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ORIGINAL INVESTIGATIONS

Distinct Subgroups in Hypertrophic Cardiomyopathy in the NHLBI HCM Registry

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ABSTRACT

BACKGROUND The HCMR (Hypertrophic Cardiomyopathy Registry) is a National Heart, Lung, and Blood Institute–funded, prospective registry of 2,755 patients with hypertrophic cardiomyopathy (HCM) recruited from 44 sites in 6 countries.

OBJECTIVES The authors sought to improve risk prediction in HCM by incorporating cardiac magnetic resonance (CMR), genetic, and biomarker data.

METHODS Demographic and echocardiographic data were collected. Patients underwent CMR including cine imaging, late gadolinium enhancement imaging (LGE) (replacement fibrosis), and T1 mapping for measurement of extracellular volume as a measure of interstitial fibrosis. Blood was drawn for the biomarkers N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (cTnT), and genetic analysis.

RESULTS A total of 2,755 patients were studied. Mean age was 49 ± 11 years, 71% were male, and 17% non-white. Mean ESC (European Society of Cardiology) risk score was 2.48 ± 0.56. Eighteen percent had a resting left ventricular outflow tract (LVOT) gradient ≥30 mm Hg. Thirty-six percent had a sarcomere mutation identified, and 50% had any LGE. Sarcomere mutation–positive patients were more likely to have reverse septal curvature morphology, LGE, and no significant resting LVOT obstruction. Those that were sarcomere mutation negative were more likely to have isolated basal septal hypertrophy, less LGE, and more LVOT obstruction. Interstitial fibrosis was present in segments both with and without LGE. Serum NT-proBNP and cTnT levels correlated with increasing LGE and extracellular volume in a graded fashion.

CONCLUSIONS The HCMR population has characteristics of low-risk HCM. Ninety-three percent had no or only mild functional limitation. Baseline data separated patients broadly into 2 categories. One group was sarcomere mutation positive and more likely had reverse septal curvature morphology, more fibrosis, but less resting obstruction, whereas the other was sarcomere mutation negative and more likely had isolated basal septal hypertrophy with obstruction, but less fibrosis. Further follow-up will allow better understanding of these subgroups and development of an improved risk prediction model incorporating all these markers. (J Am Coll Cardiol 2019;74:2333–45) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACCF = American College of Cardiology Foundation

AHA = American Heart Association

BMI = body mass index

CMR = cardiac magnetic resonance

cTnT = high-sensitivity cardiac troponin T

ECV = extracellular volume

HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

NSVT = nonsustained ventricular tachycardia

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SCD = sudden cardiac death

SSFP = steady-state free precession imaging

The HCMR (Hypertrophic Cardiomyopathy Registry) is a prospective National Heart, Lung, and Blood Institute-funded registry of 2,755 hypertrophic cardiomyopathy (HCM) patients recruited across Europe and North America (1). The primary goal of the study is to improve risk prediction for important adverse clinical outcomes in HCM by integrating cardiac magnetic resonance (CMR) imaging, biomarker, and genetic data with standard clinical and echocardiographic findings. Insights gained by HCMR will directly impact patient care by providing a systematic evidence base to inform and advance management guidelines (2) and develop predictive models (3). In current practice, risk stratification for sudden cardiac death (SCD) remains poorly resolved, particularly for patients at low and intermediate risk, limiting optimal use of implantable cardioverter-defibrillators (ICDs) (4,5). In addition, models have not yet been developed to predict other key adverse outcomes such as incident heart failure or atrial fibrillation.

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Previous large cohorts of HCM patients were gathered retrospectively and/or from 1 or a handful of specialist centers (5–7), and in general, CMR has not been systematically included (5,7). An ongoing registry in 69 centers from 18 European countries is collecting patients with HCM (n = 1,739), but also includes other nonischemic cardiomyopathies, and is only collecting variables acquired at the discretion of the clinical sites (8). For example, only 34% of patients in the latter registry underwent CMR, 46% had genetic testing, and biomarkers were not routinely collected (8). HCMR is the first large prospective registry to include rigorous CMR imaging, genetic testing, and prospective collection of blood for biomarker analysis.

Myocardial fibrosis measured by CMR has gained attention as a potential determinant of risk in patients with HCM. The presence of substantial late gadolinium enhancement (LGE), a marker of replacement fibrosis, has been associated with a 2-fold increase in SCD risk (6) and 3-fold increase in composite events (9) if present in >15% of left ventricular (LV) mass. A meta-analysis of nearly 3,000 patients from several studies demonstrated that the presence of LGE was associated with a 3.4-fold increased risk of SCD/ICD discharge, and a 1.8-fold increase in all-cause mortality (10). The extent of LGE was also associated with an increased risk of SCD/ICD discharge (1.36/10% LGE; p = 0.005) in a continuous fashion. A recent study suggests that adding LGE to American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) risk stratification, along with apical aneurysm morphology and multiple runs of nonsustained ventricular tachycardia (NSVT) improved identification of indications for ICD placement (11). Interstitial rather than replacement fibrosis may be an additional risk marker in HCM (12). HCMR is the first large multicenter study to use T1 mapping to assess extracellular volume as a surrogate for interstitial fibrosis in HCM. Integrating these markers of fibrosis and other CMR findings with clinical information, echocardiography, genotyping, and biomarker analysis may further inform risk prediction in HCM. Baseline characteristics of 2,755 patients with HCM are presented in the present paper.

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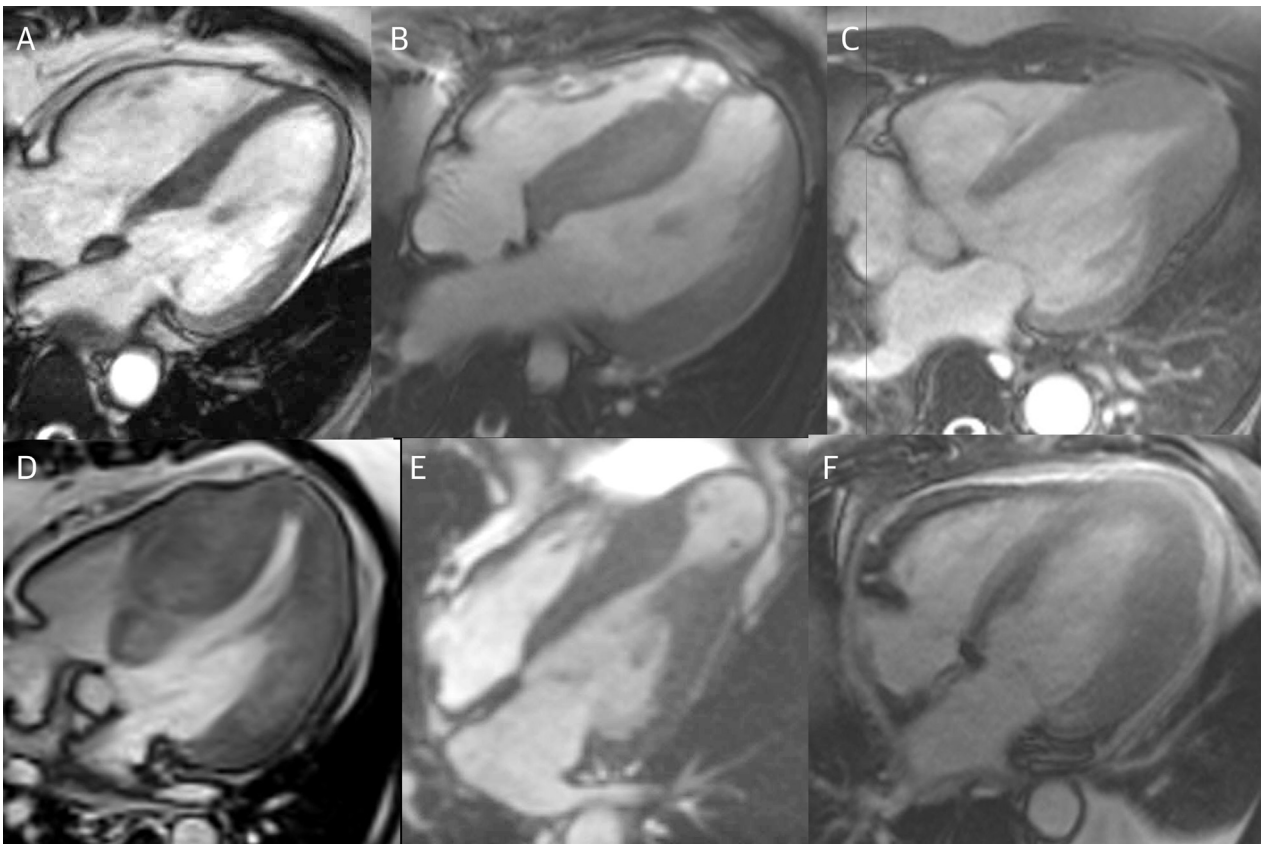
FIGURE 1 Cine Images From Individual Patients With the 6 Different Morphological Subtypes of HCM



Steady-state free precession 4-chamber long-axis cine images from individual patients with the 6 different morphological subtypes of hypertrophic cardiomyopathy (HCM) are shown. The 6 subtypes are: **(A)** localized basal septal hypertrophy; **(B)** reverse curvature septal hypertrophy; **(C)** apical HCM; **(D)** concentric HCM; **(E)** mid-cavity obstruction with apical aneurysm; or **(F)** other.

METHODS

The study design for HCMR has been previously published (1); the relevant methods are summarized here. HCMR is a prospective observational study. After written informed consent, all patients underwent standard clinical evaluation and CMR, and had blood drawn for genetic and biomarker analysis. Longitudinal follow-up is being conducted to determine the incidence of cardiovascular events, adjudicated by a clinical events committee.

INCLUSION/EXCLUSION CRITERIA. Patients included were 18 to 65 years of age with an established diagnosis of HCM defined as unexplained LV hypertrophy (wall thickness >15 mm) without cavity dilatation or known predisposing cause (uncontrolled hypertension, aortic stenosis, and so on) (2). Patients known to have other causes of infiltrative/hypertrophic cardiomyopathies such as amyloidosis, sarcoidosis, Fabry disease, Danon disease, or Noonan's syndrome, or discovered to have these diagnoses through HCMR genotyping, were excluded. Patients older than 65 years of age were excluded because they have high competing mortality risks, in particular from coronary artery disease and cancer.

Additional exclusion criteria were: 1) prior septal myectomy or alcohol septal ablation; 2) prior myocardial infarction or known coronary artery disease; 3) incessant ventricular arrhythmias; 4) inability to lie flat; 5) contraindication to contrast-enhanced CMR including pacemakers, defibrillators, intraocular metal, certain types of intracranial aneurysm clips, severe claustrophobia, and Stage IV/V chronic kidney disease; 6) diabetes mellitus with end organ damage; 7) ongoing pregnancy; or 8) inability to provide informed consent.

PATIENT ENROLLMENT. Patients were enrolled from 44 sites in the United States (n = 18), Canada (n = 4),

United Kingdom (n = 13), Italy (n = 4), Germany (n = 3), and the Netherlands (n = 2) between April 2014 and April 2017 (Online Table 1). Participating sites are experienced centers with focused care of HCM patients as well as state-of-the-art CMR capabilities. Emphasis was placed on recruiting HCM patients across the risk spectrum including higher-risk patients referred for subsequent ICD insertion. Data regarding baseline demographics and clinical variables were recorded from clinical records including data from clinically performed echocardiographic, Holter and exercise testing studies closest to the time of enrollment. ESC (European Society of Cardiology) risk score was calculated using baseline clinical and echocardiographic data (3).

CMR METHODS. CMR was performed at 1.5-T or 3.0-T on MR systems from the 3 primary vendors (General Electric, Philips Medical Systems, and Siemens Healthineers) using a standardized protocol and multichannel phased-array chest coils and electrocardiographic gating. After rapid localization of the heart, short-axis cine steady-state free precession imaging (SSFP) was performed covering the whole heart in 8-mm-thick slices (no gap). Typical cine SSFP parameters included TR/TE 3.1/1.2 ms, in-plane resolution of 2 to 2.5 mm, temporal resolution of 40 to 50 ms. Baseline T1 mapping was performed in 3 short-axis slices centered in the mid-LV, representing 16 of the 17 AHA segments in the nearly 80% of the sites that had appropriate software. The Shortened Modified Look-Locker Inversion recovery technique (ShMOLLI), using a 5(1)1(1)1 Look-Locker scheme with conditional image processing (13), was used as the recommended standard on Philips and Siemens systems, both for native and post-contrast T1 mapping acquisitions. Gadolinium contrast was administered intravenously as a bolus dose of 0.15 mmol/kg. Long-axis function by SSFP cine imaging was then obtained. Post-contrast T1 mapping acquisitions were performed in the same 3 short-axis slices as pre-contrast, starting at 5, 14, and 29 min post-contrast. LGE imaging was acquired in the same long-axis and short-axis stack locations beginning at minute 17 post-contrast with a 2-dimensional breath-hold, segmented inversion-recovery sequence (inversion time [TI] optimized by the Look-Locker sequence [TI scout] to null normal myocardium). Total imaging time was approximately 60 min.

CMR image analysis. Commercially available software (MedisSuite 3.0 and QMassMR, Medis, Leiden, the Netherlands) was used for analysis of all CMR images (cine, T1 maps, and LGE) in a core laboratory. LV mass, volumes, wall thickness, and thickening was measured according to Society for Cardiovascular Magnetic Resonance standards (14). Cine images in short-axis contiguous cuts were evaluated for LV and right ventricular volumes and myocardial mass by manually tracing endocardial and epicardial borders. Papillary muscles were included in LV volumes and excluded from LV mass. Cine images were also evaluated for morphology (15) and defined as: 1) localized basal septal hypertrophy; 2) reverse curvature septal hypertrophy; 3) apical HCM; 4) concentric HCM; 5) mid-cavity obstruction with apical aneurysm; or 6) other, that is, did not fit into the preceding 5 categories (**Figure 1**) (16). Cine images in 2- and 4-chamber long-axis cuts were evaluated for left atrial volumes using the biplane area-length method, at end-ventricular systole, before atrial contraction, and end-ventricular diastole (17).

Quantification of LGE was performed according to Society for Cardiovascular Magnetic Resonance standards (14) using both the 6 SD quantitative threshold, as well as visually (18). LGE was categorized as none, >0% to 5%, >5% to 10%, >10% to 15%, and >15% of LV mass. T1 quantification was performed on a segmental basis by nonlinear least-squares fitting of the segmental inversion recovery curves, resulting in multiple T1 measurements (1 pre- and 3 post-contrast) calculated. Gadolinium partition coefficient λ was calculated segmentally and globally by linear regression of pre- and post-contrast R1 (=1/T1) relaxation rates in myocardium, against the corresponding R1s in the blood pool of the same short-axis slice. The linear regression slope was converted to extracellular volume (ECV) using the patient's fractional blood volume of distribution (1 − hematocrit) (19). ECV index was calculated as ECV (%) times LV mass.

GENETICS. Amplicon-based sequencing for 36 cardiomyopathy-associated genes was undertaken using the Illumina MiSeq platform. Bioinformatic analysis was performed using the Genome Analysis Toolkit version 4 best practice guidelines. Variants were visually confirmed through inspection of BAM files. Variant annotation was performed using SNPEff and Ensembl's Variant Effect Predictor (VEP version 95). Data from publicly available resources (ClinVar [version 20190211] and gnomAD r2.1) and the Oxford Regional Genetics Laboratory in-house mutation database was used to inform variant classification. Following quality control, 2,636 individuals (99.1%) were deemed suitable for subsequent genetic analyses.

SERUM BIOMARKERS. Blood samples were transported on ice, processed within 60 min of phlebotomy to obtain serum and EDTA-anticoagulated plasma, aliquoted, and stored at −70°C until they were batched tested at the end of the study period in the

Biomarker Research and Clinical Trials Laboratory at Brigham and Women's Hospital. Cardiac troponin T (cTnT) was tested using the Roche (Roche Diagnostics Corporation, Indianapolis, Indiana) TnT STAT Gen 5 assay to assess for myocardial injury (19,20). The analytical measurement range for the assay is 6 to 10,000 ng/l, and coefficients of variation were 4.1% at 15.6 ng/l, 4.0% at 27.6 ng/l, and 2.5% at 1,893 ng/l. NT-proBNP was measured using the Roche proBNP II assay to assess hemodynamic or myocardial wall stress. Analytical measurement range of the assay is 5 to 35,000 pg/ml, and total imprecision of the assay was 2.5% at both 138 pg/ml and 4,578 pg/ml.

DATA MANAGEMENT AND STATISTICAL ANALYSIS. Clinical data were entered in an online data management system. Upon entry, data underwent a series of range and quality checks. Baseline arrhythmias were defined as a history of NSVT and/or atrial fibrillation. Summary statistics for continuous variables include mean ± SD and median (interquartile range). Most data were nonnormally distributed, so the nonparametric Kruskal-Wallis rank test was used to compare independent groups. The exceptions were age and body mass index (BMI) where Student's *t*-tests or analysis of variance were used. Categorical variables are summarized by number and proportion of valid (nonmissing) values and analyzed by contingency table analysis (chi-square). Odds ratios were calculated for 2 × 2 tables. Where multiple comparisons were made within tables, Bonferroni corrections were used to control Type I error rate (20). The association of morphology categories with demographic and clinical variables was assessed by contingency table analysis (chi-square) for categorical variables and 1-way analysis of variance for continuous variables. Savage Scores test was used to compare LGE distribution by morphology categories in a singly ordered (LGE) contingency table analysis (21). Statistical testing was performed with Stata, v15 (Stata Corp., College Station, Texas) and StatXact 7 (Cytel, Cambridge, Massachusetts).

RESULTS

BASELINE DEMOGRAPHICS. The number of patients enrolled at each site is shown in Online Table 1. Of 2,762 patients initially enrolled, 1,362 were enrolled in North America and 1,400 in Europe. Seven patients were subsequently excluded because they were demonstrated to be phenocopies genetically and not have HCM, leaving 2,755 for analysis. Baseline demographic and clinical information are shown in **Table 1**.

TABLE 1 Baseline Characteristics of Patients Enrolled in HCMR

	Summary Statistic	Valid
Age, yrs	49 ± 11	2,738 (99.4)
Male	1,953 (71.3)	2,740 (99.5)
Race/ethnicity		2,737 (99.3)
White	2,311 (84.4)	
Black	204 (7.4)	
Asian	205 (7.5)	
Other	18 (0.7)	
Hispanic	60 (2.2)	2,739 (99.4)
BMI, kg/m^2	29.3 ± 5.7	2,726 (98.9)
Family history of HCM		2,722 (98.9)
1st degree	600 (22.0)	
2nd degree	84 (3.1)	
Both 1st and 2nd	228 (8.4)	
Comorbidities		
Hypertension	997 (36.6)	2,726 (99.0)
Type II diabetes mellitus	213 (7.8)	2,726 (99.0)
Current smoker	387 (14.2)	2,724 (98.9)
NYHA functional class		2,692 (97.7)
I	1,792 (66.6)	
II	706 (26.2)	
III/IV	194 (7.2)	
Other clinical history		
Syncope	361 (13.2)	2,726 (98.9)
Heart failure	142 (5.2)	2,733 (98.9)
Stroke	76 (2.8)	2,733 (98.9)
Nonsustained ventricular tachycardia	196 (12.0)	1,633 (59.3)
Number of runs	3.2 ± 12.1	
Atrial fibrillation		2,723 (98.8)
Persistent	77 (2.8)	
Paroxysmal	244 (9.0)	
Symptoms at enrollment		
Chest pain	893 (32.8)	2,726 (98.9)
Dyspnea	1,184 (43.4)	2,726 (98.9)
Medications at enrollment		
Beta-blocker	1,547 (57.0)	2,714 (98.5)
Calcium-channel blocker	508 (18.7)	2,714 (98.5)
ACE/ARB	644 (23.7)	2,714 (98.5)
Disopyramide	84 (3.1)	2,714 (98.5)
Statins	741 (27.3)	2,714 (98.5)
Diuretic	314 (11.6)	2,714 (98.5)
Oral anticoagulant	251 (9.2)	2,714 (98.5)
Oral antiplatelet agent	431 (15.8)	2,714 (98.5)

Values are mean ± SD or n (%). Summary statistics based on nonmissing values of the total analyzed: 2,755.

ACE/ARB = angiotensin-converting enzyme/angiotensin receptor blocker; BMI = body mass index; HCM = hypertrophic cardiomyopathy; HCMR = Hypertrophic Cardiomyopathy Registry; NYHA = New York Heart Association functional class.

ECHOCARDIOGRAPHY. Mean maximal wall thickness was 18.6 ± 4.8 mm. Eighteen percent of participants had a peak gradient >30 mm Hg, and these patients' average gradient was 69 ± 31 mm Hg. Fifty-nine percent had mitral regurgitation, and 12% were graded as moderate or severe. Mean pulmonary artery

TABLE 2 LV and RV Volumetric Results

LV mass, g	
Male	185 ± 61
Female	142 ± 50
LV mass index, g/m^2	
Male	89 ± 27
Female	77 ± 25
Maximal wall thickness, mm	20.6 ± 4.8
LV end diastolic volume, ml	171 ± 41
LV end diastolic volume index, ml/m^2	85 ± 17
LV end systolic volume, ml	63 ± 26
LV end systolic volume index, ml/m^2	31 ± 12
LV stroke volume, ml	108 ± 24
LV stroke volume index, ml/m^2	54 ± 10
LV ejection fraction, %	64 ± 8
LV mass/EDV ratio	1.0 ± 0.3
Cardiac output, l/min	6.7 ± 1.6
Cardiac index, l/min/m^2	3.3 ± 0.7
RV mass, g	36 ± 12
RV mass index, g/m^2	18 ± 5
RV end diastolic volume, ml	152 ± 39
RV end diastolic volume index, ml/m^2	75 ± 16
RV end systolic volume, ml	50 ± 24
RV end systolic volume index, ml/m^2	24 ± 11
RV stroke volume, ml	102 ± 24
RV stroke volume index, ml/m^2	51 ± 11
RV ejection fraction, %	68 ± 10

Values are mean ± SD.
EDV = end-diastolic volume; LV = left ventricular; RV = right ventricular.

pressure was 28 ± 11 mm Hg. Maximum left atrial dimension was 4.2 ± 0.8 cm.

HOLTER MONITORING AND EXERCISE TESTING. Among 1,672 patients who had undergone clinically performed 24-h Holter monitoring, AF was seen in 4% and NSVT in 12%. The 1,520 participants who underwent clinically performed exercise treadmill testing achieved 9.7 METS on average, and 12% had a hypotensive response to exercise or failed to increase systolic blood pressure by 20 mm Hg.

CMR CINE DATA. A total of 2,651 patients completed the CMR because 38 (1.4%) had studies aborted due to claustrophobia and 52 (2%) for other reasons. The contrast dose used was 0.15 mmol/l/kg (mean 20 ± 9 ml). The rhythm at the time of the CMR was normal sinus in 93%, atrial fibrillation in 2%, and other, that is, premature ventricular contractions, bigeminy, and so on, in 5%. LV and right ventricular structure and function results derived from SSFP cine CMR images are shown in Table 2, and examples are shown in Figure 1.

There were 2,628 studies available for morphological evaluation, with the remaining 27 incomplete for morphological assessment. A total of 1,197 (46%) had isolated basal septal hypertrophy, 1,059 (38%) reverse septal curvature, 224 (8%) apical HCM, 36 (1%) concentric HCM, 79 (3%) mid-cavity obstruction with apical aneurysm, and 33 (1%) were classified as other. Demographic and clinical characteristics associated with specific morphologies are presented in Table 3. Patients with reverse septal curvature morphology were, in general, younger, had lower BMI, more likely minority, and had thicker walls, more arrhythmias, less hypertension, and less left ventricular outflow tract (LVOT) obstruction as compared with those with isolated basal septal curvature.

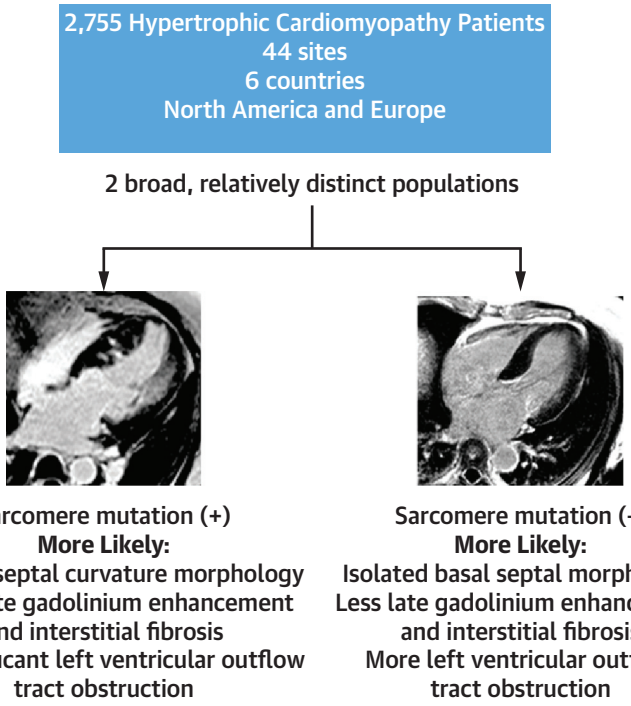
Maximal LV wall thickness of any segment was 20.6 ± 4.8 mm. Results comparing maximal LV wall thickness by baseline variables are presented in Online Table 2. Significant relationships with wall thickness were found for age, BMI, male sex, LVOT gradient ≥30 mm Hg, and sarcomere mutation positive. Left atrial width from the 3-chamber long-axis view was 4.8 ± 0.8 cm. Left atrial area from the 4-chamber long-axis view was 28.9 ± 7.6 cm^2.

TABLE 3 Demographic Differences Among HCM Morphologies

	Isolated Basal Septal (n = 1,199)	Reverse Curvature (n = 1,063)	Apical (n = 224)	Concentric (n = 36)	Apical Aneurysm (n = 79)	Other (n = 33)	Overall p Value
Age, yrs	51.6 ± 10.3*†	47.1 ± 12.0‡	51.3 ± 9.7†	50.0 ± 11.3	49.7 ± 11.4	45.8 ± 13.7	<0.001
BMI, kg/m^2	29.8 ± 5.5*	28.6 ± 5.6	28.9 ± 4.8	33.5 ± 8.1*‡§‖	28.9 ± 5.4	28.6 ± 6.2	<0.001
Male	839 (70.1)	758 (71.5)	175 (78.1)	30 (83.3)	47 (59.5)	22 (66.7)	0.014
Minority	121 (10.1)*‡	179 (16.9)‡	75 (33.5)	11 (30.6)§	22 (27.9)§	4 (12.1)	<0.001
Maximal wall thickness, mm	17.4 ± 3.6*	20.0 ± 5.2†‡	17.1 ± 4.5	22.2 ± 6.3†‡§	19.6 ± 6.0†§	16.7 ± 3.5	<0.001
LVOT gradient ≥30 mm Hg	279 (30.4)*	164 (20.8)‡	7 (5.1)§	8 (33.3)‡	13 (23.6)‡	2 (7.4)	<0.001
Arrhythmias	161 (13.5)*‡	224 (21.3)	51 (22.9)	6 (17.1)	28 (35.4)*§	6 (18.2)	<0.001
LVEF <55%	145 (12.4)	168 (16.3)	20 (9.1)	11 (30.6)‡†	13 (16.7)	4 (12.1)	0.002
HTN	504 (42.2)*	309 (29.3)	81 (36.3)	16 (44.4)	31 (39.2)	14 (42.4)	<0.001

Values are mean ± SD or n (%). Percentages are based on nonmissing values. For each variable, correction for Type I error was set at <0.0055 (0.05/9). If the overall p value was <0.0055, pairwise comparisons between morphology categories were made at p < 0.0055. *p < 0.0055 versus reverse curvature. †p < 0.0055 versus other. ‡p < 0.0055 versus apical. §p < 0.0055 versus isolated basal septal. ‖p < 0.0055 versus apical aneurysm.
BMI = body mass index; HCM = hypertrophic cardiomyopathy; HTN = hypertension; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.

CENTRAL ILLUSTRATION **Hypertrophic Cardiomyopathy: Overall Design and Findings**



Neubauer, S. et al. J Am Coll Cardiol. 2019;74(19):2333–45.

A total of 2,755 patients from 44 sites in 6 countries were recruited. Two relatively distinct populations were identified as depicted in the slide. **(Left)** Four-chamber inversion recovery gradient echo late gadolinium enhancement (LGE) image in a patient with reverse curvature asymmetric septal hypertrophy. Patchy LGE is noted in mid-septum. **(Right)** Similar orientation and image type in a patient with reverse curvature asymmetric septal hypertrophy. No LGE is noted. One group was sarcomere mutation positive, and more likely had reverse septal curvature morphology, more fibrosis, and less obstruction, whereas the other was sarcomere mutation negative, and more likely had isolated basal septal hypertrophy with obstruction and less fibrosis.

MYOCARDIAL FIBROSIS. Of 2,755 patients, 2,534 (92%) had valid LGE values to allow assessment of replacement fibrosis. LGE was present in 50% of patients based on visual criteria (Central Illustration), and in 60% based on >6 SD signal criteria. In the 50% of patients who had LGE by visual analysis, mean LGE mass was 3.7 ± 5.2% of LV mass. In patients with LGE present, ESC risk score was higher than those without LGE (2.61 ± 0.59 vs. 2.33 ± 0.49; $p < 0.001$). Only 2% of patients (n = 46) had LGE >15% of LV mass. Morphological correlates of LGE are shown in Table 4. A high proportion of patients with reverse septal curvature hypertrophy and apical aneurysm patterns had LGE, whereas isolated basal septal hypertrophy demonstrated LGE less frequently than other morphologies. The reverse septal curvature pattern was associated with the majority (79%) of cases with >10% LGE.

Comparison of the presence of LGE with baseline variables is shown in Table 5. BMI, family history of HCM, maximal wall thickness, reduced LV ejection fraction (LVEF), baseline arrhythmias, hypertension, and sarcomere mutation positive were all significantly associated with LGE presence. Patients with a family history of HCM were 1.2 times more likely to have LGE present than those without. Patients with LVEF <55% were nearly 1.3 times more likely to have

TABLE 4 **LGE Amount by HCM Morphology**

	No LGE (n = 1,265)	<5% (n = 990)	5%-10% (n = 182)	10%-15% (n = 54)	>15% (n = 46)
Isolated basal septal	767 (66.5)	353 (30.6)	25 (2.2)	8 (0.7)	0 (0.0)
Reverse curvature septal	322 (31.4)	498 (48.5)	127 (12.4)	36 (3.5)	43 (4.2)
Apical	116 (54.2)	81 (37.8)	15 (7.0)	1 (0.5)	1 (0.5)
Concentric	19 (57.6)	11 (33.3)	0 (0.0)	3 (9.1)	0 (0.0)
Apical aneurysm	25 (32.1)	35 (44.9)	13 (16.7)	5 (6.4)	0 (0.0)
Other	16 (48.5)	12 (36.4)	2 (6.1)	1 (3.0)	2 (6.1)

Values are n (%).
HCM = hypertrophic cardiomyopathy; LGE = late gadolinium enhancement.

TABLE 5 Distribution of Presence of LGE for Selected Baseline Variables

	LGE Present	Unadjusted p Value	Bonferroni Adjusted p Value
Age, yrs		0.029	0.319
≤40, n = 528	286 (54.2)		
41-64, n = 1,944	958 (49.3)		
≥65, n = 75	32 (42.7)		
BMI, kg/m^2		0.001	0.013
≤25, n = 606	338 (55.8)		
26-30, n = 974	489 (50.2)		
≥31, n = 969	451 (46.5)		
Sex		0.032	0.352
Male, n = 1,820	937 (51.5)		
Female, n =729	341 (46.8)		
Race		0.068	0.748
Minority, n = 398	183 (46.0)		
Nonminority, n = 2,149	1,095 (51.0)		
Family history of HCM		<0.001	<0.001
Yes, n = 870	489 (56.2)		
No, n = 1,669	781 (46.8)		
LVOT gradient ≥30 mm Hg		0.036	0.396
Yes, n = 455	207 (45.5)		
No, n = 1,433	733 (51.2)		
Maximal wall thickness, mm		<0.001	<0.001
≤20, n = 1,692	727 (43.0)		
21-29, n = 540	381 (70.6)		
≥30, n = 64	53 (82.8)		
Arrhythmias		<0.001	<0.001
Yes, n = 460	295 (64.1)		
No, n = 2,080	975 (46.9)		
Hypertension		<0.001	<0.001
Yes, n = 929	409 (44.0)		
No, n = 1,613	863 (53.5)		
LVEF <55%		<0.001	<0.001
Yes, n = 354	216 (61.0)		
No, n = 2,195	1,062 (48.4)		
Sarcomere mutation		<0.001	<0.001
+, n = 878	614 (69.9)		
−, n = 1,575	626 (39.8)		

Values are n (%). The p values are from chi-square distribution or Savage score test for singly ordered categories, and unadjusted for multiple testing. A Bonferroni correction would require a p value of <0.0045 to declare statistical significance at a nominal Type I error rate of 0.05 (0.05/11).

Abbreviations as in Tables 3 and 4.

LGE present. Patients with baseline arrhythmias were 1.4 times more likely to have LGE present, and those with a sarcomere mutation were 1.8 times more likely to have LGE present than those without.

There were 2,082 patients (76%) with analyzable native T1 and 2,013 (73%) with valid ECV measures. Mean native T1 of the entire LV myocardium was 972 ± 74 at 1.5-T and 1,170 ± 84 at 3.0-T. Native T1 in segments without LGE was 969 ± 74 at 1.5-T and 1,157 ± 86 at 3.0-T compared with 976 ± 74 at 1.5-T and 1,179 ± 81 at 3.0-T ($p < 0.001$ for both) in segments with LGE. There were no statistically significant differences in native T1 between the MR vendors. Pooled across field strengths, native T1 was 2% higher in women than men ($p < 0.001$) and showed modest statistically significant correlations with LGE and wall thickness, but not with age.

ECV was greater in regions with LGE (0.30 ± 0.05) than in those without (0.28 ± 0.04; $p < 0.001$). Mean ECV was greater in women (0.31 ± 0.04) than in men (0.28 ± 0.04; $p < 0.001$). For comparison purposes, ECV in normal volunteers ranges between 0.25 and 0.28, and tends to rise with age and be higher in females (22,23). Patients with higher ECV had a smaller BMI, were less likely to have a family history of HCM, had greater wall thickness, had more baseline arrhythmias, and were more likely to have a sarcomere mutation (**Table 6**). When evaluated by morphology, ECV was lowest in isolated basal septal hypertrophy compared with reverse septal curvature, apical and mid-cavity obstruction subtypes (Online Table 3). ECV index, a measure of mass of interstitium, was 49.2 ± 20.2 g in the cohort as a whole.

HCM RISK FACTORS. The mean ESC risk score (3) was 2.48 ± 0.56, suggesting that the study group is low risk. Of the enhanced ACCF/AHA risk factors (11), 12% had a family history of SCD, 13% had a history of syncope, 9% had sustained ventricular tachycardia or NSVT, 4% had wall thickness >30 mm, 2% had >15% LGE, and 3% had an apical aneurysm.

GENETICS. DNA samples were obtained from 2,661 individuals. Genetic analyses for genes that can be reliably interpreted in HCM comprise: the core sarcomeric genes (*MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *MYL2*, *MYL3*, *ACTC1*, and *TPM1*) and the well-established "phenocopy" genes (*GLA*, *PRKAG2*, *LAMP2*, and *TTR*). Overall, 29.5% (n = 774) of individuals were found to have a variant classified as "pathogenic" or "likely pathogenic" in a sarcomere gene, with variants in the *MYBPC3* (18.5%) and *MYH7* (8.0%) genes accounting for the majority. Only 3 individuals (0.11%) demonstrated a combination of 2 likely pathogenic or pathogenic variants in confirmed sarcomere genes. Seven individuals were found to harbor pathogenic variants within either *GLA* (n = 4) or *TTR* (n = 3), indicating a diagnosis of Fabry's disease or hereditary amyloidosis, respectively; these individuals were removed from all subsequent phenotypic analyses. In 12.3% of individuals (n = 325), "variants of uncertain significance" were detected in the sarcomere genes. See the Online Appendix for the approach to variants of uncertain significance. Using this approach, on the basis of

gene-specific interpretations, we dichotomized the HCMR cohort into individuals carrying a sarcomere variant, that is, sarcomere mutation positive (n = 943; 35.8%) and those who did not, that is, sarcomere mutation negative (n = 1,693; 64.2%). Using this dichotomous criterion, just under 1% of probands carried 2 sarcomere variants (and none >2).

Those who were sarcomere mutation positive were younger, had a lower BMI, were more often female and white, had a family history of HCM, and had less hypertension (Table 7), consistent with prior findings (24). However, they also were less likely to have a significant LVOT gradient, which may, in part, reflect differences in morphology because more of the sarcomere mutation-positive group demonstrated reverse curvature asymmetric septal hypertrophy (58.1%) relative to isolated basal septal hypertrophy (33.8%), ratios that were reversed in the sarcomere mutation-negative group (30.7% and 51.8%, respectively; p < 0.0001). In addition, fewer sarcomere mutation-positive individuals demonstrated apical hypertrophy (4.5% vs. 10.7%), concentric hypertrophy (0.2% vs. 2.0%), and "other" forms of hypertrophy (0.8% vs. 1.6%). Incidence of mid-cavity obstruction with apical aneurysm was similar (2.6% vs. 3.2%). LVEF was similar between groups. Sarcomere mutation-positive patients were much more likely to have any LGE as well as more extensive LGE (Table 8). Native T1 was higher at 1.5-T in sarcomere mutation-positive individuals (978 ± 76 vs. 968 ± 74; p < 0.02), but similar at 3.0-T (1,175 ± 89 and 1,167 ± 81, respectively; p = 0.21), likely due to lower number at 3.0-T and thus lower power.

BIOMARKERS. NT-proBNP and cTnT were obtained in 2,665 (97%) of the 2,755 patients in the HCMR analysis database. Online Table 4 presents comparisons of demographic and clinical variables and NT-proBNP. Because of the extreme skewness of the NT-proBNP distribution, median (interquartile range) are presented, as well as mean ± SD. Increasing age was associated with increasing NT-proBNP. Women had higher values than men as expected, obese patients had lower levels, and patients with baseline arrhythmias had higher levels. Patients with a resting LVOT gradient ≥30 mm Hg and those with a reduced LVEF had higher values. NT-proBNP levels increased as maximal wall thickness increased. The relationship between NT-proBNP and categories of LGE is presented in Figure 2. A similar relationship was seen with increasing ECV (by quartile) (Online Figure 1). NT-proBNP was significantly higher in sarcomere mutation-positive than -negative individuals (594 ± 842 vs. 520 ± 1,073; p < 0.001).

TABLE 6 Comparison of ECV by Selected Baseline Variables

	ECV	Unadjusted p Value	Bonferroni Adjusted p Value
Age, yrs		0.391	1.000
≤40, n = 417	0.29 ± 0.04		
41–64, n = 1,537	0.29 ± 0.05		
≥65, n = 58	0.30 ± 0.06		
BMI, kg/m^2		< 0.001	0.001
≤25, n = 485	0.30 ± 0.05		
26–30, n = 772	0.29 ± 0.04		
≥31, n = 752	0.29 ± 0.05		
Sex		< 0.001	0.001
Male, n = 1,417	0.28 ± 0.04		
Female, n = 596	0.31 ± 0.04		
Race		0.546	1.000
Minority, n = 323	0.29 ± 0.05		
Nonminority, n = 1,689	0.29 ± 0.05		
Family history of HCM		<0.001	0.001
Yes, n = 683	0.29 ± 0.05		
No, n = 1,322	0.30 ± 0.05		
LVOT gradient		0.178	1.000
≥30 mm Hg, n = 356	0.29 ± 0.05		
<30 mm Hg, n = 1,103	0.29 ± 0.05		
Maximal wall thickness, mm		<0.001	0.002
≤20 n = 1,337	0.29 ± 0.04		
21–29, n = 411	0.30 ± 0.05		
≥30, n = 51	0.31 ± 0.05		
Arrhythmias		<0.001	0.002
Yes, n = 368	0.30 ± 0.05		
No, n = 1,639	0.29 ± 0.04		
Hypertension		0.123	1.000
Yes, n = 718	0.29 ± 0.04		
No, n = 1,289	0.29 ± 0.05		
LVEF <55%		0.005	0.055
Yes, n = 264	0.30 ± 0.05		
No, n = 1,712	0.29 ± 0.04		
Genetics		<0.001	0.001
Sarcomere mutation +, n = 706	0.30 ± 0.05		
Sarcomere mutation −, n = 1,261	0.29 ± 0.05		

Values are mean ± SD. The p values are from Kruskal-Wallis test and unadjusted for multiple testing. A Bonferroni correction would require a p value of <0.0045 to declare statistical significance at a nominal Type I error rate of 0.05 (0.05/11).

ECV = extracellular volume; other abbreviations as in Table 3.

Normal values for cTnT for males were ≤22 ng/l and ≤14 ng/l for women (per Roche Diagnostics Corporation). Of the 2,665 patients with valid values, 282 men (15%) and 186 women (24%) had elevated cTnT. Online Table 5 presents comparisons of demographic and imaging data, and cTnT, abnormal versus normal. Women were over 1.6 times more likely to have abnormal cTnT levels than men. Those with a history of hypertension were 1.3 times more likely to have abnormal cTnT levels, and those with LVEF<55% were over 2.2 times more likely to have abnormal values. Minorities were 1.6 times more likely to have

TABLE 7 Demographic and Clinical Differences by Genetic Category

	Sarcomere Mutation (+)	Sarcomere Mutation (−)	Unadjusted p Value	Bonferroni Adjusted p Value
Age, yrs	46.2 ± 12.0	51.3 ± 10.4	<0.001	<0.001
BMI, kg/m^2	28.2 ± 5.4	29.8 ± 5.6	<0.001	<0.001
Male	65.1 (611)	75.3 (1,260)	<0.001	<0.001
Minority	28.4 (116)	37.4 (823)	0.001	0.009
Family history of HCM	54.7 (511)	22.3 (371)	<0.001	<0.001
LVOT gradient ≥30 mm Hg	19.0 (130)	26.8 (335)	<0.001	<0.001
Arrhythmias	38.1 (185)	35.4 (749)	0.255	1.000
Hypertension	21.3 (199)	45.1 (752)	<0.001	<0.001
LVEF <55%	14.2 (126)	14.2 (227)	0.983	1.000

Values are mean ± SD or n (%). A Bonferroni correction for multiplicity was made for 9 variables for nominal Type I error rate of 0.05: $p < 0.0055$ (0.05/9).

Abbreviations as in Table 3.

abnormal values, and patients with baseline arrhythmias 1.7 times more likely. As maximal wall thickness increased, so did abnormal cTnT. The relationship between cTnT and categories of LGE is presented in **Figure 2**. In both sexes, there was a stepwise increase in cTnT with categories of increasing LGE. A similar relationship was seen with increasing ECV (by quartile), although only in men (Online Figure 2). The incidence of elevated cTnT was similar in sarcomere mutation-positive and -negative groups (18% and 17%, respectively).

DISCUSSION

HCMR is the largest systematic, prospective natural history study in HCM to date which includes comprehensive CMR data in addition to other clinical metrics, genotyping, and biomarker analysis. Prior and ongoing registries are retrospective in nature and/or do not include systematic acquisition of these data (5–7). The 2,755 patients participating in HCMR reflect a broad sampling of North American and European sites, and 17% minority enrollment. A third had a family history of HCM, and a third had hypertension. Eighteen percent of patients had a LVOT gradient ≥30 mm Hg. Only 12% of patients had moderate or more mitral regurgitation. A sarcomere variant carrier yield of 35.8% is comparable to that seen for HCM in usual routine diagnostic service laboratories, confirming that the case population on which HCMR is based is representative of "real world" HCM practice. On the basis of the ESC risk scores, the patient group is of low risk.

TABLE 8 LGE Categories by Sarcomere Mutation Status

	Sarcomere Mutation (+)	Sarcomere Mutation (−)
No LGE, (n = 1,213)	264 (30.1)	949 (60.3)
>0%–5%, (n = 965)	458 (52.2)	507 (32.2)
>5%–10%, (n = 177)	101 (11.5)	76 (4.8)
>10%–15%, (n = 53)	33 (3.8)	20 (1.3)
>15%, (n = 45)	22 (2.5)	23 (1.5)

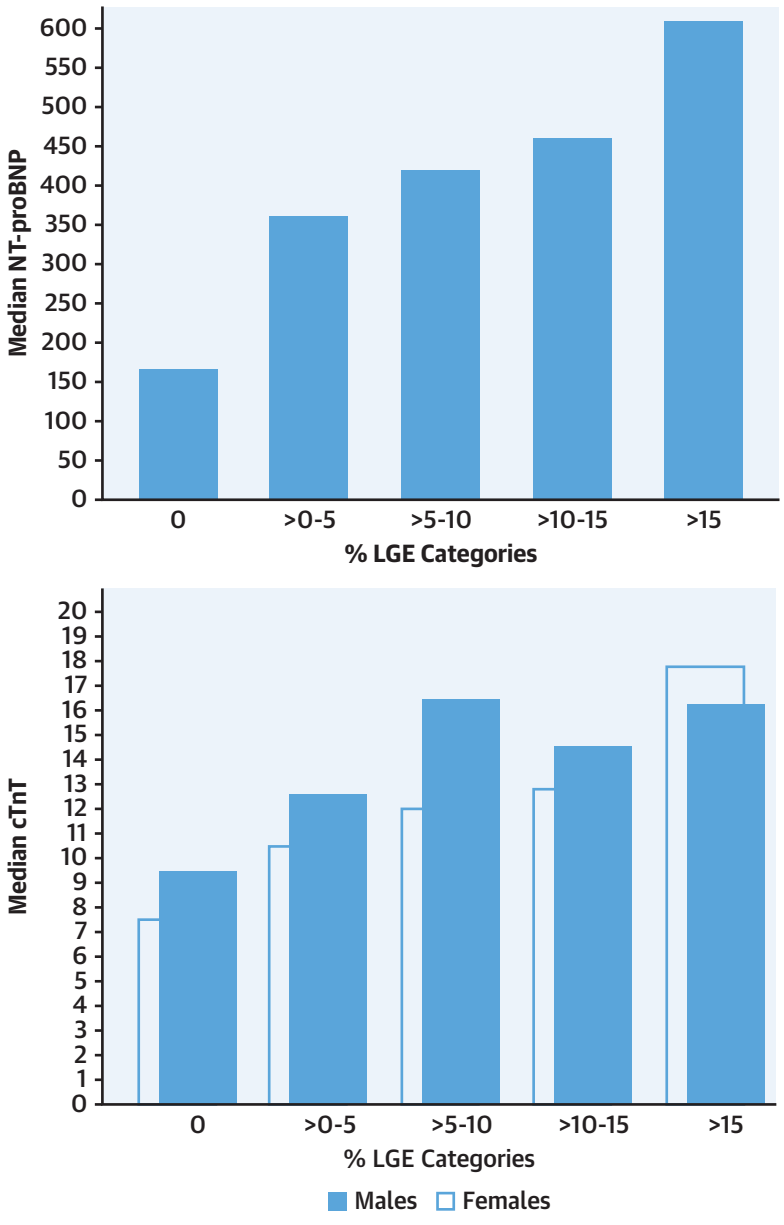
Values are n (%). Late gadolinium enhancement (LGE) categories were not equally distributed for sarcomere positive (+) and negative (−) groups ($p < 0.001$).

The major contribution of the present study lies in the CMR, genetic, and biomarker findings and their interrelationships in this population. Two relatively distinct populations were identified in HCMR (**Central Illustration**). One was sarcomere mutation positive and more likely to demonstrate reverse septal curvature morphology, have more extensive LGE, but less resting LVOT obstruction. The second group was sarcomere mutation negative and more likely to demonstrate isolated basal septal hypertrophy, with less LGE, but more LVOT obstruction. The first of these groups represents the Mendelian form of familial HCM, whereas the second group presumably has multifactorial disease (25), as evidenced by the higher burden of causes of secondary LV hypertrophy (hypertension, high BMI, male sex, older age, and so on). The finding that significant resting outflow obstruction indicates a lower likelihood of the familial form of HCM was not suspected. It is also notable that apical HCM is also less likely to reflect sarcomeric HCM.

Myocardial replacement fibrosis is prevalent (50%), although the frequency of extensive LGE is less than that noted in the study by Chan et al. (6) in which the 4 sites included were highly specialized referral centers. Patients with LGE had thicker walls, more baseline arrhythmias, and were more likely to be sarcomere mutation positive, in keeping with the concept of a higher burden of LGE in clearly identified genetic disease. One prior study of 82 patients showed that the extent of LGE had an odds ratio of 2.1 to predict mutation-positive HCM (26). The ESC risk score increases modestly with any LGE compared with no LGE. Whether the presence and/or extent of LGE improves risk stratification compared to the ESC risk score remains to be determined with longer follow-up. One recent study does suggest it adds to ACCF/AHA guidelines for identification of patients who subsequently require an ICD (11).

The vast majority of patients in this study (86%) have a form of asymmetric septal hypertrophy, either isolated basal or reverse curvature. Patients with the reverse curvature form were younger, less commonly had hypertension, and were more likely sarcomere mutation positive. They represented most of the

FIGURE 2 **Relationship of Biomarkers to Increasing Amounts of LGE**



N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (cTnT) were measured in each patient, as was the extent of late gadolinium enhancement (LGE) as a % of left ventricular mass on cardiac magnetic resonance. **(Top)** Median NT-proBNP showing increasing levels relative to patients with increasing amounts of LGE ($p < 0.001$ for trend). **(Bottom)** Similar trend shown for cTnT (separated by sex due to different normal values) with $p < 0.001$ for trend for both.

cases of >10% LGE, providing further data for a link between genetics, morphology, and fibrosis. Follow-up will test whether this morphological subtype with its link to sarcomere mutation positivity and increased fibrosis is a risk factor for outcome events. The other morphological subgroup with extensive LGE was the mid-cavity obstruction with apical aneurysm subtype, which has been shown to be associated with higher risk and adds to ACCF/AHA risk stratification (11,27).

In the HCMR cohort, there was evidence of interstitial fibrosis indicated by the elevated mean

ECV when compared with prior measurements using the same techniques in normal controls (28,29). ECV was mildly elevated even in regions without LGE, suggesting that interstitial fibrosis is a characteristic of HCM. Similar to LGE, increased wall thickness, baseline arrhythmias, and sarcomere mutation positivity were associated with interstitial fibrosis. Unlike LGE, there was more interstitial fibrosis in women.

The 2 biomarkers that were measured were both elevated in subsets of patients in this cohort. NT-proBNP was elevated in subsets with resting LVOT gradient ≥30 mm Hg, reduced LVEF, more baseline arrhythmias, and sarcomere mutation positive. CTnT was higher in minorities and patients with hypertension, LVOT gradient ≥30 mm Hg, increased wall thickness, and reduced LVEF. Whether elevated biomarkers are predictive of worse outcome in HCM will only be clarified with further follow-up. This is an understudied area, especially for NT-proBNP (30). One smaller study in Japan demonstrated worse outcomes with increasing levels of troponin (31). cTnT has been shown to improve risk prediction in women, but only in the setting of coronary heart disease (30). Both biomarkers demonstrated stepwise increases in relationship to LGE extent and ECV. Because LGE extent is a marker of SCD/ICD discharge in HCM, it may be that elevated biomarkers are a synergistic risk marker with either or both replacement and interstitial fibrosis. This points to the importance of developing a multivariable model using all of these potential risk markers to predict outcome events once follow-up is long enough to allow sufficient numbers of events to occur.

STUDY LIMITATIONS. This cohort excluded patients with HCM who had prior invasive septal therapy or ICD placement. Although minority recruitment was less than planned, the overall numbers may allow analysis of subpopulation differences and will likely be hypothesis-generating. The echocardiographic data were derived from clinical echo reports, and thus protocols were not standardized. Therefore, reporting of provoked obstruction was incomplete. Stress testing and Holter monitoring at entry were also not protocol-driven and thus were not performed in every patient. Although the use of ECV reduces the impact of magnetic field choice for T1 mapping, all T1 mapping techniques may be method and vendor-dependent.

CONCLUSIONS

The HCMR study population is characteristic of patients with low-risk HCM by ESC risk score. Ninety-three percent had no or only mild functional limitation. These patients have predominantly septal hypertrophy, 18% have resting LVOT gradient ≥30 mm Hg, and one-half have LGE. Over a third are sarcomere mutation positive. Interstitial fibrosis is prevalent even in segments without LGE. Serum biomarkers are elevated and relate to both replacement and interstitial fibrosis in a graded fashion. Two relatively distinct populations were identified. One group was sarcomere mutation positive and more likely had reverse septal curvature morphology, more fibrosis, and less resting obstruction, whereas the other was sarcomere mutation negative and more likely had isolated basal septal hypertrophy with resting obstruction and less fibrosis. Further follow-up will allow development of a model inclusive of the demographic, clinical, echocardiographic, CMR, biomarker, and genetic variables that best predict risk of major adverse cardiac events in HCM.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with hypertrophic cardiomyopathy and a sarcomere mutation associated with reversed septal curvature, more extensive myocardial fibrosis, and less resting ventricular outflow tract obstruction can be distinguished from others without this sarcomere mutation, who more often have isolated basal septal hypertrophy with less fibrosis and greater resting obstruction.

TRANSLATIONAL OUTLOOK: Further analysis of this registry and other sources should facilitate patient-specific risk profiling on the basis of demographic, echocardiographic, cardiac magnetic resonance, genetic, and biomarker data to identify those at risk of heart failure, arrhythmias, and other adverse outcomes, including mortality.

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KEY WORDS biomarkers, cardiac magnetic resonance, fibrosis, hypertrophic cardiomyopathy, late gadolinium enhancement

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.