Distinct Subgroups in Hypertrophic Cardiomyopathy:

Baseline Results from HCMR (NHLBI HCM Registry)

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Abstract

Background: The Hypertrophic Cardiomyopathy Registry (HCMR) is an NHLBI-funded, prospective registry of 2755 patients with HCM recruited from 44 sites in 6 countries.

Objectives: HCMR was designed to improve risk prediction in HCM by incorporating cardiovascular 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 (ECV) as a measure of interstitial fibrosis. Blood was drawn for biomarker (N-terminal pro brain natriuretic peptide, NTproBNP and high sensitivity troponin T, cTnT) and genetic analysis.

Results: A total of 2755 patients were studied. Mean age was 49±11 years, 71% were male, and 17% non-white. Mean ESC risk score was 2.48±0.56. Twenty four % had a resting left ventricular outflow tract (LVOT) gradient ≥30mmHg. Thirty six percent had a sarcomere mutation identified. Fifty percent had any LGE, which was more common and extensive in patients who were sarcomere mutation (+), had reverse septal curvature morphology and no significant resting LVOT obstruction. Those without LGE were more likely sarcomere mutation (-), had isolated basal septal hypertrophy, and more LVOT obstruction. Interstitial fibrosis was present in segments both with and without LGE. Serum NTproBNP and cTnT levels correlated with increasing LGE and ECV in a graded fashion.

Conclusions: The HCMR population has characteristics of mild-to-moderate risk HCM. Baseline data separated patients broadly into 2 categories. One group was sarcomere mutation (+), more likely had reverse septal curvature morphology, more fibrosis, but less resting

obstruction whereas the other was sarcomere mutation (-), 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 of these markers.

Condensed Abstract

HCMR is a prospective registry of 2755 hypertrophic cardiomyopathy patients from 44 sites in 6 countries. Patients underwent cardiovascular magnetic resonance including cine imaging, late gadolinium enhancement imaging (LGE), and T1 mapping for measurement of extracellular volume and had blood drawn for biomarkers and genetics. Patients with sarcomere mutations more commonly had LGE and reverse septal curvature morphology but less resting outflow obstruction. Serum biomarkers correlated with the extent of LGE and ECV. Further follow-up will allow development of a useful risk prediction model incorporating these markers.

Key Words

Hypertrophic cardiomyopathy
Cardiovascular magnetic resonance
Biomarkers
Fibrosis
Late gadolinium enhancement

Abbreviations

HCM – hypertrophic cardiomyopathy
CMR – cardiovascular magnetic resonance
LGE – late gadolinium enhancement

ECV – extracellular volume

NTproBNP – N-terminal pro-brain natriuretic peptide

cTnT – high sensitivity troponin T

LVOT – left ventricular outflow tract

Introduction

The Hypertrophic Cardiomyopathy Registry (HCMR) is a prospective NHLBI-funded registry of 2755 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 cardiovascular 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 utilization of implantable-cardioverter defibrillators (ICD's).(4,5) In addition, models have not yet been developed to predict other key adverse outcomes such as incident heart failure or atrial fibrillation.

Previous large cohorts of HCM patients were gathered retrospectively and/or from one 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=1739), but also includes other non-ischemic 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 LV mass. A meta-analysis of nearly 3000 patients from several studies demonstrated that the presence of LGE was associated with a 3.4 fold increased risk of SCD/ICD discharge and 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 (ACCF)/American Heart Association (AHA) risk stratification, along with apical aneurysm morphology and multiple runs of 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 2755 patients with HCM are presented in the present manuscript.

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, 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 ages 18-65 with an established diagnosis of HCM defined as unexplained LVH (wall thickness >15cm) without cavity dilatation or known predisposing cause (uncontrolled hypertension, aortic stenosis, etc.)(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 were excluded as 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 CAD 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 U.S. (18), Canada (4), United Kingdom (13), Italy (4), Germany (3), and the Netherlands (2) between April, 2014 and April, 2017 **(Supplemental 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 implantation. 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 risk score was calculated using baseline clinical and echocardiographic data(3). ACCF/AHA risk score was calculated based on presence

or absence of 3 major risk factors (family history of SCD, history of syncope, and maximal wall thickness>30mm.(2)

CMR methods

CMR was performed at 1.5 or 3 Tesla (T) on MR systems from the 3 primary vendors (General Electric, Philips Medical Systems, Siemens Healthineers) using a standardized protocol and multi-channel channel phased-array chest coils and electrocardiographic (ECG) gating. After rapid localization of the heart, short axis cine steady state free precession imaging (SSFP) was performed covering the whole heart in 8mm thick slices (no gap). Typical cine SSFP parameters included TR/TE 3.1/1.2 msec, in-plane resolution of 2-2.5 mm, temporal resolution of 40-50 msec. 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 minutes post-contrast. LGE imaging was acquired in the same long axis and short-axis stack locations beginning at minute 17 post-contrast with a 2D 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 minutes.

CMR Image Analysis

Commercially available software (MedisSuite 3.0 and QMassMR, Medis Inc., Leiden, NL) 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 SCMR standards.(14) Cine images in short-axis contiguous cuts were evaluated for LV and RV 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, i.e. 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 bi-plane area-length method, at end-ventricular systole, before atrial contraction, and end-ventricular diastole.(17)

Quantification of LGE was performed according to SCMR standards(14) using both the 6 S.D. quantitative threshold as well as visually.(18) LGE was categorized as none, >0-5%, >5-10%, >10-15% and >15% of LV mass. T1 quantification was performed on a segmental basis by non-linear least-squares fitting of the segmental inversion recovery curves, resulting in multiple T1 measurements (one 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 R1's 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 (http://snpeff.sourceforge.net) 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 minutes 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, IN) TnT STAT Gen 5 assay to assess for myocardial injury (19,20). The analytical measurement range (AMR) for the assay is 6-10000 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 1893 ng/L. The N-terminal fragment of the propeptide of B-type natriuretic peptide (NT-proBNP) was measured using the Roche proBNP II assay to assess hemodynamic or myocardial wall stress. AMR of the assay is 5-35,000 pg/mL and total imprecision of the assay was 2.5% at both 138 pg/mL and 4578 pg/mL.

Data Management and Statistical Analysis

Clinical data were entered in an on-line data management system. Upon entry, data underwent a series of range and quality checks. Summary statistics for continuous variables include mean ± standard deviation, median and interquartile range and minimum and maximum values. When data were non-normally distributed, the nonparametric Wilcoxon rank-sum test was used to compare independent groups, otherwise t-tests were used. Categorical variables are summarized by number and percent of valid (non-missing) values and analyzed by contingency table analysis (chi-square). Where multiple comparisons were made, Bonferroni corrections were used to control Type I error rate. Association of baseline demographic and clinical variables with presence of LGE (yes/no) and elevated cTnT (defined by gender) was assessed with logistic regression. Baseline arrhythmias were defined as a history of nonsustained ventricular tachycardia and/or atrial fibrillation. Model fit was assessed by the Hosmer-Lemeshow goodness-of-fit test. Multiple linear regression was used to assess the association of demographic and clinical variables with ECV, NTproBNP and maximal wall thickness. Normality of ECV, NTproBNP and maximal wall thickness was assessed with the Kolmogorov-Smirnov test, and if not normally distributed, transformed as appropriate for analysis. Model fit was assessed by analysis of residuals for normality. The association of morphology categories with demographic and clinical variables was assessed by contingency table analysis (chi-square) for categorical variables and one-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.(20) Statistical testing was performed with Stata, v15 (Stata Corp., College Station, TX) and StatXact 7 (Cytel, Inc., Cambridge, MA).

Results

Baseline Demographics

Number of patients enrolled at each site is shown in **Supplemental Table 1**. Of 2762 patients initially enrolled, 1362 were enrolled in North America and 1400 in Europe. Seven patients were subsequently excluded as they were demonstrated to be phenocopies genetically and not have HCM, leaving 2755 for analysis. Baseline demographic and clinical information are shown in **Table 1**.

Echocardiography

Mean maximal wall thickness was 18.6±4.8 mm. Sixty-four % of participants had resting LV outflow tract obstruction with mean gradient 27±32 mm Hg. Fifty-nine % had mitral regurgitation and 12% were graded as moderate or severe. Mean pulmonary artery pressure was 28±11 mm Hg. Maximum left atrial dimension was 4.2±0.8 cm.

Holter Monitoring and Exercise Testing

Among 1672 patients who had undergone clinically-performed 24 hour Holter monitoring, AF was seen in 4% and nonsustained ventricular tachycardia in 12%. The 1520 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 20mm Hg.

HCM Risk Scores

The mean ESC risk score (3) was 2.48±0.56 and the mean ACCF/AHA risk score was 0.38±0.57, suggesting that the study group is, on average, at low-intermediate risk. Sixty six % had no ACCF/AHA risk factors, 29% had 1, 5% had 2, and 1 patient had 3.

CMR Cine Data

A total of 2651 patients completed the CMR as 38 (1.4%) had studies aborted due to claustrophobia and 52 (2%) for other reasons. The contrast dose used was 0.15 mM/kg (mean 20±9 ml). The rhythm at the time of the CMR was normal sinus in 93%, atrial fibrillation in 2 % and other, e.g. PVC's, bigeminy, etc., in 5%. LV and RV structure and function results derived from SSFP cine CMR images are shown in **Table 2** and examples are shown in **Figure 1**.

There were 2628 studies available for morphologic evaluation with the remaining 36 incomplete for morphologic assessment. 1197 (46%) had isolated basal septal hypertrophy, 1059 (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, had thicker walls, less hypertension, lower EF, and less LVOT obstruction as compared to those with isolated basal septal curvature.

Maximal LV wall thickness of any segment was 20.6±4.8 mm. Results of multivariable linear regression of maximal LV wall thickness (natural logarithm transformation) are presented in **Supplemental Table 2**. Weak, but significant correlations with wall thickness were found with age (r=-0.16), BMI (r=0.10), male gender (r=0.11), LVOT gradient≥30 mm Hg (r = 0.20), and sarcomere mutation (+) (r=0.16). 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.

Myocardial fibrosis

Of 2755 patients, 254 (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 standard deviation 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). and the ACCF/AHA risk score was higher than those without LGE (0.41±0.60 vs. 0.35±0.55, p <0.02). Only 2% of patients (n=46) had LGE>15% of LV mass. Morphologic correlates of LGE are shown in **Table 4**. A high percentage 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.

Logistic regression analysis for the presence of LGE is shown in **Table 5**. Male gender, maximal wall thickness, LVEF, baseline arrhythmias, and sarcomere mutation (+) were all significantly associated with LGE presence adjusted for other variables in the model. Male patients were nearly 1.5 times more likely to have LGE present. Patients with LVEF < 55% were nearly 1.4 times more likely to have LGE present. Patients with baseline arrhythmias were over 2 times more likely to have LGE present and those with a sarcomere mutation were 3.5 times more likely to have LGE present than those without. For every category of LGE, there was a stepwise fall in LVEF, although mean LVEF remained in the normal range even in the higher categories of LGE. Maximal wall thickness was weakly correlated with LGE (r=0.16, p<0.001). For every 1 mm increase in wall thickness, LGE as % of LV mass increased by 1%.

There were 2082 patients (76%) with analyzable native T1 and 2013 (73%) valid ECV measures. Mean native T1 of the entire LV myocardium was 972±74 at 1.5T and 1170±84 at 3T.

Native T1 in segments without LGE was 969±74 at 1.5T and 1157±86 at 3.0T compared to 976±74 at 1.5T and 1179±81 at 3T ($p<0.001$ 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 females than males ($p<0.001$) 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 those without (0.28±0.04, $p<0.001$). There was a weak, but significant relationship noted between LGE and ECV ($R^2=0.015$, $p<0.001$. Mean ECV was greater in females (0.31±0.04) than in males (0.29±0.04, $p<0.001$). For comparison purposes, ECV in normal volunteers ranges between 0.25-0.28 and tends to rise with age and be higher in females (21,22). Patients with higher ECV had smaller BMI, were more likely female, had greater wall thickness, lower ejection fraction, more baseline arrhythmias, and were more likely to have a sarcomere mutation (**Table 6)**. Maximal wall thickness correlated weakly to ECV ($r=0.11$, $p<0.001$). When evaluated by morphology, ECV was lowest in isolated basal septal hypertrophy compared to reverse septal curvature, apical and mid-cavity obstruction subtypes (**Supplemental Table 3).** ECV index, a measure of mass of interstitium, was 49.2±20.2g.

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 two 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 all subsequent phenotypic analyses. In 12.3% (n=325) of individuals, "variants of uncertain significance (VUS)" were detected in the sarcomere genes. See **Supplemental Material** for the approach to VUS. Using this approach, based on gene-specific interpretations, we dichotomized the HCMR cohort into individuals carrying a sarcomere variant, i.e. 'sarcomere mutation positive' (n=943; 35.8%) and those who did not, i.e. 'sarcomere mutation negative' (n=1693; 64.2%). Using this dichotomous criterion, just under 1% of probands carried 2 sarcomere variants (and none more than 2).

Those who were sarcomere mutation (+) were younger, had a lower BMI, more often female and white, had a family history of HCM, and had less hypertension, **Table 7,** consistent with prior findings.(23) However, they also were less likely to have a significant LVOT gradient which may, in part, reflect differences in morphology as more of the sarcomere mutation (+) demonstrated reverse curvature asymmetric septal hypertrophy (58.1%) relative to isolated basal septal hypertrophy (33.8%), ratios that were reversed in the sarcomere mutation (-) group (30.7% and 51.8%, respectively), $p<0.0001$. In addition, fewer sarcomere mutation (+) 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 was similar (2.6% vs. 3.2%). LVEF was similar between groups. Sarcomere mutation (+) patients were much more likely to have any LGE as well as more extensive LGE **(Table 8).** Native T1 was higher at 1.5T in sarcomere mutation (+) individuals (978±76 vs. 968±74, $p<0.02$), but similar at 3T (1175±89 and 1167±81, respectively, $p=0.21$), likely due to lower n at 3T and thus lower power.

ECV was higher in sarcomere mutation (+) patients (0.30±0.04) than in sarcomere mutation (-) patients (0.29±0.05, p<0.001).

Biomarkers

NTproBNP and cTnT were obtained in 2,665 (97%) of the 2,755 patients in the HCMR analysis database. **Supplemental Table 4** presents data from a multivariable regression of demographic and clinical data and log transformed NTproBNP. Increasing age was associated with increasing NTproBNP. Females had higher values than males as expected, obese patients had lower levels, and patients with baseline arrhythmias had higher levels. Patients with a resting LVOT gradient ≥30mm Hg and those with a reduced LVEF had higher values. NTproBNP levels increased as maximal wall thickness increased. The relationship between NTproBNP and categories of LGE is presented in **Figure 2 (Left panel)**. A similar relationship was seen with increasing ECV (by quartile). **(Supplemental Figure 1)** NTproBNP was significantly higher in sarcomere mutation (+) than (-) individuals (594±842 vs. 520±1073, p < 0.001).

Normal values for cTnT for males were ≤ 22 ng/L and ≤14 ng/L for females (per Roche Diagnostics Corporation). Of the 2665 patients with valid values, 282 males (15%) and 186 females (24%) had elevated cTnT. **Supplemental Table 5** presents data from a logistic regression of demographic and imaging data and cTnT, abnormal vs. normal. Males were less likely to have abnormal cTnT levels. Those with a history of hypertension were 1.5 times more likely to have abnormal cTnT levels and those with LVEF<55% were over 2.5 times more likely to have abnormal values. Minorities were nearly 2 times more likely to have abnormal values as were patients with baseline arrhythmias. As maximal wall thickness increased, the odds of abnormal cTnT increased by 11%. The relationship between cTnT and categories of LGE is presented in **Figure 2 (Right panel)**. In both genders, 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 males. **(Supplemental Figure 2)** The incidence of elevated cTnT was similar in sarcomere mutation (+) and (-) groups (18% and 17%, respectively). NTproBNP was higher in sarcomere (+) than (-) groups (594±842 vs. 520±1073, respectively, $p<0.001$).

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 2755 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. A quarter of patients had a LVOT gradient ≥30mm 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. Based on ESC and ACCF/AHA risk scores, the patient group is of low-intermediate risk.

The major contribution of the present study lies in the CMR, genetic, and biomarker findings and their inter-relationships in this population. Two relatively distinct populations were identified in HCMR. **(Central Illustration)** One was sarcomere mutation (+), and more likely to demonstrate reverse septal curvature morphology, have more extensive LGE, but less resting LVOT obstruction. The second group was sarcomere mutation (-), 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(24), as evidenced by the higher burden of causes of secondary LVH (hypertension, high BMI, male sex, and older age, etc.). 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 were more likely male, had thicker walls, had more baseline arrhythmias, and were more likely to be sarcomere mutation (+), 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.(25) The ESC and ACCF/AHA risk scores increases modestly with any LGE compared to 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 (+). They represented most of the cases of >10% LGE, providing further data for a link between genetics, morphology, and fibrosis. Interestingly, there was more LGE in patients without resting LVOT obstruction. This is consistent with findings in other smaller cohorts(26) and is likely due to the fact that more of the LGE was seen in reverse septal curvature subtype which in turn, has less LVOT obstruction due to the location of maximal hypertrophy. Follow-up will test whether

this morphologic subtype with its link to sarcomere mutation positivity and increased fibrosis is a risk factor for outcome events. The other morphologic subgroup with extensive LGE was the midcavity obstruction with apical aneurysm subtype, which has been shown to be associated with higher risk and improves upon ACCF/AHA risk stratification.(11,27)

In the HCMR cohort, there was evidence of interstitial fibrosis indicated by the elevated mean ECV when compared to 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 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 females.

The 2 biomarkers that were measured were both elevated in subsets of patients in this cohort. NTproBNP was elevated subsets with resting LVOT gradient≥30mm Hg, reduced LVEF, more baseline arrhythmias, and sarcomere mutation (+). CTnT was higher in minorities and patients with hypertension, 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 NTproBNP.(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. Since 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.

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. While 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 to intermediate-risk HCM by ESC risk score. These patients have predominantly septal hypertrophy, two thirds have evidence of resting LVOT obstruction,with a mean gradient of 27 mm Hg, , and about half have LGE. Over a third are sarcomere mutation (+). 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 (+) and more likely had reverse septal curvature morphology, more fibrosis, and less resting obstruction whereas the other was sarcomere mutation (-), 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 mild-to-moderate risk HCM.

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Clinical Perspective

Competency in Medical Knowledge: Two relatively distinct populations in HCM were identified. One group was sarcomere mutation (+) and more likely had reverse septal curvature morphology, more fibrosis, and less resting obstruction whereas the other was sarcomere mutation (-), and more likely had isolated basal septal hypertrophy with resting obstruction and less fibrosis.

Translational Outlook

Data from the Hypertrophic Cardiomyopathy Registry will enable creation of a patient-specific risk profile incorporating demographic, echocardiographic, CMR, genetic, and biomarker risk markers to predict subsequent risk of sudden cardiac death, heart failure, and atrial fibrillation.

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Figure Legends

Central Illustration – The overall design and findings of HCMR are shown here. 2755 patients from 44 sites in 6 countries were recruited. Two relatively distinct populations were identified as depicted in the slide. Left – 4 chamber inversion recovery gradient echo 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.

Figure 1. Steady state free precession 4-chamber long axis cine images from individual patients with the 6 different morphologic subtypes of HCM. The six subtypes shown are: 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

Figure 2. Relationship of biomarkers to increasing amounts of late gadolinium enhancement (LGE). N-terminal pro-brain natriuretic peptide (NTproBNP) and high sensitivity troponin T (cTnT) were measured in each patient as was the extent of LGE as a % of left ventricular mass on cardiac magnetic resonance imaging. Left – Median NTproBNP showing increasing levels relative to patients with increasing amounts of LGE ($P<0.001$ for trend). Right

– similar trend shown for cTnT (separated by gender due to different normal values) with $p<0.001$ for trend for both.

Table 1. Baseline characteristics of patients enrolled in HCMR.

Variable	Summary statistic	Valid n (%)
Age (years)	49 ± 11	2738 (99.4)
Male gender	1953 (71.3)	2740 (99.5)
Race / Ethnicity		2737 (99.3)
White	2311 (84.4)	
Black	204 (7.4)	
Asian	205 (7.5)	
Other	18 (0.7)	
Hispanic	60 (2.2)	2739 (99.4)
BMI (kg/m^2)	29.3 ± 5.7	2726 (98.9)
Family history of HCM		2722 (98.9)
1st degree	600 (22.0)	
2nd degree	84 (3.1)	
Both 1^{st} and 2^{nd}	228 (8.4)	
Comorbidities		
Hypertension	997 (36.6)	2726 (99.0)
Type II diabetes mellitus	213 (7.8)	2726 (99.0)
Current smoker	387 (14.2)	2724 (98.9)
NYHA		2692 (97.7)
Class I	1792 (66.6)	
Class II	706 (26.2)	
Class III/IV	194 (7.2)	
Other clinical history		
Syncope	361 (13.2)	2726 (98.9)
Heart failure	142 (5.2)	2733 (98.9)
Stroke	76 (2.8)	2733 (98.9)
Nonsustained ventricular tachycardia Number of runs	196 (12.0) 3.2 ± 12.1	1633 (59.3)
Atrial fibrillation		2723 (98.8)
Persistent	77 (2.8)	
Paroxysmal	244 (9.0)	
Symptoms at enrollment		
Chest pain	893 (32.8)	2726 (98.9)
Dyspnea	1184 (43.4)	2726 (98.9)
Medications at enrollment		
Beta blocker	1547 (57.0)	2714 (98.5)
Calcium channel blocker	508 (18.7)	2714 (98.5)
ACE/ARB	644 (23.7)	2714 (98.5)

Disopyramide	84 (3.1)	2714 (98.5)
Statins	741 (27.3)	2714 (98.5)
Diuretic	314 (11.6)	2714 (98.5)
Oral anticoagulant	251 (9.2)	2714 (98.5)
Oral antiplatelet agent	431 (15.8)	2714 (98.5)

Summary statistics are mean ± 1 standard deviation for continuous variables; n (%) for categorical variables.
Summary statistics based on non-missing values (Valid n) of total analyzed: 2755

Table 2. LV and RV volumetric results.

Variable	**Mean ± SD**
LV mass (g)	
Males	185±61
Females	142±50
LV mass index (g/m^2)	
Males	89±27
Females	77±25
Maximal wall thickness (mm)	20.6±4.8
LV end diastolic volume (ml)	171±41
LV end diastolic volume index	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

Table 3. Demographic differences amongst HCM morphologies.

	Isolated basal septal	Reverse curvature	Apical	Concentric	Apical aneurysm	Other	Overall p value
Variable	N=1199	N=1063	N=224	N=36	N=79	N=33	
Age (years)	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 ≥ 30mm Hg	279 (30.4)	164 (20.8) ‡†	7 (5.1) ‡	8 (33.3) †	13 (23.6) †	2 (7.4)	< 0.001
Arrythmias	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

Data are mean ± 1 standard deviation for continuous variables; n (%) for categorical variables.
Percentages based on non-missing values.
Comparison p values within morphology categories adjusted with Bonferroni correction ($p \leq 0.0033$ for significance).

*p<0.05 vs. reverse curvature
†p<0.05 vs. apical
^p<0.05 vs. apical aneurysm
§p<0.05 vs. other
‡p<0.05 vs. isolated basal septal

Table 4. LGE amount by HCM morphology.

	No LGE N=1265	**<5%** N=990	**5-10%** N=182	**10-15%** N=54	**>15%** N=46
Morphology					
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%)

Table 5. Logistic regression results for the presence of LGE.

Variables	**Odds Ratio**	**95% CI**	**p value**
Age (10 yr increments)	1.047	0.942 – 1.164	0.395
BMI (5 kg/m^2)	0.895	0.809 – 0.989	0.029
Male	1.469	1.158 – 1.864	0.002
Minority	0.806	0.594 – 1.093	0.166
Family history of HCM	0.997	0.764 – 1.250	0.855
LVOT gradient ≥30mm Hg	0.799	0.620 – 1.030	0.084
Maximal wall thickness	1.131	1.102 – 1.161	< 0.001
Arrhythmias	2.159	1.641 – 2.841	< 0.001
Hypertension	0.930	0.733 – 1.182	0.555
LVEF < 55%	1.333	0.974 – 1.823	0.073
Sarcomere mutation +	3.458	2.691 – 4.443	< 0.001

Table 6. Multivariable regression results for log transformed ECV.

Variable	Regression Coefficient	95% CI	Correlation	p value
Age (10 yr increments)	0.007	0.001 : 0.015	0.050	0.090
BMI (5 kg/m^2)	-0.016	-0.023 : -0.008	-0.112	< 0.001
Male	-0.069	-0.068 : -0.051	-0.206	< 0.001
Minority	0.007	-0.016 : 0.029	0.015	0.567
Family history of HCM	0.010	-0.009 : 0.028	0.029	0.314
LVOT gradient ≥30mm Hg	0.010	-0.009 : 0.029	0.028	0.311
Maximal wall thickness	0.004	0.002 : 0.005	0.105	< 0.001
Arrhythmias	0.040	0.020 : 0.060	0.060	< 0.001
Hypertension	0.002	-0.016 : 0.020	0.007	0.823
LVEF < 55%	0.030	0.006 : 0.054	0.066	0.014
Sarcomere mutation +	0.029	0.010 – 0.048	0.091	0.002

Table 7. Demographic and clinical differences by genetic category.

Variable	Sarcomere mutation (+) % (n)	Sarcomere mutation (-) % (n)	p value
Age (years)	46.2 ± 12.0	51.3 ± 10.4	< 0.001
BMI (kg/m^2)	28.2 ± 5.4	29.8 ± 5.6	< 0.001
Male	65.1 (611)	75.3 (1260)	< 0.001
Minority	28.4 (116)	37.4 (823)	0.001
Family history of HCM	54.7 (511)	22.3 (371)	< 0.001
LVOT gradient ≥30mm Hg	19.0 (130)	26.8 (335)	< 0.001
Arrhythmias	38.1 (185)	35.4 (749)	0.255
Hypertension	21.3 (199)	45.1 (752)	< 0.001
LVEF < 55%	14.2 (126)	14.2 (227)	0.983

Table 8. LGE categories by sarcomere mutation status.

Category (n)	**Sarcomere mutation (+) N (%)**	**Sarcomere mutation (-)**
No LGE (1213)	264 (30.1)	949 (60.3)
>0–5% (965)	458 (52.2)	507 (32.2)
>5–10% (177)	101 (11.5)	76 (4.8)
>10–15% (53)	33 (3.8)	20 (1.3)
>15% (45)	22 (2.5)	23 (1.5)

LGE categories were not equally distributed for sarcomere + and - groups ($p < 0.001$).