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ORIGINAL RESEARCH

Gene-Tiered Interpretation of Sarcomere VUS Refines Risk Stratification in Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND The clinical significance of sarcomere variants of uncertain significance (VUS) in hypertrophic cardiomyopathy (HCM) remains unclear. Despite their increasing prevalence, VUS are often regarded as clinically nonactionable.

OBJECTIVES The authors evaluated genotype-phenotype and genotype-outcome associations by variant pathogenicity, focusing on gene-tiered sarcomere VUS in an Asian HCM cohort.

METHODS We retrospectively analyzed 438 Korean patients with HCM undergoing targeted genetic testing. Patients were categorized by sarcomere variant status: no sarcomere variant, VUS in genes with limited evidence (nondef9), VUS in genes with definitive HCM evidence (def9), and pathogenic or likely pathogenic (P/LP) in the sarcomere panel. We compared clinical and imaging phenotypes, and a composite endpoint of major adverse cardiovascular events, using Firth-penalized Cox models.

RESULTS P/LP variants were identified in 163 of 438 patients (37.2%), and def9 and nondef9 VUS in 83 (18.9%) and 85 (19.4%) patients, respectively. def9 VUS carriers exhibited intermediate phenotypic and prognostic features between P/LP and genotype-negative patients, whereas nondef9 VUS carriers clinically resembled genotype-negative HCM. During a median follow-up of 6.4 years (IQR: 2.7-10.7 years), the primary endpoint occurred in 29 of 438 patients (6.6%). Modeled as an ordinal variable across these 4 groups, the classification showed a stepwise increase in risk of the primary endpoint (HR: 1.62; 95% CI: 1.08-2.63; $P = 0.019$), which was unchanged after adjustment for family history of HCM and maximum left ventricular wall thickness.

CONCLUSIONS Sarcomere VUS do not represent a homogeneous category. Gene-tier stratification may refine variant interpretation and clinical management in HCM, particularly in populations under-represented in current variant databases. (JACC Asia. 2026;■:■-■) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACMG = American College of Medical Genetics and Genomics

CMR = cardiac magnetic resonance

CV = cardiovascular

HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter-defibrillator

IEV = intermediate-effect variant

IRB = institutional review board

LV = left ventricular

LVOT = left ventricular outflow tract

NGS = next-generation sequencing

nondef9 = nondefinitive 9

P/LP = pathogenic or likely pathogenic

SCD = sudden cardiac death

VT = ventricular tachycardia

VUS = variant of uncertain significance

Hypertrophic cardiomyopathy (HCM) is one of the most common inherited heart disorders, with an estimated prevalence of approximately 0.2% to 0.5% in the general population.[1,2] Given the associated risk of sudden cardiac death (SCD), particularly in young individuals,[3] genetic testing and family screening have become integral components of HCM management. Current clinical guidelines recommend genetic testing to facilitate cascade screening of relatives and to support the differential diagnosis of unexplained cardiac hypertrophy.[4,5]

Despite the widespread implementation of genetic testing in HCM, the clinical interpretation of sarcomere variants remains challenging, particularly for variants of uncertain significance (VUS). Pathogenic or likely pathogenic (P/LP) variants are considered causative for HCM, whereas VUS lack sufficient evidence to support pathogenicity and therefore remain clinically nonactionable in current practice.[4,6-8] However, data from a large multicenter registry suggested that patients carrying sarcomere VUS exhibit an intermediate risk of adverse outcomes between those with pathogenic sarcomere variants and genotype-negative HCM, raising questions regarding the clinical neutrality of VUS.[9] Reports indicating that a small portion of sarcomere VUS can be reclassified as P/LP over time further complicate the clinical application of VUS results.[10-12]

Furthermore, the rapid expansion of multigene sequencing panels has substantially increased the absolute number of reported VUS.[13,14] The diagnostic uncertainty is particularly pronounced in the Asian population, because current major genomic reference databases are predominantly derived from populations of European ancestry. Asian patients with HCM experience a disproportionately high rate of VUS classification, which severely complicates their clinical management.[15,16] Therefore, a more refined assessment of genotype-phenotype and genotype-outcome associations across variant classifications is needed to bridge the gap between genetic testing and clinical decision-making, specifically for Asian patients carrying VUS.

Accordingly, we sought to determine in a large Korean HCM cohort whether sarcomere VUS represents a phenotypically and prognostically distinct subgroup of HCM rather than a clinically neutral genetic category, by comparing clinical characteristics and outcomes across 4 groups (ie, no sarcomere variant, VUS in genes with limited evidence, VUS in genes with definitive HCM evidence, and P/LP in the sarcomere panel).

METHODS

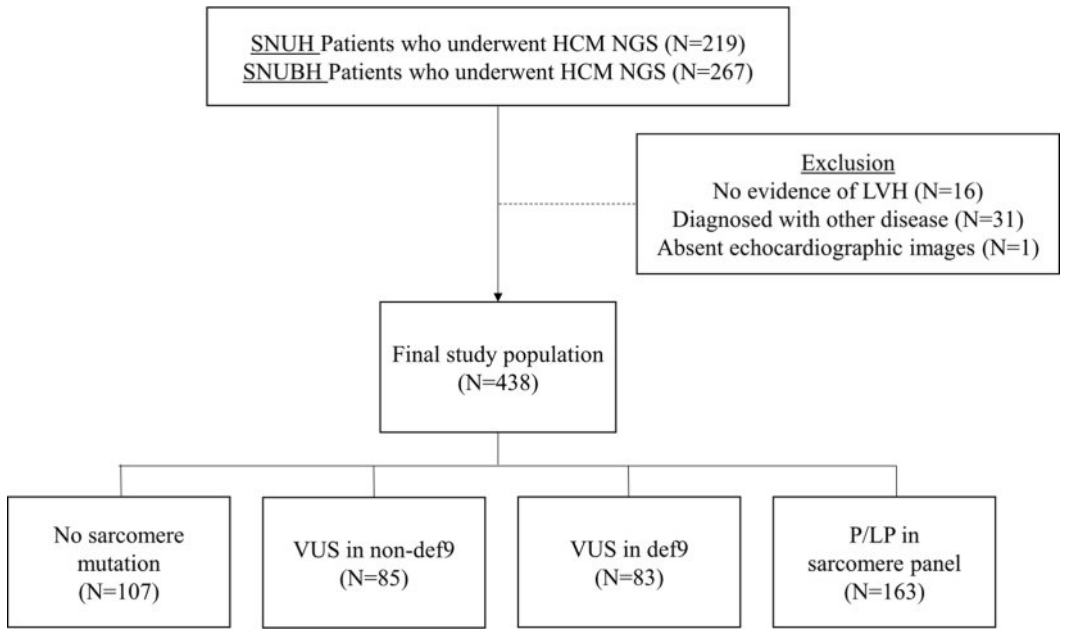
STUDY POPULATION. This multicenter retrospective cohort study included patients with a final diagnosis of HCM who underwent next-generation sequencing (NGS)-based genetic testing for diagnostic evaluation in probands at 2 tertiary referral hospitals. In our routine practice, cascade testing in relatives was performed by targeted Sanger sequencing of the proband-identified variant, not by an NGS panel. As a result, relatives are systematically underrepresented in this NGS panel-based cohort. Among 438 patients, 431 (98.4%) were probands, and 7 (1.6%) were relatives.

HCM was diagnosed based on unexplained left ventricular (LV) hypertrophy, defined by maximal end-diastolic wall thickness ≥15 mm at any LV segment (or ≥13 mm in individuals with a family history of HCM), as assessed by transthoracic echocardiography or cardiac magnetic resonance (CMR), in the absence of other cardiac or systemic conditions capable of causing LV hypertrophy.[4,17,18] All 438 patients (100%) underwent echocardiography at the time of initial diagnosis, whereas CMR was performed in 382 patients (87.2%) at various time points during follow-up according to clinical indication. To avoid temporal bias across the cohort, baseline phenotype assessment in this study relied on the initial transthoracic echocardiogram.

Patients who did not meet diagnostic criteria for HCM on imaging, those diagnosed with HCM phenocopies (including Anderson-Fabry disease, glycogen storage disease, and transthyretin cardiac amyloidosis), and those without available echocardiographic data were excluded. The final study population comprised 438 patients aged ≥15 years at the time of genetic testing: 195 patients from Seoul National University Hospital and 243 patients from Seoul National University Bundang Hospital (**Figure 1**). Clinical follow-up was conducted at the discretion of the attending physician, with clinical assessment, electrocardiography, and transthoracic echocardiography at intervals adjusted to clinical symptoms, signs, and SCD risk.

DATA COLLECTION. Clinical data, including demographic characteristics, established predictors of SCD, diagnostic test results, and outcome-related records, were obtained from electronic health records. The risk of SCD was estimated using the HCM risk-SCD score model, which incorporates age, family

FIGURE 1 Study Population Flow of Patient Selection



Of 486 patients undergoing next-generation sequencing (NGS)-based genetic testing, 48 were excluded because of hypertrophic cardiomyopathy (HCM) phenocopies, absence of left ventricular hypertrophy, or lack of adequate echocardiography, leaving 438 patients classified into 4 analytical groups. P/LP = pathogenic or likely pathogenic; SCD = sudden cardiac death; VUS = variant of uncertain significance.

history of SCD, maximal LV wall thickness, left atrial diameter, maximal LV outflow tract (LVOT) gradient, nonsustained ventricular tachycardia (VT), and unexplained syncope.[19] Echocardiographic parameters were collected to assess phenotypic differences according to genetic status. Echocardiography and CMR images, along with clinical and genetic data were reviewed in a blinded fashion to classify HCM phenotypes.

The study protocol was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB no. J-2602-013-1713) and Seoul National University Bundang Hospital (IRB no. B-2004-604-409), with a waiver of written informed consent because of the retrospective study design. All analyses were conducted in accordance with the principles of the Declaration of Helsinki. This observational study follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[20]

ENDPOINTS. The primary endpoint was HCM-related major events, which comprised of cardiovascular (CV) death, aborted SCD, appropriate implantable cardioverter-defibrillator (ICD) shock, and heart transplantation. The SCD-equivalent composite outcome included fatal SCD, aborted SCD, and appropriate ICD shock. CV death was defined as death resulting from acute myocardial infarction, SCD, heart failure, stroke, CV procedures, CV hemorrhage, and other CV causes.[21] Aborted SCD was defined as survival following sudden cardiac arrest due to documented ventricular fibrillation or sustained VT requiring external defibrillation or cardiopulmonary resuscitation. ICD therapies delivered for ventricular fibrillation or sustained VT were considered appropriate.[19] Antitachycardia pacing was not considered appropriate ICD therapy.[22] Clinical events were ascertained from the time of the first HCM diagnosis to the date of the last follow-up or the occurrence of the primary endpoint, whichever came first.

GENE TESTING. Genetic testing was performed in patients with a confirmed or suspected diagnosis of HCM, at the discretion of the attending physicians with patients' consent. NGS-based panels targeting HCM-associated genes were used, and the genes included in each panel are listed in Supplemental Table 1. Variants identified in 23 genes encoding sarcomere structural components were included in the analysis, whereas variants in genes associated

with HCM phenocopies or nonsarcomere cardiomyopathies were excluded (Supplemental Table 2). To minimize the heterogeneous effect of VUS across genes with different levels of gene-disease validity, we have anchored the gene-tier definition to the recent ClinGen Hereditary Cardiovascular Disease Gene Curation Expert Panel recuration.[23] This framework classifies 9 sarcomere genes (*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL2, MYL3, ACTC1,* and *TNNC1*) as having definitive evidence for autosomal dominant HCM ("sarcomere-positive HCM" category; def9 genes). The remaining 14 genes in the panel, with limited, disputed, or non-HCM-specific evidence, comprise the nondefinitive 9 (nondef9) genes.

The pathogenicity of detected variants was evaluated according to the 2015 American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology guidelines with application of the ClinGen Cardiomyopathy Expert Panel gene-specific specifications.[24,25] Variant interpretation included assessment of gene-specific evidence supporting HCM causality, including population allele frequencies, in silico predictive data, functional studies, and available segregation data. Based on this evaluation, variants were classified as P/LP, VUS, or benign/likely benign by laboratory medicine physicians. Two centralized variant review steps were performed for this study. First, all sarcomere variants from patients enrolled through December 2022 were reviewed and harmonized using the ClinVar consensus and ACMG/Association for Molecular Pathology criteria. Second, in May 2026, all sarcomere variants with discordant classification across the laboratories were rereviewed and finalized to a concordant call.

Patients were divided into 4 groups for the analysis: 1) no sarcomere variant group (genotype-negative; no P/LP or VUS in the 23 sarcomere genes); 2) nondef9 VUS group, comprising patients with VUS in nondef9 genes in the absence of any P/LP variant (VUS_nondef9); 3) def9 VUS group, comprising patients with VUS in def9 genes in the absence of any P/LP variant (VUS_def9); and 4) P/LP group, comprising patients carrying at least 1 P/LP variant.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or median with IQR, as appropriate, and categorical variables as n (%). Baseline characteristics were compared across sarcomere variant classifications using one-way analysis of variance or the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Pairwise comparisons among the 4 groups were performed only when the overall test was significant, using Welch's 2-sample Student's *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. All pairwise *P* values were adjusted by the Holm method.

Time-to-event outcomes were analyzed using Kaplan-Meier survival curves, with between-group differences assessed using the log-rank test. Cox proportional hazards regression models with Firth's penalized partial likelihood approach were used to estimate HRs and profile likelihood-based 95% CIs, given the limited number of outcome events and the potential for small-sample bias.[26] Multivariable Cox models were adjusted for age and sex and stratified by institution. Morphologic subtype, maximal wall thickness, LVOT obstruction, SCD-related factors, and comorbidities were not included in the adjusted models because these variables were considered potential downstream manifestations of genotype.[10,27] The proportional hazards assumption was assessed using Schoenfeld residuals and was not violated.

Sarcomere variant classification was first modeled as a 4-group categorical variable, with the genotype-negative group as the reference, to estimate the risk of each group separately. It was then analyzed as an ordinal variable coded 0 to 3 (genotype-negative, VUS_nondef9, VUS_def9, and P/LP), an order prespecified to reflect increasing evidence for pathogenicity, so that a single HR per step captured whether risk increased across the gradient.

Three additional sensitivity analyses were performed: 1) a proband-only analysis (N = 431) excluding the 7 relatives to verify independence of observations; 2) the primary ordinal Cox model rerun with adjustment for family history of HCM and maximum LV wall thickness to assess confounding by baseline phenotype severity and, in the subset with available CMR (N = 376), with adjustment for the presence of late gadolinium enhancement; and 3) a sensitivity analysis accounting for competing risks. For competing risk analysis, cumulative incidence functions were estimated and compared by Gray's test, and the ordinal association was re-estimated using Fine-Gray subdistribution hazard models, treating death (and heart transplantation for the SCD-equivalent endpoint) as competing events. A stratified comparison of truncating vs missense variants was performed within P/LP carriers to assess whether the outcome differed by variant mechanism.

Statistical significance was defined using a 2-sided *P* value <0.05. All analyses were performed using R, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

BASELINE CHARACTERISTICS. Baseline clinical characteristics of 438 patients are summarized in Table 1. The mean age at the time of genetic testing was 56.3 ± 14.2 years, and 298 of 438 patients (68.0%) were men. A family history of HCM was present in 24 of 438 patients (5.5%), and 60 of 438 patients (13.7%) had a family history of SCD. Septal HCM was the most common morphologic subtype (44.7%, 196 of 438), followed by apical HCM (22.4%, 98 of 438). The mean maximal LV wall thickness was 19.1 ± 4.2 mm, and LVOT obstruction was present in 90 of 438 patients (20.5%). The mean LV ejection fraction was 64.0 ± 7.2%. Left atrial enlargement was common, with a mean left atrial diameter of 43.2 ± 7.6 mm and a left atrial volume index of 46.6 ± 19.6 mL/m^2. Normal diastolic function was observed in 25.8% of patients (113 of 438).

P/LP sarcomere gene variants were identified in 163 of 438 patients (37.2%), and clinically insignificant sarcomere gene variants (benign or likely benign) or no sarcomere variants were observed in 107 of 438 patients (24.4%). VUS in def9 and nondef9 were identified in 83 and 85 of 438 patients (18.9% and 19.4%), respectively.

Among P/LP carriers (N = 163), variants were most frequently identified in *MYBPC3* (78 patients, 47.9%), followed by *MYH7* (50 patients, 30.7%) (Supplemental Table 3). Three patients carried 2 P/LP variants in different sarcomere genes, and 2 patients carried 2 distinct P/LP variants in *MYBPC3*. The most frequently identified P/LP variant was *TNNI3* c.434 G > A (p.Arg145Gln), which was present in 20 patients.

A total of 385 unique sarcomere variants were identified across the cohort, with full available annotations provided in Supplemental Table 4. The majority of the 80 unique def9 VUS (80.0%, 64/80) were absent from the Genome Aggregation Database, indicating that def9 VUS in this cohort were overwhelmingly rare variants. In titin and obscurin, the 2 largest nondef9 genes by variant count, missense variants predominated (87.4% [104 of 119] and 86.4% [38 of 44], respectively). Consistent with the known gene-specific disease mechanisms in HCM, all P/LP variants in *MYH7* were missense, whereas the majority of *MYBPC3* variants were truncating variants.

BASELINE CHARACTERISTICS BY SARCOMERE VARIANT CLASSIFICATION. Baseline characteristics differed significantly according to sarcomere variant classification (Table 2). Patients with P/LP variants

TABLE 1 Baseline Characteristics

Variables	N (%) or Mean ± SD	Missing (%)
Age at the time of genetic testing	56.3 ± 14.2	0 (0)
Institution		0 (0)
SNUBH	243 (55.5)	
SNUH	195 (44.5)	
Male	298 (68.0)	0 (0)
Morphologic subtype of HCM		0 (0)
Septal	196 (44.7)	
Apical	98 (22.4)	
Diffuse	61 (13.9)	
Mixed	68 (15.5)	
Others/atypical	15 (3.4)	
Family history of HCM	24 (5.5)	0 (0)
SCD-related factors		
Family history of SCD	60 (13.7)	0 (0)
Nonsustained VT	111 (25.3)	0 (0)
Syncope	43 (9.8)	0 (0)
Maximal LV wall thickness ≥30 mm	12 (2.8)	2 (0.5)
HCM risk-SCD score	2.1 (1.4-3.5)	2 (0.5)
ICD implantation	71 (16.2)	0 (0)
Comorbidity		
Diabetes mellitus	52 (11.9)	0 (0)
Hypertension	176 (40.2)	0 (0)
Chronic kidney disease	10 (2.3)	0 (0)
End-stage kidney disease	2 (0.5)	0 (0)
Atrial fibrillation	38 (8.7)	0 (0)
Prior history of PCI	2 (0.5)	0 (0)
Prior history of stroke	28 (6.4)	0 (0)
Echocardiography		
Maximal LV wall thickness, mm	19.1 ± 4.2	2 (0.5)
Maximal LVOT pressure gradient, mm Hg	6.6 (3.5-19.9)	0 (0)
LVOT obstruction	90 (20.5)	0 (0)
LV end-diastolic diameter, mm	45.6 ± 5.4	2 (0.5)
LV end-systolic diameter, mm	27.8 ± 5.0	3 (0.7)
LV ejection fraction, %	64.0 ± 7.2	2 (0.5)
E, m/s	0.6 (0.5-0.8)	2 (0.5)
A, m/s	0.6 (0.5-0.8)	28 (6.4)
E/e'	13.7 ± 5.7	3 (0.7)
LV GLS (absolute value)	14.1 ± 4.6	144 (32.9)
LA diameter, mm	43.2 ± 7.6	2 (0.5)
LAVI, mL/m^2	46.6 ± 19.6	35 (8)
Diastolic function		0 (0)
Normal diastolic function	113 (25.8)	
Grade 1 (abnormal relaxation)	202 (46.1)	
Grade 2 (pseudonormal pattern)	99 (22.6)	
Grade 3 (restrictive filling pattern)	14 (3.2)	
Absence of A wave	10 (2.3)	
Diastolic dysfunction ≥2	113 (25.8)	0 (0)
PASP, mm Hg	31.6 ± 7.5	163 (37.2)

A = late diastolic mitral inflow velocity; E = early diastolic mitral inflow velocity; E/e' = ratio of early diastolic mitral inflow velocity to mitral annular early diastolic velocity; GLS = global longitudinal strain; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LA = left atrial; LAVI = left atrial volume index; LV = left ventricular; LVOT = left ventricular outflow tract; PASP = pulmonary artery systolic pressure; PCI = percutaneous coronary intervention; SCD = sudden cardiac death; SNUH = Seoul National University Hospital; SNUBH = Seoul National University Bundang Hospital; VT = ventricular tachycardia.

TABLE 2 Baseline Characteristics Stratified by Sarcomere Variant Classification

Variable	No Sarcomere Variant (n = 107)	VUS in Nondef9 (n = 85)	VUS in def9 (n = 83)	P/LP in Sarcomere Panel (n = 163)	*P* Value	Pairwise Comparisons (Holm P < 0.05)
Age at the time of genetic testing	59.8 ± 12.8	61.3 ± 12.2	55.0 ± 14.1	52.2 ± 14.7	<0.001	Vn vs P/LP (<0.001), Neg vs P/LP (<0.001), Vn vs Vd (0.009), Neg vs Vd (0.048)
Male	81 (75.7)	62 (72.9)	61 (73.5)	94 (57.7)	0.005	Neg vs P/LP (0.022)
Institution, n (% within institution)					<0.001	
SNUBH (n = 243)	83 (34.2)	30 (12.3)	43 (17.7)	87 (35.8)		
SNUH (n = 195)	24 (12.3)	55 (28.2)	40 (20.5)	76 (39.0)		
Per-group p (SNUBH vs SNUH)[a]	<0.001	<0.001	0.532	0.560		
Morphologic subtype of HCM					<0.001	
Septal	34 (31.8)	32 (37.6)	41 (49.4)	89 (54.6)		
Apical	35 (32.7)	29 (34.1)	13 (15.7)	21 (12.9)		
Diffuse	21 (19.6)	14 (16.5)	9 (10.8)	17 (10.4)		
Mixed	16 (15.0)	8 (9.4)	13 (15.7)	31 (19.0)		
Others/atypical	1 (0.9)	2 (2.4)	7 (8.4)	5 (3.1)		
Family history of HCM	2 (1.9)	1 (1.2)	4 (4.8)	17 (10.4)	0.005	Neg vs P/LP (0.040), Vn vs P/LP (0.040)
SCD-related factors						
Family history of SCD	16 (15.0)	7 (8.2)	10 (12.0)	27 (16.6)	0.307	
Nonsustained VT	15 (14.0)	19 (22.4)	20 (24.1)	57 (35.0)	0.001	Neg vs P/LP (0.001)
Syncope	9 (8.4)	10 (11.8)	7 (8.4)	17 (10.4)	0.837	
Maximal LV wall thickness ≥30 mm	0 (0.0)	1 (1.2)	3 (3.7)	8 (4.9)	0.047	
HCM risk-SCD score	1.9 (1.3-2.8)	2.0 (1.3-2.6)	2.1 (1.5-3.7)	2.7 (1.7-4.3)	<0.001	Neg vs P/LP (<0.001), Vn vs P/LP (0.005), Neg vs Vd (0.036), Vd vs P/LP (0.036)
ICD implantation	11 (10.3)	6 (7.1)	11 (13.3)	43 (26.4)	<0.001	Vn vs P/LP (0.003), Neg vs P/LP (0.010)
Comorbidities						
Diabetes mellitus	18 (16.8)	13 (15.3)	7 (8.4)	14 (8.6)	0.108	
Hypertension	56 (52.3)	39 (45.9)	32 (38.6)	49 (30.1)	0.002	Neg vs P/LP (0.002)
Chronic kidney disease	3 (2.8)	2 (2.4)	3 (3.6)	2 (1.2)	0.775	
End stage kidney disease	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.6)	0.823	
Atrial fibrillation	7 (6.5)	7 (8.2)	9 (10.8)	15 (9.2)	0.757	
Prior history of PCI	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.13	
Prior history of stroke	15 (14.0)	4 (4.7)	2 (2.4)	7 (4.3)	0.007	Neg vs Vd (0.029), Neg vs P/LP (0.043)
Echocardiographic parameters						
Maximal LV wall thickness, mm	18.3 ± 3.3	17.8 ± 3.6	19.3 ± 4.4	20.2 ± 4.6	<0.001	Vn vs P/LP (<0.001), Neg vs P/LP (<0.001)
Maximal LVOT pressure gradient, mm Hg	6.8 (2.7-18.5)	7.0 (4.7-16.0)	4.8 (2.6-11.7)	6.8 (3.7-29.0)	0.688	
LVOT obstruction	22 (20.6)	17 (20.0)	12 (14.5)	39 (23.9)	0.385	
LV end-diastolic diameter, mm	46.6 ± 5.1	47.3 ± 5.5	45.7 ± 4.9	44.0 ± 5.5	<0.001	Vn vs P/LP (<0.001), Neg vs P/LP (<0.001)
LV end-systolic diameter, mm	28.6 ± 4.7	28.2 ± 4.5	28.2 ± 4.9	26.9 ± 5.3	0.024	Neg vs P/LP (0.032)
LV ejection fraction, %	64.8 ± 6.5	64.7 ± 6.2	63.4 ± 6.3	63.5 ± 8.3	0.333	
E, m/s	0.6 (0.5-0.7)	0.6 (0.5-0.8)	0.6 (0.5-0.7)	0.6 (0.5-0.8)	0.816	
A, m/s	0.7 (0.6-0.8)	0.7 (0.5-0.8)	0.6 (0.5-0.7)	0.6 (0.4-0.8)	<0.001	
E/e'	13.1 ± 5.2	14.3 ± 5.9	12.7 ± 5.2	14.1 ± 6.0	0.146	
LV GLS (absolute value)	13.7 ± 4.1	14.6 ± 4.5	13.9 ± 4.5	14.0 ± 5.0	0.721	
LA diameter, mm	42.1 ± 6.3	44.0 ± 8.3	43.5 ± 7.8	43.3 ± 7.9	0.339	
LAVI, mL/m^2	43.3 ± 13.9	46.2 ± 18.7	46.6 ± 20.4	49.1 ± 22.5	0.151	
Diastolic function					0.028	
Normal diastolic function	23 (21.5)	20 (23.5)	27 (32.5)	43 (26.4)		
Grade 1	63 (58.9)	39 (45.9)	38 (45.8)	62 (38.0)		
Grade 2	16 (15.0)	22 (25.9)	15 (18.1)	46 (28.2)		

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TABLE 2 Continued

Variable	No Sarcomere Variant (n = 107)	VUS in Nondef9 (n = 85)	VUS in def9 (n = 83)	P/LP in Sarcomere Panel (n = 163)	*P* Value	Pairwise Comparisons (Holm P < 0.05)
Grade 3	2 (1.9)	3 (3.5)	0 (0.0)	9 (5.5)		
Absence of A wave	3 (2.8)	1 (1.2)	3 (3.6)	3 (1.8)		
Diastolic dysfunction ≥2	18 (16.8)	25 (29.4)	15 (18.1)	55 (33.7)	0.005	Neg vs P/LP (0.021)
PASP, mm Hg	30.3 ± 7.4	32.8 ± 7.3	31.0 ± 7.9	32.2 ± 7.4	0.22	

Continuous variables are presented as mean ± SD; categorical variables as n (%). Overall *P*-values are from Kruskal-Wallis (continuous) or chi-square (categorical) tests across the 4 groups. The right-hand column lists pairwise comparisons with Holm-adjusted $P < 0.05$ (Neg = No sarcomere variant; Vn = VUS in nondef9; Vd = VUS in def9; PLP = P/LP in sarcomere panel). [a]The institutional distribution is reported as within-institution percentages (rows sum to 100% across the 4 genetic groups). The overall distribution differed between institutions (chi-square, $P < 0.001$), driven by differences in the proportions of patients without any detectable sarcomere variant (SNUBH 34.2% vs SNUH 12.3%; $P < 0.001$) and VUS in nondef9 (SNUBH 12.3% vs SNUH 28.2%; $P < 0.001$), both consistent with the broader gene panel used at SNUH. The proportions of VUS in def9 (SNUBH 17.7% vs SNUH 20.5%; $P = 0.532$) and P/LP in the sarcomere panel (SNUBH 35.8% vs SNUH 39.0%; $P = 0.560$) were institution-invariant.

VUS = variants of uncertain significance. Other abbreviations are defined in the footnote of Table 1.

and VUS in def9 were younger at the time of genetic testing compared with those carrying VUS in nondef9 or no variants (52.2 ± 14.7, 55.0 ± 14.1, 61.3 ± 12.2, and 59.8 ± 12.8 years, respectively; $P < 0.001$) and were less likely to be male. The distribution of sarcomere genetic status was significantly different across the institution, especially in patients with VUS in nondef9 or no sarcomere variant. Phenotypes characterized by septal hypertrophy, including septal and mixed forms, predominated among patients with P/LP sarcomere variants or def9 VUS, accounting for approximately 70% of cases. In contrast, apical or diffuse HCM was more frequently observed in patients with nondef9 VUS or without sarcomere gene variants.

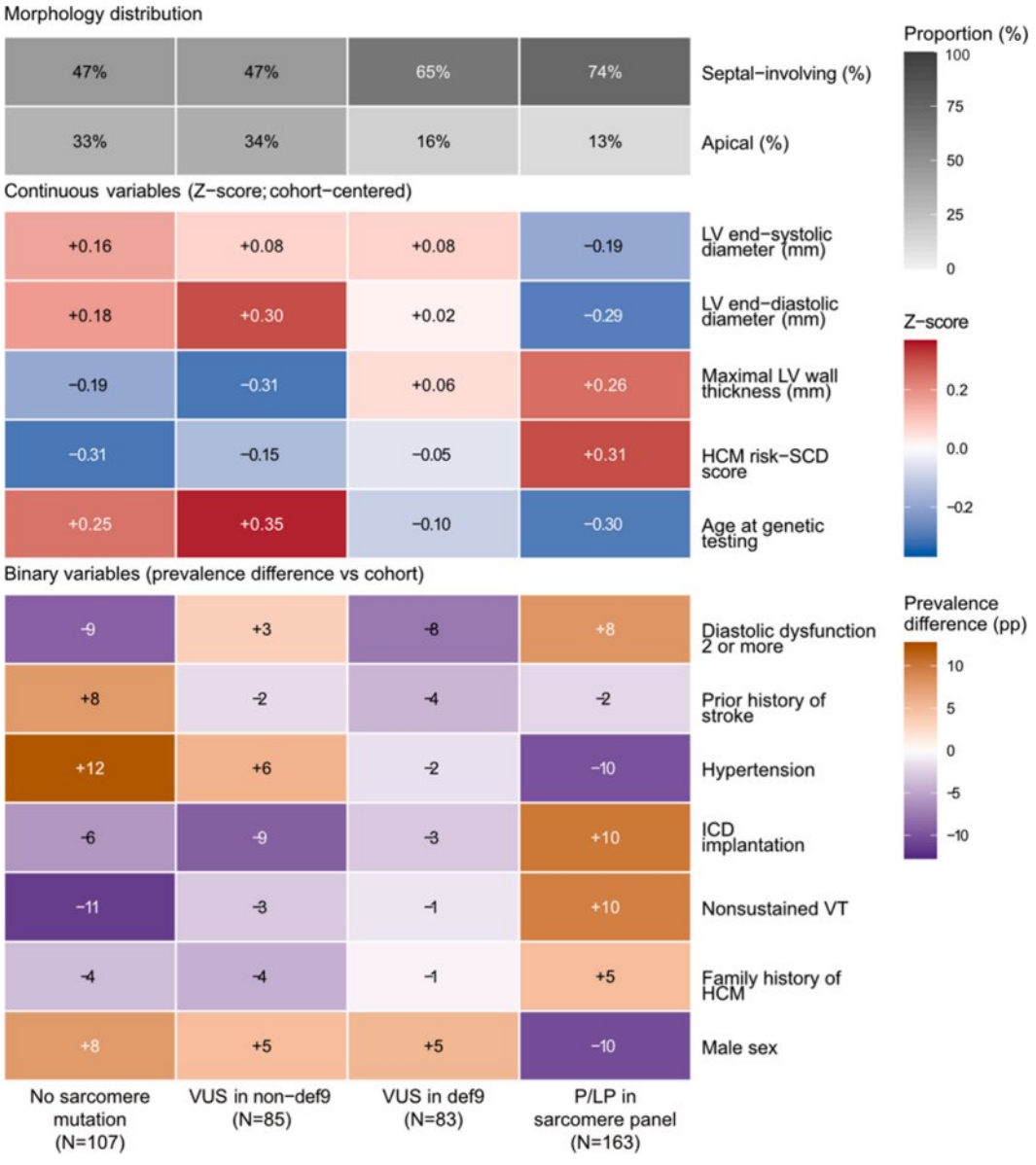
Patients with P/LP variants had a higher prevalence of nonsustained VT compared with those without sarcomere variants, which was associated with a higher rate of ICD implantation. Notably, HCM Risk-SCD scores showed significant differences among patients with P/LP, def9-VUS, and those without a sarcomere variant. In addition, patients carrying P/LP variants showed greater maximal LV wall thickness and smaller LV end-diastolic dimensions than those with nondef9 VUS and without a sarcomere variant. Figure 2 illustrates phenotypic heterogeneity according to sarcomere variant classification, highlighting the intermediate clinical profiles of patients harboring def9 VUS.

CLINICAL OUTCOMES ACCORDING TO SARCOMERE GENETIC STATUS. During a median follow-up duration of 6.4 years (IQR: 2.7-10.7 years), the primary endpoint occurred in 29 of 438 patients (6.6%), including 19 events that occurred among carriers of P/LP sarcomere variants. The SCD-equivalent composite outcome developed in 24 of 438 patients (5.5%), of whom 15 were P/LP variant carriers. The median follow-up duration was 4.9 (1.5-8.5) years in patients without sarcomere variants, 7.2 (3.6-12.3) years and 6.6 (2.7-12.4) years in those with nondef9 and def9 VUS, respectively, and 5.7 (2.7-9.9) years in those with P/LP variants. The incidence of the primary endpoint and SCD-equivalent composite outcome was significantly higher in patients with P/LP sarcomere variants compared with those without sarcomere variants ($P = 0.003$ and 0.018, respectively; Table 3).

Kaplan-Meier analysis showed a significant difference in event-free survival across sarcomere variant classifications for the primary endpoint and the SCD-equivalent endpoint (log-rank $P = 0.006$ and 0.024, respectively) (Figure 3). The 10-year cumulative incidence of the primary endpoint rose across the 4 groups, from 2.8% (95% CI: 0.0-8.0) in patients without sarcomere variants to 17.6% (8.3-26.0) in P/LP carriers (Table 3). Among the individual components of these 2 endpoints, aborted SCD occurred more frequently in patients with P/LP sarcomere gene variants, whereas no statistically significant differences were observed for the other components (Table 3).

To further quantify the association between sarcomere genetic status and clinical outcomes, multivariable Firth-penalized Cox proportional hazards models were constructed. After adjustment for age and sex and stratification by institution, P/LP variants were independently associated with an increased risk of the primary endpoint when modeled as separate variables compared with no sarcomere variant (HR: 4.55; 95% CI: 1.09-42.03; $P = 0.035$), whereas def9 and nondef9 VUS were not (Table 4). When sarcomere variant classification was modeled as an ordinal variable reflecting increasing pathogenic potential (no sarcomere variant → nondef9 VUS → def9 VUS → P/LP variants), a significant dose-response relationship was observed, with a progressively higher risk of the primary endpoint across the

FIGURE 2 **Standardized Heatmap of Clinical and Echocardiographic Features by Genetic Group**



Standardized clinical and morphological characteristics across the 4 analytical groups. Top (greyscale): Proportions of apical and septal-involving hypertrophic cardiomyopathy (HCM) morphology. Middle (red-blue, anchored at 0): Group means of patient-level *Z*-scores for continuous variables (centered and scaled across n = 438). Bottom (purple-orange, anchored at 0): Within-group prevalence minus cohort prevalence for binary variables, in percentage points. Continuous and binary use distinct diverging palettes (red-blue and purple-orange, respectively) so that *Z*-score and prevalence-point magnitudes are visually separable. Variables shown were significant at $P < 0.05$ in Table 2 univariate comparisons. ICD = implantable cardioverter-defibrillator; LV = left ventricular; other abbreviations as in Figure 1.

4 genetic groups (HR: 1.62; 95% CI: 1.08-2.63; $P = 0.019$) (Table 4).

SENSITIVITY ANALYSIS AND SUBGROUP ANALYSIS. The first sensitivity analysis, excluding the 7 relatives (N = 431), showed an ordinal HR per group step of 1.61 (95% CI: 1.07-2.61; $P = 0.020$), consistent with the primary analysis (Supplemental Table 5, Supplemental Figure 1). The second sensitivity analysis, adjusting for family history of HCM and maximum LV wall thickness, showed that the ordinal HR remained 1.62 (95% CI: 1.07-2.64; $P = 0.021$), indicating that the

TABLE 3 Outcomes Stratified by Sarcomere Variant Classification

Outcome	No Sarcomere Variant (n = 107)	VUS in Nondef9 (n = 85)	VUS in def9 (n = 83)	P/LP in Sarcomere Panel (n = 163)	*P* Value	Pairwise Comparisons (Holm $P < 0.05$)
HCM-related major events						
Crude incidence	1 (0.9)	3 (3.5)	6 (7.2)	19 (11.7)	0.003	Neg vs P/LP (0.003)
Kaplan-Meier estimates (95% CI)						
5-y	0.0% (0.0-0.0)	2.9% (0.0-6.8)	4.4% (0-9.3)	7.2% (2.7-11.5)	0.006 (log-rank)	
10-y	2.8% (0.0-8.0)	2.9% (0.0-6.8)	8.6% (0.8-15.8)	17.6% (8.3-26.0)		
SCD-equivalent composite outcome						
Crude incidence	1 (0.9)	3 (3.5)	5 (6.0)	15 (9.2)	0.018	Neg vs P/LP (0.021)
Kaplan-Meier estimates (95% CI)						
5-y	0.0% (0.0-0.0)	2.9% (0.0-6.8)	4.4% (0-9.3)	5.9% (1.7-9.9)	0.024 (log-rank)	
10-y	2.8% (0.0-8.0)	2.9% (0.0-6.8)	6.4% (0.0-12.5)	15.1% (6.1-23.3)		
Individual components of the 2 endpoints						
Cardiovascular death	0 (0.0)	2 (2.4)	1 (1.2)	4 (2.5)	0.395	
Fatal SCD	0 (0.0)	2 (2.4)	0 (0.0)	3 (1.8)	0.268	
Aborted SCD	1 (0.9)	0 (0.0)	2 (2.4)	9 (5.5)	0.042	
Appropriate ICD shock	0 (0.0)	1 (1.2)	3 (3.6)	4 (2.5)	0.201	
Heart transplantation	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0.318	
Other endpoints						
All-cause death	0 (0.0)	5 (5.9)	5 (6.0)	6 (3.7)	0.030	
Myectomy	2 (1.9)	5 (5.9)	4 (4.8)	9 (5.5)	0.462	
HF admission	7 (6.5)	4 (4.7)	5 (6.0)	14 (8.6)	0.755	

Categorical outcomes are presented as n (%). Overall *P* values are from Fisher exact test across the 4 groups. Kaplan-Meier estimates are cumulative incidences at 5 and 10 y (1 − survival), accounting for censoring, with 95% CIs. The accompanying *P* value is from the log-rank test for the overall between-group comparison across the entire follow-up, not for a specific landmark. The right-hand column lists pairwise comparisons with Holm-adjusted $P < 0.05$ among the 4 genetic groups; group abbreviations are as defined in Table 2.

HF = heart failure. Other abbreviations are defined in the footnotes of Tables 1 and 2.

genotype-stratified risk gradient was not explained by baseline phenotype severity. In the subset with available CMR (N = 376), the ordinal association remained unchanged after adjustment for the presence of late gadolinium enhancement (adjusted HR: 1.61; 95% CI: 1.07-2.59; $P = 0.020$), which was not itself associated with the endpoint.

The stepwise increase in risk persisted in a competing-risk sensitivity analysis. The cumulative incidence of each endpoint differed across the 4 groups (Gray's test $P = 0.006$ and 0.025 for the primary and SCD-equivalent endpoints, respectively), whereas competing events did not differ across groups ($P = 0.16$ and 0.25). Fine-Gray subdistribution hazard models were consistent with the primary cause-specific analyses (subdistribution HR per step, 2.05 [95% CI: 1.35-3.11] for the primary endpoint and 1.92 [1.24-2.98] for the SCD-equivalent endpoint).

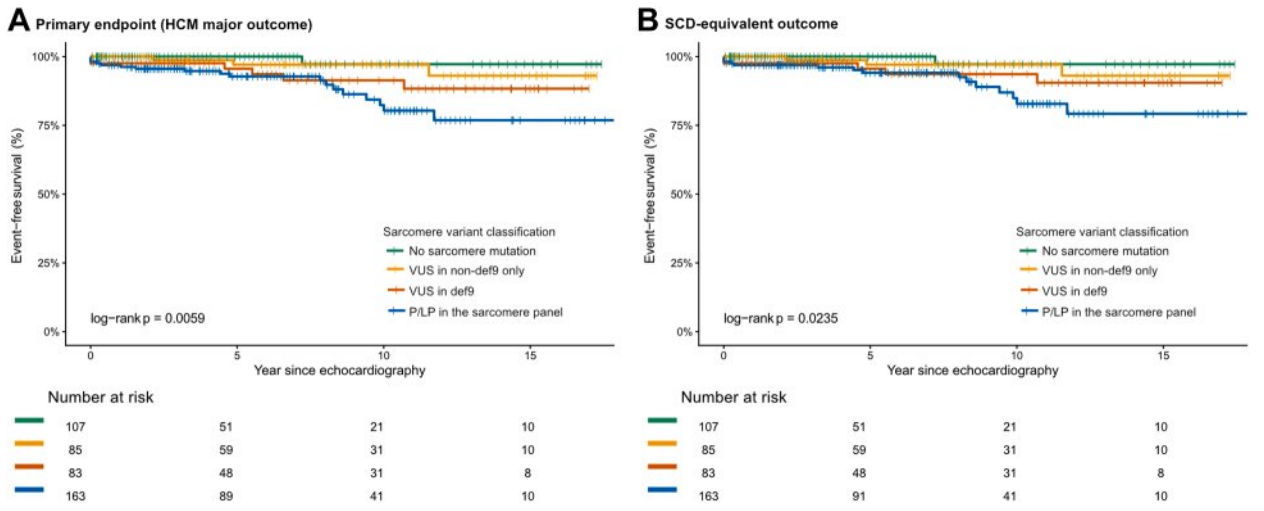
In the subgroup analysis restricted to P/LP carriers, truncating and missense variants demonstrated similar risk for the primary outcome (log-rank $P = 0.82$; Firth-penalized Cox HR: 1.02; 95% CI: 0.38-2.57; $P = 0.96$; Supplemental Figure 2).

DISCUSSION

In this multicenter cohort of Asian patients with HCM, we observed distinct differences in baseline characteristics, cardiac phenotype, and clinical outcomes according to sarcomere variant classification. Patients carrying P/LP variants in the sarcomere panel exhibited the highest risk profile, whereas carriers of VUS in the def9 genes demonstrated intermediate phenotypic and clinical features between P/LP carriers and patients without sarcomere variants. In contrast, carriers of VUS in nondef9 genes showed clinical profiles closely resembling those of genotype-negative patients. An ordinal Cox model revealed a graded risk gradient across these 4 groups, with an HR of 1.62 per group step (95% CI: 1.08-2.63; $P = 0.019$), and this gradient remained unchanged after adjustment for family history of HCM and maximum LV wall thickness. These findings indicate that sarcomere VUS do not represent a homogeneous or clinically neutral category and underscore the need for a more nuanced interpretation of variant classification to guide risk stratification, particularly in Asian HCM populations where variant interpretation faces persistent ancestral data gaps (**Central Illustration**).

The clinical implications of VUS have been increasingly investigated in patients with HCM. Ho et al[9] demonstrated that patients carrying sarcomere VUS exhibit an intermediate phenotype, characterized by earlier disease onset and worse clinical outcomes compared with genotype-negative patients.

FIGURE 3 Kaplan-Meier Curves by Sarcomere Genetic Status



Cumulative event-free survival from the primary endpoint (hypertrophic cardiomyopathy [HCM]-related major events) and sudden cardiac death (SCD)-equivalent outcome stratified by the 4-group genetic classification (no sarcomere variant, variant of uncertain significance [VUS] in nondef9 sarcomere genes, VUS in def9 sarcomere genes, and pathogenic or likely pathogenic [P/LP] in the sarcomere). Differences between groups were assessed using the log-rank test. (A) HCM-related major events are a composite of cardiovascular death, aborted sudden cardiac death, appropriate implantable cardioverter-defibrillator shock, and heart transplantation. (B) SCD-equivalent composite outcome includes SCD, aborted SCD, and appropriate implantable cardioverter-defibrillator (ICD) shock.

This finding from a large-scale registry with long-term follow-up suggests that a subset of VUS may confer pathogenic potential despite not meeting the stringent criteria of ACMG guidelines. However, the reproducibility of this observation across independent cohorts and the mechanisms by which VUS contribute to phenotypic and prognostic heterogeneity in HCM remain incompletely understood. Moreover, expanding NGS panels makes VUS interpretation increasingly complex.

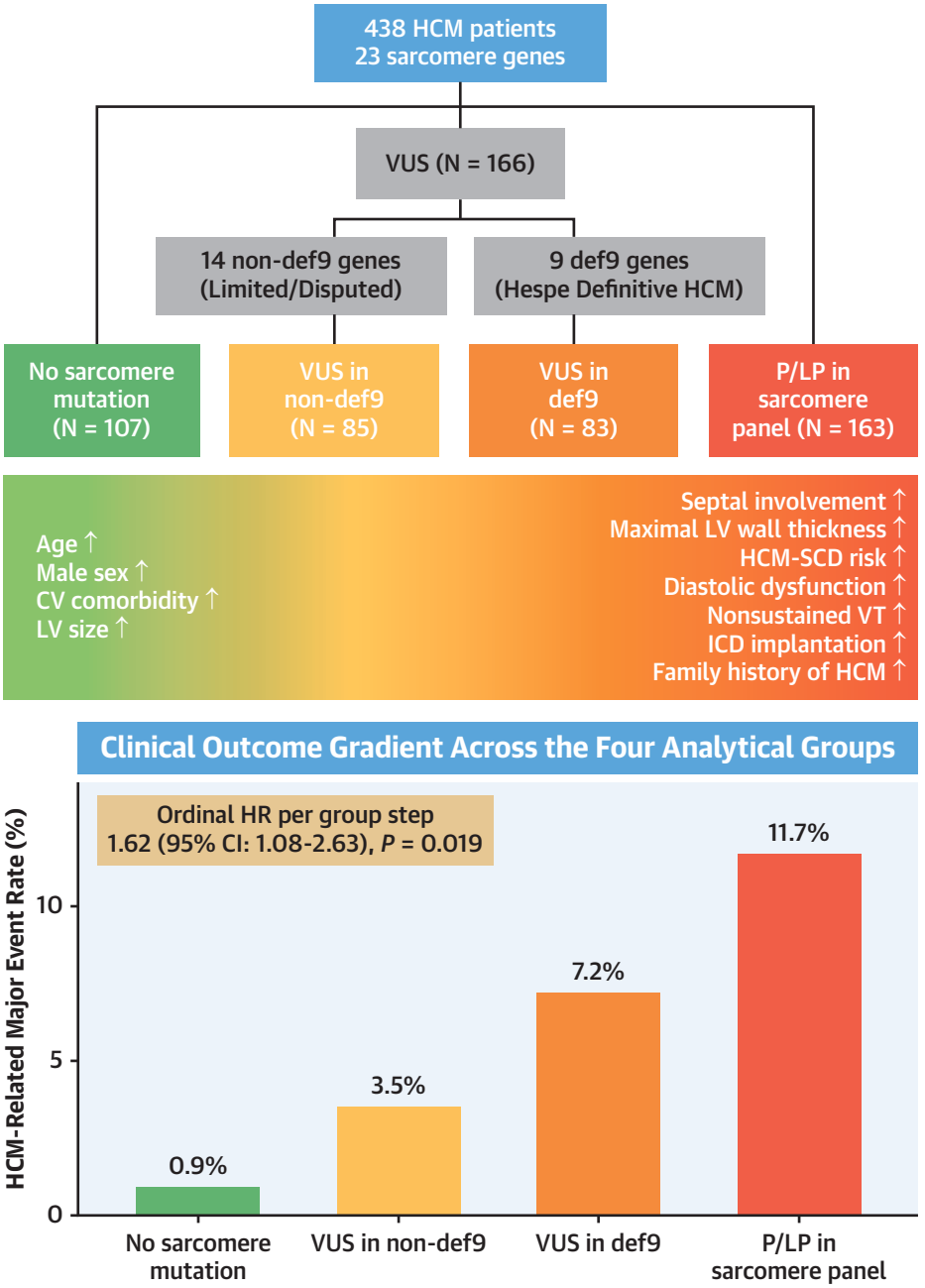
García-Hernández et al[28] recently introduced the concept of intermediate-effect variants (IEVs) to describe variants with moderate effect sizes and intermediate allele frequencies that modulate disease expression. In their large European HCM cohort, 14 IEVs accounted for 6.1% of HCM cases, supporting an oligogenic disease model in which variants with intermediate effects contribute additively to disease expression. Our findings align with this framework. The def9 VUS group in our cohort displayed intermediate phenotypic and prognostic features between genotype-negative patients and P/LP carriers. Notably, the specific IEV catalog validated in European populations did not transfer to our Asian cohort, indicating population specificity of IEV lists. Therefore, whether this intermediate signal from the

TABLE 4 Multivariable Firth-Penalized Cox Regression Analyses for HCM-Related Major Events

Model 1			Model 2 (Genetic Burden, Trend)		
Variable	**HR (95% CI)**	***P* Value**	**Variable**	**HR (95% CI)**	***P* Value**
Age at the time of genetic testing	0.96 (0.93-0.98)	0.002	Age at the time of genetic testing	0.96 (0.94-0.98)	0.002
Male	0.72 (0.34-1.61)	0.417	Male	0.73 (0.34-1.63)	0.431
No sarcomere variant	Reference		Genetic burden	1.62 (1.08-2.63)	0.019
VUS in nondef9	2.23 (0.36-23.31)	0.396			
VUS in def9	3.24 (0.67-31.39)	0.155			
P/LP in sarcomere panel	4.55 (1.09-42.03)	0.035			

Models were adjusted for age and sex and stratified by institution. In model 2, genetic burden was modeled as an ordinal variable (0 = no sarcomere variant, 1 = VUS in nondef9, 2 = VUS in def9, 3 = P/LP in sarcomere panel) reflecting increasing pathogenic potential to assess a dose-response relationship between genetic burden and the risk of the primary outcome. All abbreviations are defined in the footnote of Tables 1 and 2.

CENTRAL ILLUSTRATION **Sarcomere Variant Classification and Clinical Outcomes in Hypertrophic Cardiomyopathy**



Choi H-M, et al. JACC Asia. 2026;■(■):■-■.

Among 438 patients with hypertrophic cardiomyopathy (HCM) who underwent next-generation sequencing, sarcomere variants were classified into 4 analytical groups based on gene tier and American College of Medical Genetics and Genomics (ACMG) classification: no sarcomere variant (n = 107), variant of uncertain significance (VUS) in nondef9 sarcomere genes (n = 85), VUS in def9 sarcomere genes (n = 83), and pathogenic or likely pathogenic (P/LP) in the sarcomere panel (n = 163). Upper. Patients carrying VUS in def9 sarcomere genes demonstrated phenotypic features and clinical event rates intermediate between genotype-negative patients and P/LP carriers, while VUS in nondef9 genes closely resembled the genotype-negative phenotype. Lower. HCM-related major event rates rise stepwise across the 4 analytical groups with a significant ordinal trend (HR: 1.62; 95% CI: 1.08-2.63; $P = 0.019$). CV =cardiovascular; ICD = implantable cardioverter-defibrillator; LC = left circumflex; LV =left ventricular; P/LP = pathogenic/likely pathogenic; SCD = sudden cardiac death; VT = ventricular tachycardia.

def9 VUS in our cohort reflects true intermediate-effect biology like IEVs, or an averaging effect of potentially pathogenic and benign variants, cannot be determined from our data. Nevertheless, unlike the binary classification of pathogenic or benign, variants in this intermediate category present a quantitative risk that lies between genotype-negative and P/LP carriers, warranting a shift toward a continuous risk model in HCM management.

Sarcomere VUS carriers currently follow distinct management pathways from P/LP carriers. Contemporary HCM guidelines do not recommend cascade genetic testing for family members of patients with VUS,[4] and recent guidelines for SCD prevention consider ICD implantation reasonable in patients with intermediate 5-year SCD risk scores and P/LP sarcomere variant (class IIa), but not in those carrying VUS.[8] However, our findings suggest that def9 VUS should not be treated as clinically equivalent to genotype-negative status, because these carriers display intermediate phenotypic and prognostic features. Stratifying VUS by gene tier may help refine decisions on cascade testing, ICD implantation, and eligibility for emerging precision medicine strategies, including gene-based therapy.[29,30] At the same time, overinterpretation of VUS in nondef9 genes should be avoided, as these variants appear to carry little additional risk beyond genotype-negative status.

The clinical dilemma is particularly pronounced in Asian populations. Asian patients with HCM exhibit distinct genetic, phenotypic, and prognostic profiles compared with European cohorts.[15,31,32] However, because current major genomic databases are largely derived from populations of European ancestry, genetic variants identified in Asian patients are frequently classified as VUS because of the lack of ethnic-specific allele frequency data. Consequently, Asian patients with HCM show a disproportionately high rate of VUS classification compared with populations of European ancestry.[15] Consistent with this population-specific gap, none of the 14 IEVs recently validated in a European HCM cohort[28] were identified in our cohort, highlighting that variant catalogs validated in 1 population may not generalize to others.

Several biological and structural mechanisms may underlie the gradient of clinical features observed across the 4 genetic groups. First, VUS in def9 genes likely include a mixture of true IEVs, currently underclassified pathogenic variants, and benign variants. The cohort-level intermediate phenotype and prognosis observed in this group may therefore reflect averaging across these biological categories, rather than a uniform intermediate effect at the variant level. Second, VUS in nondef9 genes, most of which encode Z-disc and giant scaffolding proteins, may primarily reflect classification uncertainty rather than a true biological contribution to disease. Decades of HCM genetic research have focused on thick and thin filament genes, so segregation data, functional assays, and population-level evidence have accumulated predominantly in these genes.[33] Therefore, variants identified in scaffolding and giant sarcomere-associated genes are less likely to meet the ACMG evidence threshold for P/LP classification, regardless of their actual functional impact.[23] At the same time, the temporal pathophysiology of HCM may explain why echocardiographic measures showed different patterns across groups: diastolic abnormalities, which develop early in disease progression, were significantly more prevalent in P/LP carriers, whereas LV ejection fraction and global longitudinal strain, which typically decline at later disease stages, did not differ across groups.

STUDY LIMITATIONS. First, genetic testing was not performed in all patients with HCM, resulting in a relatively limited sample size for genotype-phenotype and outcome analyses. Accordingly, selection bias cannot be completely excluded, and the distribution of sarcomere variant classifications in this cohort may not fully represent that of the overall HCM population. Specifically, the number of HCM-related major events among genotype-negative patients was very small, which may have contributed to imprecision in risk estimates and wide CIs. The observed event rate in this group was lower than that reported in prior cohorts,[9] potentially reflecting selection bias due to the shorter follow-up period. Although we introduced Firth's penalization approach to survival analysis to mitigate bias arising from a small number of events, these findings should be interpreted with caution and warrant validation in larger, more diverse populations with long-term follow-up. Second, the composition of NGS panels varied over time and across institutions, which might have influenced the observed distribution of sarcomere variants. The significant difference in the distribution of sarcomere variants across institutions in genotype-negative patients and nondef9 VUS carriers reflects the different number of genes included in the genetic testing panel at each institution. Although all panels consistently included 9 sarcomere genes with definitive evidence for HCM causality (def9), caution is warranted when generalizing the findings beyond this gene set. Third, right ventricular function was not systematically measured and was therefore not included in the analysis. CMR findings, including

late gadolinium enhancement, were also excluded from the primary phenotypic comparison to maintain a time-invariant baseline, as CMR was performed at variable timepoints during follow-up rather than at initial diagnosis. Fourth, the registry did not capture the exact number of visit-level encounters, and follow-up frequency was determined at the discretion of the attending physicians. Lastly, variant interpretation is a dynamic process, and current classifications may be revised as functional, segregation, or population-frequency evidence accumulates. To further clarify the clinical significance of sarcomere VUS, large-scale prospective studies using standardized gene panels or whole-genome sequencing with longer follow-up are warranted.

In conclusion, in this large multicenter Asian HCM cohort, VUS in def9 sarcomere genes showed intermediate phenotypic and prognostic features between genotype-negative patients and P/LP variant carriers, whereas VUS in nondef9 genes clinically resembled genotype-negative HCM. A graded risk gradient was observed across these 4 genetic groups in multivariable analysis. These findings indicate that sarcomere VUS do not represent a homogeneous category, and that stratification by gene tier may refine variant interpretation and clinical management in HCM, especially in populations under-represented in current variant databases.

DATA SHARING STATEMENT The data sets analyzed during the current study are not publicly available because of institutional restrictions. A minimally anonymized data set can be requested by contacting the corresponding authors.

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KEY WORDS genotype, hypertrophic cardiomyopathy, phenotype, sudden cardiac death, variant of uncertain significance

APPENDIX For Supplemental tables, figures and references, please see the online version of this paper.