Supplemental Material

A Novel Patient-Patient Network Medicine Approach to Refine Hypertrophic Cardiomyopathy Subgrouping: Implications for Risk Stratification

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Methods

Data cleaning and imputation. In the original cohort, there were 3,412 patients and 53 variables. We then conducted a missingness analysis **(Supplemental Figure 1)**. We removed variables with very large (>20%) missingness (N=1 variable, echocardiographic right ventricular systolic pressure), and then identified 3,059 patients that had <5 missing variables. Among these patients, we focused on 2,430 patients for which the variables 'age at diagnosis' and 'lung disease' were available (as these variables had the overall second and third largest missingness rate). The remaining variables (N=52), which were included in further analyses, had <10% missing entries. Imputations were performed by replacing the missing entries with the mean of the corresponding variables. From this approach, we obtained a study cohort with 2,430 patients and 52 variables.

Patient stratification and analysis of module # 15. To divide the network into smaller sizes of modules, i.e. subgroups, we used a modularity optimization approach called the Louvain Community Detection Algorithm implemented in a python package NetworkX. This approach used a fast heuristic method to optimize a modularity function, which leads to a natural network decomposition.

Statistical methods: For categorical variables, data are presented as N (%). For continuous variables, data are presented as mean ± SD and median [IQR] when distributed normally and non-normally, respectively. Comparisons between modules involving categorical variables was performed using the Chi-square analysis. For some analyses involving module #15, multivariable linear regression was performed using module assignment as the response variable and all the 52 variables as predictor variables. Only variables from the model that were also associated with a

statistical difference or trend toward difference between module #15 vs. the comparator group when analyzed by Student t-test are reported here to avoid emphasizing false-positive findings. For Student t-test analyses involving systolic blood pressure, diastolic blood pressure, and left atrial size, N=2 outliers (>2SD from the mean) were removed from module #15. $P<0.05$ was considered significant.

Supplemental Table 1. Categorical variables that were included in the patient-patient network.

Variable name	Value
Sex	0=Female, 1=Male
Reason leading to diagnosis (choice=Symptoms/ Event)	0=No, 1=Yes
Reason leading to diagnosis (choice=Family Screening)	0=No, 1=Yes
Reason leading to diagnosis (choice=Routine ECG)	0=No, 1=Yes
Reason leading to diagnosis (choice=Murmur)	0=No, 1=Yes
Reason leading to diagnosis (choice=Other)	0=No, 1=Yes
Family history of SCD secondary to HCM	0=No, 1=Yes
NSVT on ambulatory Holter monitoring	0=No, 1=Yes
Apical aneurysm	0=No, 1=Yes
Symptoms at first visit: Dyspnea	0=No, 1=Yes
Symptoms at first visit: Chest pain	0=No, 1=Yes
Symptoms at first visit: Fatigue	0=No, 1=Yes
Symptoms at first visit: Presyncope	0=No, 1=Yes
Symptoms at first visit: Palpitations	0=No, 1=Yes
Atrial fibrillation prior to first visit	0=No, 1=Yes
Out of hospital Cardiac arrest prior to first visit	0=No, 1=Yes
Appropriate ICD shocks for VT/VF prior to first visit	0=No, 1=Yes
Hypertension	0=No, 1=Yes
Hyperlipidemia	0=No, 1=Yes
Chronic kidney disease	0=No, 1=Yes
Diabetes mellitus	0=No, 1=Yes
Thyroid disease	0=No, 1=Yes
Obstructive sleep apnea	0=No, 1=Yes
Lung disease	0=No, 1=Yes
Family history of HCM	0=No, 1=Yes
Family history of end stage HCM	0=No, 1=Yes
Family history of heart transplant due to HCM	0=No, 1=Yes
SAM	0=No, 1=Yes
Severe aortic stenosis	0=No, 1=Yes
Apical HCM	0=No, 1=Yes
End-stage HCM	0=No, 1=Yes
Stress echocardiogram performed in patient evaluation	0=No, 1=Yes

ECG, electrocardiogram; SCD, sudden cardiac death; HCM, hypertrophic cardiomyopathy; NSVT, non-sustained ventricular tachycardia; ICD, implantable cardioverter defibrillator; VF, ventricular fibrillation; SAM, systolic anterior motion of the mitral valve.

Supplemental Table 2. Established Clinical Risk Factors for HCM Sudden Death Risk Stratification

Risk Factor	
Prior History of cardiac arrest or sustained VT	>30 seconds of ventricular tachycardia
Family history of sudden death from HCM	Sudden death judged definitively or likely due to HCM in ≥ 1 first or close relative ≤50 years of age
Massive LV hypertrophy	chamber by echocardiography and/or CMR; consideration for this morphologic marker is also given to borderline values of ≥28 mm in individual patients at the discretion of the treating cardiologist. For pediatric HCM patients a maximal LV wall thickness with Z-score ≥6 may be considered a risk factor.
Syncope	One or more unexplained episodes involving acute transient loss of consciousness, judged by history unlikely to be of neurocardiogenic (vasovagal) etiology with greatest weight as a risk marker occurring within 6 months of evaluation with more remote syncope less relevant
HCM with systolic dysfunction	Systolic dysfunction with ejection fraction ≤50% by echocardiography or CMR, usually in potential transplant candidates without outflow obstruction.
LV apical aneurysm	Apical aneurysm formation independent of size
Extensive LGE on CMR	A linear relationship is present between LGE and SCD risk. Diffuse and extensive LGE, either quantified or estimated by visual inspection, comprising ≥ 15% of LV mass is associated with significant increase in SCD risk.
NSVT on ambulatory monitor	≥3 consecutive ventricular beats at ≥120 bpm for <30 seconds on at least 24 hours of ambulatory monitoring. In adult patients, it would seem most appropriate to place greater weight on NSVT as a risk marker when runs are frequent (≥3), longer (≥10 beats) and faster (200 bpm) occurring usually over 24-48 hours of monitoring.

CMR, cardiovascular magnetic resonance; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; NSVT, non-sustained ventricular tachycardia; SCD, sudden cardiac death; HCM, hypertrophic cardiomyopathy.