)[b]	30.2 (8.1)	29.0 (6.9)	.003
Proband, No. (%)	197 (96.5)	2035 (90.0)	.005
Family history of hypertrophic cardiomyopathy, No. (%)	54 (26.3)	901 (39.8)	<.001
Genetic characteristics			
Genetic testing performed, No. (%)	111 (54.1)	1404 (62.1)	.03
Sarcomere positive, No. (%)[c]	29 (26.1)	569 (40.5)	.006
Causal sarcomere gene, No. (%)[c]			.10
ACTC1	0	4 (0.7)	
MYBPC3	22 (75.9)	321 (56.4)	
MYH7	4 (13.8)	175 (30.8)	
MYL2	0	11 (1.9)	
MYL3	0	1 (0.2)	
TNNI3	1 (3.5)	13 (2.3)	
TNNT2	0	25 (4.4)	
TPM1	2 (6.9)	7 (1.2)	
Multiple[d]	0	12 (2.1)	
Clinical characteristics			
Hypertension, No. (%)	75 (36.6)	594 (26.3)	.002
Systolic blood pressure, mean (SD), mm Hg	128 (17)	124 (18)	.11
NYHA III or IV symptoms, No. (%)	36 (22.6)	174 (15.8)	<.001
ESC sudden cardiac death risk score, median (IQR)[e]	2.1 (1.5-3.6)	2.2 (1.6-3.3)	.96
Baseline echocardiographic findings			
Maximal left ventricular thickness, mean (SD), mm	17.6 (6.3)	17.0 (5.7)	.21
Maximum left ventricular thickness normalized to body surface area, mean (SD), mm	9.5 (3.8)	9.1 (3.7)	.30
Apical hypertrophy, No. (%)	14 (8.1)	96 (5.3)	.12
Left ventricular ejection fraction, mean (SD), %	67 (9)	66 (10)	.12
Maximum left ventricular outflow tract gradient, mean (SD), mm Hg	45 (43)	49 (46)	.46
Left ventricular outflow tract gradient >30 mm Hg, No. (%)	42 (42.4)	662 (48.0)	.33
Left atrial diameter, mean (SD), mm	42.7 (10.1)	44.6 (10.9)	.04
Left atrial diameter normalized to body surface area, mean (SD), mm	21.8 (6.2)	23.1 (6.5)	.04
Severe mitral regurgitation, No. (%)	2 (1.5)	39 (2.9)	.07

Abbreviations: ESC, European Society of Cardiology; NYHA, New York Heart Association; SHaRe, Sarcomeric Human Cardiomyopathy Registry.

[a] Percentage of patients with missing data on key variables are as follows. Body mass index: full cohort (7.8%), black patients (7.3%), and white patients (7.8%); proband: full cohort (0.53%), black patients (0.49%), and white patients (0.53%); NYHA class: full cohort (21.4%), black patients (22.4%), and white patients (21.3%); ESC risk score: full cohort (40.1%), black patients (34.6%), and white patients (40.6%); left ventricular ejection fraction: full cohort (15.7%), black patients (14.2%), and white patients (15.8%); left ventricular outflow tract gradient: full cohort (46.8%), black patients (57.6%), and white patients (54.6%); and left atrium diameter: full cohort (24.9%), black patients (24.4%), and white patients (25.0%).

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Denominator reflects those who underwent genetic testing. Sarcomere-positive patients with pathogenic or likely pathogenic mutations on any of the 8 sarcomere-encoding genes, which encode actin (*ACTC1* [OMIM 102540]), myosin binding protein C (*MYBPC3* [OMIM 600958]), myosin heavy chain (*MYH7* [OMIM 160760]), cardiac troponin T (*TNNT2* [OMIM 191045]), cardiac troponin I (*TNNI3* [OMIM 191044]), alpha tropomyosin (TPM1 [OMIM 191010]), and myosin essential and regulatory light chains (MLY2 [OMIM 160781], MYL3 [OMIM 160790]).

[d] Patients with multiple pathogenic or likely pathogenic sarcomeric mutations either in the same gene or across different genes.

[e] The ESC risk score calculation for implantable cardioverter-defibrillator placement incorporates age, left atrium size, left ventricular thickness, presence of left ventricular outflow tract obstruction, history of sudden cardiac disease or syncope, and presence of nonsustained ventricular tachycardia on Holter monitor.[19]

[18.6%]) and atrial fibrillation (in 35 black patients [17.1%] vs 608 white patients [26.9%]). Black patients did not have an increased hazard of the overall composite outcome or its individual components on univariable analysis.

Multivariable Analysis

Despite adjustment for severity of obstruction, black patients were less likely to undergo septal reduction therapies compared with white patients (odds ratio, 0.65; 95% CI, 0.42-

Table 2. Rates of Procedures and Clinical Outcomes Among Black and White Patients With Hypertrophic Cardiomyopathy

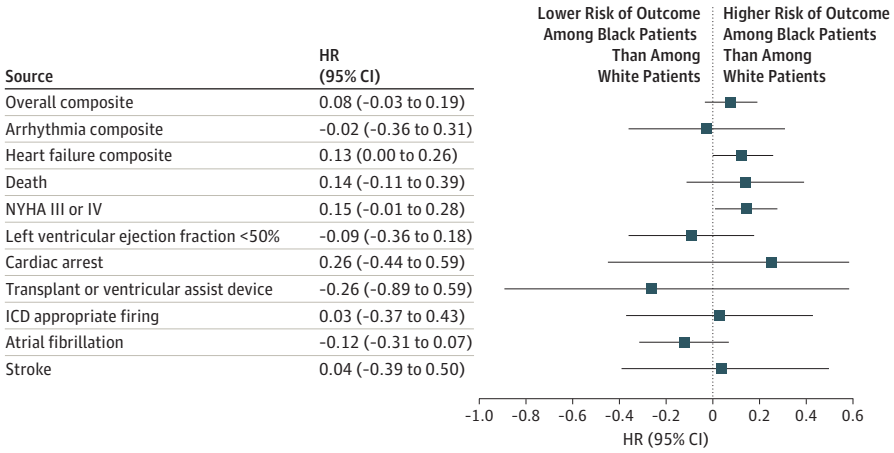
Procedure and Outcome	No. (%)		P Value
	Black Patients (n = 205)	White Patients (n = 2262)	
Procedures			
Septal reduction therapy	30 (14.6)	521 (23.0)	.007
Septal reduction category[a]			.03
Alcohol ablation only	2 (6.7)	59 (11.3)	NA
Myectomy only	28 (93.3)	447 (85.8)	NA
Both alcohol ablation and myectomy	0	15 (2.9)	NA
ICD implantation	68 (33.2)	724 (32.0)	.79
Clinical outcomes			
All-cause mortality	13 (6.3)	119 (5.3)	.43
Sudden cardiac death	0	16 (0.7)	.45
Resuscitated cardiac arrest	11 (5.4)	74 (3.3)	.17
ICD appropriate firing[b]	6 (2.9)	92 (4.1)	.54
Atrial fibrillation	35 (17.1)	608 (26.9)	<.001
Stroke	10 (4.9)	80 (3.5)	.43
Transplant or left ventricular assist device	2 (1.0)	56 (2.5)	.17
NYHA functional class III-IV	51 (24.8)	440 (19.5)	.050
Ejection fraction <50%	11 (5.4)	159 (7.0)	.37
Ventricular arrhythmia composite	16 (7.8)	157 (6.9)	.75
Overall composite	91 (44.4)	1003 (44.3)	>.99

Abbreviations: ICD, implantable cardioverter-defibrillator; NA, not applicable; NYHA, New York Heart Association.

[a] Overall (n = 551), black patients (n = 30), and white patients (n = 521).

[b] Exclusive of antitachycardia pacing.

Figure. Composite End Points and Individual Components in Black vs White Patients With Hypertrophic Cardiomyopathy



ICD indicates implantable cardioverter-defibrillator; NYHA, New York Heart Association.

0.97; P = .02). Black patients had lower odds of atrial fibrillation after adjustment for age and left atrial diameter (odds ratio, 0.62; 95% CI, 0.42-0.90; P = .001). Black race was independently associated with the development of NYHA class III or IV heart failure after adjustment for sarcomere status, age at diagnosis, hypertension, presence of obstruction, and body mass index (HR, 1.97; 95% CI, 1.34-2.88; P < .001) (**Table 3**).

Subgroup Analysis

Subgroup analysis was performed to explore differences in selected outcomes between black and white patients with sarcomeric mutations (n = 598 overall; n = 29 black patients). Unadjusted HRs by race are summarized in eTable 1 in the Supplement. Risk of all-cause mortality and the ventricular arrhythmia composite were similar between racial groups. There was an increased risk of NYHA class III or IV heart failure among black patients with sarcomeric HCM (unadjusted HR, 1.45; 95% CI, 1.08-1.94; P < .001). Black patients had an increased hazard of the overall composite outcome (HR, 4.10; 95% CI, 2.25-7.47) in association with higher frequency of NYHA functional class III or IV heart failure. On multivariable analysis accounting for age at diagnosis, hypertension, the presence of obstructive physiology, and body mass index, black race was independently associated with NYHA III or IV heart failure, with an adjusted HR of 4.07 (95% CI, 2.33-7.10; P < .001) (eTable 2 in the Supplement).

Table 3. Multivariable Model Examining Association of Race With NYHA Class III or IV Heart Failure Among 1422 Black and White Patients

Variable	Hazard Ratio (95% CI)	*P* Value
Black race	1.97 (1.34-2.88)	<.001
Age at diagnosis	1.02 (1.01-1.03)	<.001
Hypertension	1.01 (0.78-1.29)	.96
Obstruction[a]	1.81 (1.42-2.31)	<.001
Sarcomere status[b]		
Sarcomere positive	1.69 (1.30-2.20)	<.001
Sarcomere VUS	1.61 (1.08-2.39)	.02
Body mass index	1.06 (1.05-1.08)	<.001

Abbreviation: VUS, variants of unknown significance.

[a] Left ventricular outflow tract gradient >30 mm Hg on baseline echocardiography.

[b] Sarcomere-positive patients with pathogenic or likely pathogenic mutations on any of the 8 sarcomere-encoding genes; *ACTC1* (OMIM 102540), *MYBPC3* (OMIM 600958), *MYH7* (OMIM 160760), *MYL2* (OMIM 160781), *MYL3* (OMIM 160790), *TNNI3* (OMIM 191044), *TNNT2* (OMIM 191045), and *TPM1* (OMIM 191010). Sarcomere VUS is defined as patients with VUS in any of the 8 sarcomere-encoding genes. Total event rate was 304 events.

Discussion

This analysis of a large multicenter cohort with 26 594 patient-years of follow-up found differences in the disease experience between self-identified black and white patients with HCM. Compared with white patients, black patients were younger at diagnosis, were less likely to have disease associated with sarcomere mutations, and had a higher burden of functionally limited heart failure despite a lower burden of atrial fibrillation. In addition, racial differences in clinical management were identified. Black patients were less likely to be referred for subspecialty HCM care, were less likely to undergo invasive septal reduction therapies despite similar degrees of obstruction, and less frequently underwent genetic testing. Among the general population, racial inequities in cardiovascular disease, particularly heart failure, are well-established.[8-11] Our results suggest that disparities may also be present among patients with HCM.

Racial Differences in Genetic Architecture and Cause of HCM

The prevalence of sarcomeric HCM was lower among black patients compared with white patients. Among patients who underwent genetic testing, black patients were 36% less likely to have pathogenic or likely pathogenic sarcomere variants identified as the cause of disease. The lower yield of genetic testing among black patients in the cohort was not associated with lower rates of family history of HCM[20] because the differences persisted even when analyses were restricted to patients with a family history of HCM. Exploratory analyses were performed to investigate whether sarcomere mutations were associated with more severe clinical disease among black vs white patients with HCM. The small number of black patients with pathogenic or likely pathogenic sarcomere variants limited analyses, and no obvious differences in mortality or malignant arrhythmias could be detected. However, black patients with sarcomeric HCM had a 4-fold higher risk of NYHA class III and IV heart failure compared with white patients.

Although the likelihood of having actionable results from genetic testing was lower among black patients, variants of unknown significance were detected at higher rates than in white patients who have HCM. Although this may suggest differences in underlying genetic architecture among groups of different ancestry, differences may be associated with racial inequalities in the diagnostic framework. The higher prevalence of variants of unknown significance among black patients likely reflects the relative paucity of representative ancestry inclusion in reference cohorts and insufficient genotyping of black patients with HCM. Thus, variant classification algorithms do not accurately predict pathogenicity in historically underrepresented minorities.[21] More robust genomic investigations and improved methods to determine variant pathogenicity, particularly in nonwhite ancestry groups are needed.[17,22] These limitations are being addressed by large genomic reference cohorts more inclusive of individuals with African ancestry.[23] These efforts should allow more accurate determinations of whether variants are likely to be associated with disease among racial/ethnic minority group populations.

The identification of a sarcomere mutation is not the clinical terminus of genetic testing. At present, the principal clinical benefit of HCM genetic testing is to enable cascade screening whereby at-risk family members can be effectively identified in whom HCM-related complications can be averted. However, several factors that influence the uptake of cascade screening differ by race and limit black families from realizing the full potential afforded by genetic testing. In the present study, we observed that black patients were less likely to have been diagnosed through family screening. Future efforts should be tailored to address the genetic counseling and testing needs of all patients, especially those who have been most marginalized historically.

Comorbidities, such as hypertension and obesity, may have different consequences in patients from different ancestry groups. For example, previous studies have reported that black patients showed more prominent hypertrophic remodeling in association with modest pressure overload.[1,24] In contrast, pressure overload is not thought to exaggerate hypertrophic remodeling in sarcomeric HCM, indicating that distinct pathways, genetic and otherwise, may be associated with cardiac hypertrophy in response to increased load vs sarcomere gene mutations.[25] In SHaRe, patients were carefully evaluated to exclude hypertensive hypertrophic heart disease, but the prevalence of hypertension was higher among black patients with HCM. Clinically relevant left ventricular hypertrophy may be associated with background hypertension more frequently in certain ancestry groups and may involve different pathways than those triggered by sarcomere mutations. Moreover, interstitial and replacement fibrosis may also vary by ancestry and be associated with differential heart failure expression. Future investigation with more diverse cohorts into potential ancestry-based differences in disease pathways associated with hypertrophic remodeling and fibrosis are needed.

Racial Differences in Clinical Expression and Management

Inequities in care provision, underrecognition of disease leading to delays in timely management, barriers to accessing care, and undetermined environmental factors, such as lower socioeconomic status, may be associated with race-based disparities in black patients with HCM, as seen in other studies examining the treatment of black patients with heart disease.[16,26-28] The low proportion of black patients in the present cohort suggests that there was reduced referral for subspecialty HCM care. On the basis of black population census data and using an HCM prevalence of 0.2% in the general population,[29] the number of black patients in the cohort represents only 29% of the expected cases from the cities in which these centers are located compared to 160% of the expected cases among white patients.[30] This difference likely reflects barriers to accessing care and subsequent underdiagnosis among black patients,[26,27] compounded by racial inequities in referral patterns. Black patients may be underdiagnosed because their hypertrophy and heart failure may be assumed to be secondary to hypertension.[31] Furthermore, the lower rates of genetic testing for black patients in the cohort may also be associated with reduced levels of cascade screening for and subsequent diagnosis of at-risk family members.

Previous studies examining the association of race with HCM outcomes have been limited in size, scope, and methods.[4,32-34] As such, no racial differences have been identified. In this study, not only were black patients more likely to present with severe heart failure symptoms (NYHA class III or IV), black race was independently associated with an increased hazard of incident NYHA class III or IV heart failure. Despite playing an important role in heart failure progression during previous studies,[17,35-38] hypertension, obstruction, and obesity were not associated with the increased hazard of heart failure progression among black patients in SHaRe. The risk of heart failure was increased among black patients who had sarcomeric mutations compared with white patients who had sarcomeric mutations, suggesting that structural racism, characterized by disparate access to care and inequities in clinical management, rather than underlying biologic causes, may be associated with differential outcomes.[39]

The lower rates of invasive septal therapies are consistent with a previous study[40] and were found in the context of similar mean gradients and rates of obstructive physiologic characteristics between racial groups. These findings mirror results from other studies[26,27,41,42] demonstrating lower referral of black patients for advanced cardiac care, including cardiac catheterization, cardiac resynchronization therapy, and cardiology specialty visits. Among those who received septal reduction therapies, black patients were less likely to undergo alcohol septal ablation, possibly because of their younger age compared with white patients. Disparate access to appropriate clinical management may partly be associated with the greater symptom burden seen among black patients. Lower rates of atrial fibrillation and smaller left atrial diameter among black patients who had HCM in the present cohort were consistent with results from a previous study[40] of black patients in the general population.

Limitations

Our study has the inherent limitations of a retrospective registry-based observational investigation, including survival bias and lack of conclusions regarding causality. Given the nature of the tertiary referral centers from which this cohort was recruited, referral bias may limit the generalizability of these results. Although this was one of the largest multicenter cohorts in which the association of race with clinical outcomes was evaluated, it remains underpowered to detect significance in some of the rarer outcomes, such as sudden death. Furthermore, we cannot account for levels of perceived discrimination or differences in socioeconomic status, both of which may contribute to worse prognosis.[43,44] More precise measures of heart failure severity, such as cardiopulmonary exercise testing or *N*-terminal B-type natriuretic peptide levels, are needed to compliment the NYHA class differences described here. Race was self-identified; however, geographic ancestry to replace the social construct of race is well supported.[1,45]

Conclusions

To date, nearly all studies of disease expression and prognosis in HCM reflect the experience of white patients.[3,4] This study adds insight into the disease experience of HCM in black patients. Black patients with HCM were diagnosed at younger age, were less likely to have disease caused by sarcomere mutations, had a greater burden of symptomatic heart failure, and were more likely to be obese and hypertensive compared with white patients. These findings may suggest that the presence of ancestry-based differences in underlying disease pathways is associated with hypertrophic remodeling. Our findings also suggest that racial inequities in health care access and delivery are associated with lower use of subspecialty referral, invasive septal reduction therapy, and genetic testing among black patients with HCM. Despite significant advances in the understanding of the molecular pathogenesis in HCM and successes of modern treatment, racial disparities exist, reflective of the state of general cardiovascular health in the United States.[5] Increased minority group representation in genomic and cohort studies and for addressing barriers for appropriate diagnosis and receipt of specialized care appears to be needed. As disease-modifying therapies to interrupt progressive remodeling and adverse outcomes in HCM are investigated, increased attention to equity appears to be important.

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