Joseph A. Hill, MD, PhD June 16, 2025  
Circulation, Editor-in-Chief

Dear Dr. Hill,

On behalf of all authors, we are pleased to submit our manuscript, **“Differences in Disease Trajectory, Comorbidities, and Mortality in Sarcomeric and Non-Sarcomeric Hypertrophic Cardiomyopathy,”** for consideration as an Original Research Article in Circulation.

Hypertrophic cardiomyopathy (HCM) is a heterogeneous disorder in which sarcomere‐gene variants are well-recognized drivers of adverse outcomes, yet more than half of affected patients are genetically elusive. How genotype influences the interplay among comorbidities, disease progression, and mortality has not been examined. Our study addresses this gap by analyzing 6,120 patients enrolled in the international Sarcomeric Human Cardiomyopathy Registry (SHaRe) who underwent standardized genetic testing with a median 5.3 years of follow-up.

Our principal findings are:

1. **Sarcomeric HCM confers a distinctly malignant course.** Patients harboring pathogenic or likely pathogenic sarcomere variants experienced earlier disease onset, higher burden of atrial fibrillation, ventricular arrhythmias, and LV systolic dysfunction, and twice the rate of HCM-related death, dying on average 7.8 years younger than genotype-negative counterparts.
2. **Non-sarcomeric HCM clusters with modifiable risk factors.** Obesity, hypertension, and LV outflow obstruction were nearly twice as prevalent in genotype-negative disease, suggesting a causal contribution of metabolic and haemodynamic stressors and underscoring the opportunity for aggressive risk-factor management.
3. **Genotype modifies the impact of pivotal clinical events.** Atrial fibrillation and LV systolic dysfunction carried substantially greater downstream risk of ventricular arrhythmias, severe heart failure, and death in sarcomeric HCM, highlighting the need for heightened surveillance and earlier intervention in this subgroup.

These observations refine risk stratification and illuminate genotype-specific therapeutic targets.

The manuscript is original, has not been published, and is not under review elsewhere. All authors have read and approved the submission. Institutional review boards at all participating centers approved the study, and written informed consent was obtained from all participants. We believe our work will be of keen interest to Circulation’s readership and would be honored by your consideration.

Sincerely,

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